

Comprehensive Review of the Relative Clinical Utility of B-Type Natriuretic Peptide and N-Terminal Pro-B-Type Natriuretic Peptide Assays in Cardiovascular Disease

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Abstract: Measurable B-type natriuretic peptides, which are largely produced by the left ventricle, include B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). These proteins are released by cardiomyocytes in response to wall-tension and neurohumoral signals. In this review the literature is summarized to date with respect to the approved indications for testing which include the diagnostic evaluation and prognosis of heart failure. PubMed in 2009 was searched and 5496 references were reduced to 242 studies that reported on either diagnosis, prognosis, screening, or monitoring of heart failure. In head-to-head diagnostic comparisons, 58 studies measured both assays, and 11 studies in adults that included at least 100 patients compared commercially available tests. We performed the analogous search in acute coronary syndromes (ACS) and found 82 articles of which 11 papers focused on the study of BNP and NT-proBNP in either stable angina, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. For heart failure diagnosis, BNP and NT-proBNP had similar decision statistics; however, while optimal diagnostic cutpoints for both markers varied depended on age and degree of renal dysfunction, and the clinical application; NT-proBNP had a much more widely variable optimal cutpoint than did BNP. Sufficient evidence for clinical utility of both tests exists for other applications of prognosis, screening, and monitoring of heart failure. In addition, both tests have a role in the risk stratification of all forms of ACS. Future trials of clinical strategies are warranted using these tools in advancing both inpatient and outpatient management of heart failure and ACS.

Keywords: B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, heart failure, diagnosis, prognosis, systematic review, hospitalization, mortality.

INTRODUCTION

Recently it has been recognized and shown that tests for B-type natriuretic peptide and for the amino terminal fragment NT-proBNP are accurate and useful markers of heart failure (HF). These tests have been shown to improve physicians' ability to diagnose HF in symptomatic patients. Accurate diagnosis of HF without these markers has been difficult in the past, particularly in acutely ill patients, in part because symptoms such as dyspnea, fatigue, and edema are relatively non-specific [1-3]. These symptoms are also common in obese and elderly patients with a variety of medical problems and in those with respiratory disease, making diagnosis of HF more challenging [3]. Indeed, the accuracy of clinical assessment of HF by history, physical exam, and conventional testing alone has been fallible, particularly in female, elderly, and obese patients [4, 5].

BNP and NT-proBNP are invaluable tools for physicians to introduce early intervention and to manage patient care [6-8]. Annual costs of treating HF patients in the United States are estimated at \$65 billion, 70% of which is due to hospitalization. Half of HF patients are readmitted to the hospital within 6 months of discharge and 10% are readmitted twice

[9]. Fewer readmissions by BNP or NT-proBNP guided therapy can significantly impact the costs associated with this prevalent disease.

BNP and NT-proBNP have been shown to be sensitive and accurate markers of HF and have been shown to be superior for predicting HF relative to other markers of cardiac dysfunction [10-17]. The gene for BNP is located on chromosome 1 (Fig. 1) and can be rapidly activated in response to signal transduction from the myocyte cell wall. After protein synthesis, BNP is cleaved from the precursor molecule, proBNP by corin into the active BNP hormone and the inactive NT-proBNP fragment. Biologically active BNP is released from cardiomyocytes in response to wall tension, which according to the law of Laplace, is determined by the pressure within and the radius of the chamber. Since the left ventricle has the greatest mass by far of all the cardiac chambers, these natriuretic peptides largely reflect the dynamic wall tension experienced by the left ventricle that occurs with pressure and volume overload and neurohumoral activation in heart failure [11,18] with levels of these markers relating to the severity of HF symptoms and cardiac dysfunction [10,19-21]. In the setting of acute and chronic right ventricular pressure overload, both BNP and NT-proBNP can be elevated but not typically to the levels seen in left ventricular failure. All assays for BNP and NT-proBNP recognize epitopes on the parent peptide proBNP, thus, in the setting of acute decompensated heart failure, it is believed

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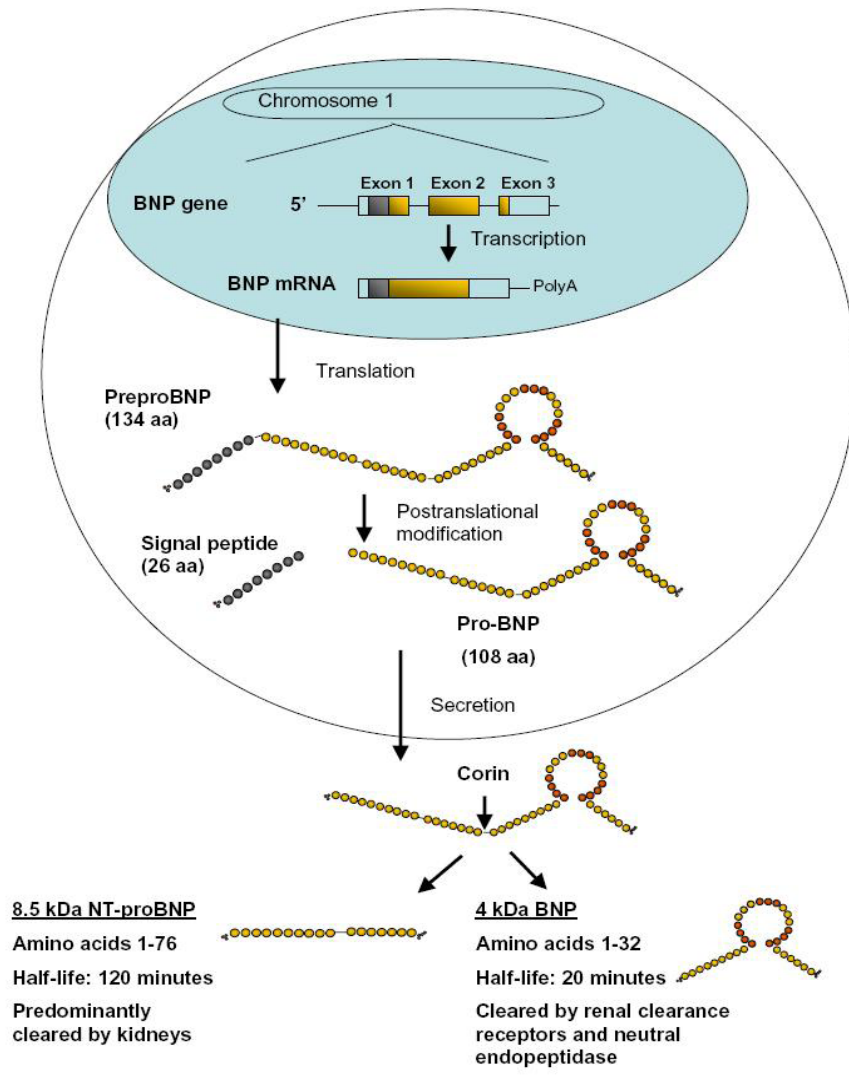


Fig. (1). Synthesis and secretion of natriuretic peptides from cardiomyocytes.

that levels of these proteins reflect both “immature” and mature peptide products [22]. In addition, fragment peptides are known to be in the circulation of patients with heart failure (BNP3-32 and BP6-32) and glycosylation of both BNP and NT-proBNP can occur as with many proteins to a variable degree depending on levels of glycemia and circulatory durations of the peptides [23, 24]. Both BNP and NT-proBNP rise quickly in the setting decompensation and have sustained elevation provided increased wall tension and neurohumoral activation remain present [12-17].

There are some differences that may affect the relative usefulness of these two markers in different patient populations which will be discussed in this paper. For example, BNP has a shorter half-life than NT-proBNP because they are cleared by different mechanisms. Thus levels of NT-proBNP are higher than those of BNP despite being produced at a theoretical 1:1 ratio. While the predominant pathway for clearance of NT-proBNP is by renal excretion, BNP appears to have a multiple clearance pathways including NP clearance receptors in the kidney and peripheral tissues as well as degradation by plasma neutral endopeptidase (vasculature), meprin A (kidneys), and neprilysin (brain) [25-27].

Thus, BNP levels are less affected by renal dysfunction alone than are levels of NT-proBNP [9, 28]. However levels of both peptides can be elevated in the setting of chronic kidney disease and loss of renal mass and this may give a misleading elevation of one or both suggests suggesting cardiac decompensation.

METHODS

The Pubmed database was searched in 2009 using the following terms: “Brain natriuretic peptide [text word] OR “Natriuretic Peptide, Brain”[MeSH Term] OR “pro-brain natriuretic peptide (1-76)”[MeSH Term] OR “B-type natriuretic peptide”[Text Word]. This search gave 5496 references and when searched within these terms for primary studies that investigated the analysis of these markers for the diagnosis, prognosis determination and treatment monitoring of HF patients, 242 references were found. This list was further reduced to include only studies that specifically tested the sensitivity, specificity and accuracy of these tests as primary means for determining diagnosis or prognosis in adult HF patients or those that directly compared the two assays (108 references, 58 of which were studies that compared the

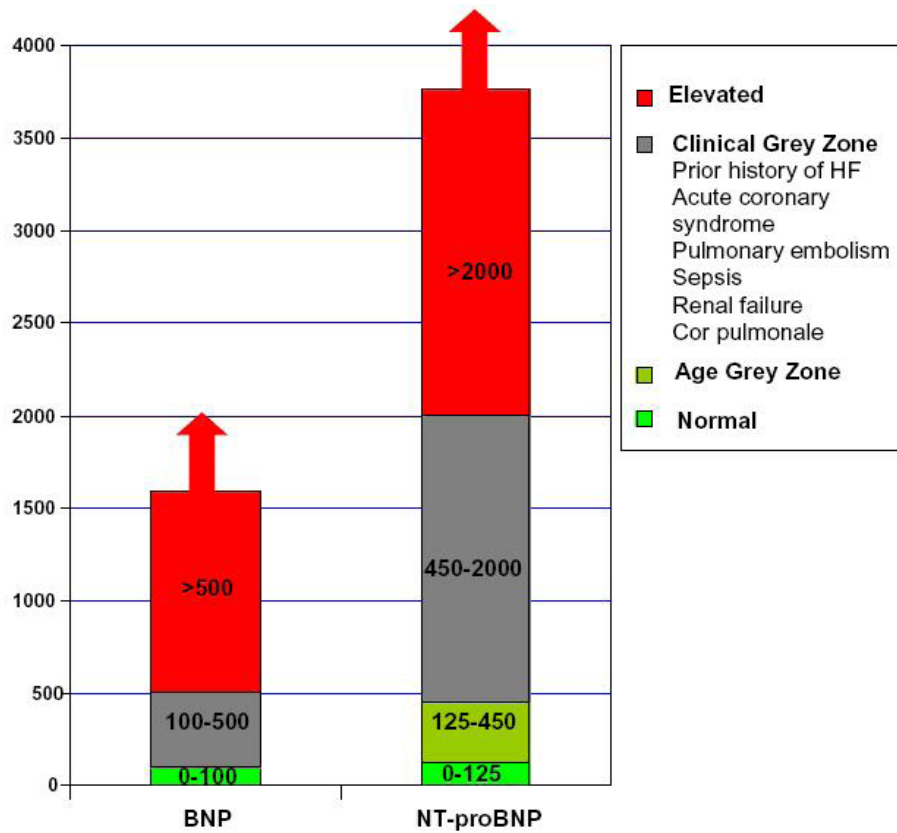


Fig. (2). Comparison of the diagnostic categories of BNP and NT-proBNP values as summarized in the clinical studies for the diagnosis of HF in symptomatic patients.

two assays). The yield was narrowed by excluding direct comparison studies that did not include measures of sensitivity, specificity and area under receiver operator characteristic curve and studies on pediatric patients, those with less than 100 patients and those using obsolete radioimmunoassays for BNP or NT-proBNP.

We performed the analogous search by using the terms BNP and acute coronary syndrome in the PubMed database and found 82 articles. Among those articles, we excluded all which were not focused on either BNP or NT-proBNP and ischemic heart disease, but also on other cardio biomarkers and heart failure. This search resulted in 11 articles that were focused only on the study of BNP and NT-proBNP in either

stable angina, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction.

DIFFERENTIAL DIAGNOSIS IN PATIENTS WITH ACUTE DYSPNEA

BNP and NT-proBNP levels are sensitive, specific and quantitative markers of HF [12, 17]. In general, more clinical data exists for BNP but both markers have been shown to be clinically useful in the diagnosis of HF in patients presenting with acute dyspnea in emergency departments (ED) and in determining the prognosis of HF patients [10, 29]. Testing for these markers is recommended by multiple heart failure guidelines including those from the European Society of

Table 1. Summary of Data from Studies that Examined BNP as a Diagnostic Aid in Symptomatic Patients with Suspected Heart Failure

Size	Optimal Cutpoint	Sens	Spec	PPV	NPV	Acc	AUC	Assay	Reference
52	22 pg/mL	93	90	87	95	91	ND	Not stated in methods.	Davis [12]
250	ND	94	94	92	96	94	0.98	TRIAGE (Biosite)	Dao <i>et al.</i> [35]
1586	100 pg/mL	90	76	77	90	84	0.90	TRIAGE (Biosite)	Maisel <i>et al.</i> [36]
70	200 pg/mL	100	97	97	100	99	ND	TRIAGE (Biosite)	Villacorta <i>et al.</i> [37]
308	250 pg/mL	78	90	87	83	84	0.87	TRIAGE (Biosite)	Ray <i>et al.</i> [38]

Abbreviations: Size, study size; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy; AUC, area under the receiver operating characteristic curve; ND, not determined in the study and not able to be determined by the data provided by the study.

Table 2. Summary of Data from Studies Testing NTproBNP as a Diagnostic Aid in Suspected HF

Size	Optimal Cutpoint (pg/mL)	Sens	Spec	PPV	NPV	Acc	AUC	Type assay	Reference
100	115	93	90	98	74	92	0.96	Elecsys (Roche)	Bayes-Genis <i>et al.</i> [40]
122	1760	90	96	97	87	93	0.82	Elecsys (Roche)	Zaninotto <i>et al.</i> [39]
1256	450 (<50 yrs) 900 (50-75 yrs) 1800 (>75 yrs)	90	85	78	99	87	0.94	Elecsys (Roche)	Januzzi <i>et al.</i> [43]

Abbreviations: Size, study size; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy; AUC, area under the receiver operating characteristic curve.

Cardiology, the American College of Cardiology/American Heart Association and the National Academy of Biochemistry [30-33].

Using tests for BNP or NT-proBNP improves diagnosis of HF in patients presenting with acute dyspnea in the ED as demonstrated in several seminal studies (Tables 1 & 2) [12, 34-41]. The use of optimal cutoff values allows physicians to quickly rule out or rule in HF as a cause of patient symptoms.

Multiple single center studies demonstrated the usefulness of BNP as a diagnostic tool in the ED [12, 34-41] and this was validated by the Breathing Not Properly (BNP) Multinational Study [42]. In this study, BNP was tested in a large (N=1586) multicenter, prospective, blinded, and adjudicated format, and it demonstrated that utilization of BNP testing lead to more accurate diagnoses than ED physician judgment based on patient history, physical findings, chest x-ray, and other laboratory values [42]. In the BNP Multinational Study, the authors determined that the optimal cutoff values of 100 pg/mL yielded a sensitivity of 90% and a specificity of 76%. A recent meta-analysis of the studies of the usefulness of BNP testing determined that testing for BNP was useful for improving accurate diagnosis of HF in ED patients presenting with acute dyspnea, particularly when the symptoms of HF were mild [29]. Multiple studies have shown that NT-proBNP is also highly useful in diagnosing dyspneic patients in the ED (Table 2) [39, 40]. The ProBNP Investigation of Dyspnea in the ED (PRIDE) study (N=600) evaluated whether using NT-proBNP assay could enhance the accuracy of HF diagnoses in ED patients [43, 44]. NT-proBNP at cutpoints of >450 pg/mL for patients <50 years of age and >900 pg/mL for patients \geq 50 years of age were highly sensitive and specific for the diagnosis of acute HF ($p < 0.001$). Similar to the findings for BNP, this study concluded that awareness of patient NT-proBNP levels together with clinical judgment gave superior results than either method alone [43, 44]. Thus both markers appear to exhibit equivalent performance in diagnosing symptomatic patients. In addition, both BNP and NT-proBNP have been shown to be useful in diagnosing HF in symptomatic patients in other departments of the hospital and in symptomatic patients presenting to their general practitioners [45-47]. It is important to point out that elevation of one or both markers calls for a differential diagnosis to be constructed with includes decompensated heart failure, acute coronary ischemia, pulmonary embolism, cor pulmonale, sepsis, renal insufficiency, and in rare cases recurring arrhythmias.

Both tests have been shown to have a positive economic impact on the cost of patient care. In the BNP for Acute Shortness of Breath Evaluation (BASEL) Trial, it was shown that utilization of BNP testing in the ED decreased the total time from initial presentation to initiation of treatment from 90 to 63 minutes. In addition, BNP results decreased the rate of admission from 85% to 75% and reduced the total costs of treatment in this patient population from \$7264 to \$5310 [48]. The IMPROVE-CHF study showed that NT-proBNP also could significantly decrease costs associated with patient care. Use of NT-proBNP testing reduced the duration of time spent in the ED by 21% and the rate of readmission by 35%. Medical costs were reduced in the patient population analyzed from \$6129 to \$5180 over 60 days as a result of including the test in managing patient care [49].

NT-proBNP has a longer half-life *in vivo* than does BNP and it has been argued that because of this, it may be a more sensitive than BNP. However, several head-to-head comparisons have been done to compare BNP and NT-proBNP assays, and together these data suggest that they are generally equivalent in terms of sensitivity and specificity in the general population (Table 3). BNP and NT-proBNP assays vary in sensitivity and specificity depending upon the platform used, the patient population, and the diagnostic cutpoint used, which may all account for some of the heterogeneity in the data [50-53]. Three separate meta-analyses of data from clinical studies have been done on the body of work directly comparing the sensitivity and specificity these two assays for diagnosing HF patients [50, 54, 55]. Two of these analyses concluded that they are generally equivalent in their sensitivity in accurately diagnosing HF in symptomatic patients [50, 54]. Interestingly, one meta-analysis specifically addressed the functionality of these tests in different age groups and concluded that BNP is superior, particularly in older patients [54]. Thus, the longer half-life and higher measurable levels of NT-proBNP do not translate to superior sensitivity, and in fact BNP may have better accuracy in elderly patients and those with chronic kidney disease. Both peptides are elevated modestly in the setting of diastolic HF but not typically to the levels achieved in patients with decompensated systolic HF.

RELATIVE VALUE OF BNP AND NT-PROBNP IN HEART FAILURE PROGNOSIS

In addition to their usefulness in diagnosing HF in symptomatic patients, BNP and NT-proBNP are able to provide prognostic information and improve admission decisions in

Table 3. Summary of Head-to-Head Studies which Compared the BNP and NTproBNP Assays as a Diagnostic Aid in Suspected Heart Failure Patients

BNP Assay	Optimal Cutpoint (pg/mL)	Sens	Spec	PPV	NPV	Acc	AUC	NTproBNP Assay	Optimal Cutpoint (pg/mL)	Sens	Spec	PPV	NPV	Acc	AUC	Refs
TRIAGE (Biosite)	60	94	70	63	98	80	0.89	ECLIA (Roche)	340	80	87	76	89	84	0.89	[120]
TRIAGE (Biosite)	150	94	61	60	94	73	0.82	ECLIA (Roche)	1000	97	63	61	97	77	0.84	[121]
TRIAGE (Biosite)	250	73	91	86	81	83	0.85	ECLIA (Roche)	1500	75	76	71	80	76	0.80	[122]
TRIAGE (Biosite)	290	76	88	73	89	84	0.84	ECLIA (Roche)	1360	77	86	71	90	83	0.85	[123]
MEIA (Abbott)	295	80	86	87	78	83	0.92	ECLIA (Roche)	825	87	81	84	84	84	0.90	[124]
ADVIA (Bayer)	79	95	96	95	96	96	0.98	ECLIA (Roche)	817	98	94	93	97	96	0.98	[125]
ADVIA (Bayer)	21	81	72	49	92	74	0.84	ECLIA (Roche)	143	87	87	70	95	87	0.93	[126]
ADVIA (Bayer)	35	69	49	82	68	84	0.60	ECLIA (Roche)	235	53	78	89	33	59	0.67	[127]
TRIAGE (Biosite)	100	79	72	59	87	74	0.80	ECLIA (Roche)	125	98	35	35	97	57	0.85	[128]

Abbreviations: Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy; AUC, area under the receiver operating characteristic curve; Refs, references.

patients with diagnosed HF. In the context of patient care, it has been proposed that because of its shorter half-life *in vivo*, BNP may be more useful than NT-proBNP to track improvement following therapeutic intervention and in acute HF because it is more sensitive to rapid hemodynamic changes in response to treatment [56]. Several studies have tested the value of each marker in guiding patient care [49, 57-60].

Measurement of BNP levels has been shown to accurately identify high-risk chronic HF patients. In one study the authors found that patients with BNP levels above 350 pg/mL were five times more likely to die or be readmitted for HF if discharged [61]. Patients with levels over 700 pg/mL had 15 times the risk of death or readmission, which occurred in 90% of the patients in the study [61]. The BNP assay was able to predict adverse patient outcomes with an area under the ROC curve of 0.83. In another study of 325 ED patients, BNP levels above 480 pg/mL could predict adverse outcomes with a sensitivity of 68% and a specificity of 88% and area under the ROC curve of 0.87 [62]. BNP assays have strong prognostic value in both elderly and diabetic patients [63, 64] and may be a stronger predictor in women compared to men [65].

NT-proBNP levels also correlate well with patient prognosis. Studies using multiple measurements of NT-proBNP in HF patients during treatment suggest that the absence of a decrease in levels during hospitalization correlates with mortality or readmission within 6 months of discharge [66-69]. In one study, the authors concluded that a reduction of less than 30% was predictive of death with area under the ROC curve 0.78 [70], while another concluded that using admis-

sion levels of NT-proBNP of >986 pg/mL could predict one-year mortality with area under the ROC curve 0.76 [71]. Schou *et al.* determined that every time NT-proBNP doubled, the hazard ratio for death increased by 56% and that for readmission increased by 19% [72]. A PRIDE substudy showed that NT-proBNP was able to give valuable prognostic information in patients with diabetes [73].

Several studies have been done to directly compare the prognostic performance of BNP and NT-proBNP. One study compared these markers in chronic HF patients and did not find significant differences in their accuracy [74] while another found that NT-proBNP had increased prognostic power over BNP for all cause mortality in acute decompensated HF patients [75]. In accordance with the ability of these markers to provide prognostic information in HF patients, multiple studies have shown that they both may improve admission decisions in HF patients. Direct comparisons of the relative value of BNP and NT-proBNP to guide HF patient care have not been made. Several studies in CAD patients with no overt symptoms of HF suggest similarly that both markers provide valuable prognostic information in earlier disease states and that NT-proBNP may provide a slight advantage [68, 76, 77].

RELATIVE ADVANTAGES OF BNP AND NT-PROBNP IN DIFFERENT PATIENT POPULATIONS

Several factors other than cardiac function affect levels of BNP and NT-proBNP including gender, age, BMI, renal disease, and certain pulmonary conditions [78-80]. Some of these factors can influence the accuracy of these assays for determining diagnosis and prognosis in HF patients. Levels

of both BNP and NT-proBNP are elevated in certain types of pulmonary disease such as cor pulmonale, lung cancer, and pulmonary embolism [81-83]. Baseline levels of both BNP and NT-proBNP are lower in obese patients in normal patients and in those with heart failure [84-87]. This relationship appears to be independent of left ventricular function and hemodynamics. The mechanism by which levels of BNP and NT-proBNP are decreased in obese patients is poorly understood. NPR-C receptors that bind BNP are expressed on adipose tissue. However the observation that both BNP and NT-proBNP are decreased in obese patients suggests that rather than enhanced clearance *via* NPR-C receptors, reduced production of BNP/NT-proBNP is responsible for the decreased levels observed in overweight patients [88]. In one study NT-proBNP levels fell below optimal cutoff values in 15% of obese patients with HF while BNP levels were falsely negative in 20% of obese patients, suggesting that NT-proBNP levels may be slightly less affected by BMI than BNP [89]. However it is clear that for both markers, BMI must be taken into account when interpreting results, particularly if levels are close to indicated cutoff values [9]. Race and gender may influence levels but do not negatively impact the usefulness of either marker in diagnosing HF in dyspneic subjects [79,80].

BNP is more effective than NT-proBNP as an independent marker for HF in elderly patients, particularly in those with renal disease (9, 10, 74). The Breathing Not Properly study showed a correlation between eGFR and BNP in patients with and without HF. Thus, patients with chronic kidney disease (CKD) do have elevated levels of BNP. However, if the cutpoint for BNP is increased by 200 pg/mL, an acceptable area under the curve of 0.80 exists for BNP as a marker for HF in CKD patients [28]. Elevation of NT-proBNP in contrast is much more accentuated in elderly patients and in those with renal disease in part because it is solely cleared by the kidneys. This elevation of NT-proBNP is so dramatic that the values may give false positives, and thus different cutoff values must be used [9, 31, 32, 90]. In a PRIDE substudy, the authors found that using a cutpoint of 1200 pg/mL for patients with GFR < 60 mL/min/1.73m² gave an acceptable AUC of 0.88, with sensitivity of 89% and a specificity of 72% [90]. This is one of the main differences that have been found between the two assays and may be a significant advantage of the BNP assay for diagnostic purposes because HF is most prevalent in elderly patients [91-94]. In contrast, several studies have also shown that there is no difference in the correlation of BNP and NT-proBNP and the prognostic utility of these markers in patients with renal disease [95, 96].

In conclusion, both tests can accurately diagnose HF in elderly patients or in those with renal disease. However, a simpler diagnostic algorithm is associated with BNP results than NT-proBNP results for diagnostic purposes, which must take age and renal dysfunction into consideration when determining cutoff values.

SCREENING ASYMPTOMATIC PATIENTS AT RISK FOR LEFT VENTRICULAR DYSFUNCTION

Several studies have tested the usefulness of BNP or NT-proBNP in screening asymptomatic populations for heart failure. BNP and NT-proBNP are suboptimal for identifying asymptomatic cardiac dysfunction in the general population

[97-100]. In a population with low prevalence of heart failure, low levels of BNP or NT-proBNP may be able to rule out heart failure, but high values are not specific enough to rule in heart failure [97]. Although not useful for screening the general population, BNP and NT-proBNP tests may be beneficial for screening at risk populations for significant cardiac impairment for heart failure [101-103].

In patients at high risk for heart failure, BNP testing was able to identify patients with underlying cardiac dysfunction [101]. Heidenreich *et al.* showed that it is economically feasible to use a BNP cutoff value of 24 pg/mL to determine which patients to screen further using other, more expensive methods such as echocardiography [104]. Using this cutoff significantly decreased the costs of diagnosing patients with suspected cardiac dysfunction. In another study, BNP was used to test patients over the age of 65 and a group with a high number of cardiac risk factors [100]. The authors found that BNP was effective at screening for HF patients with area under the ROC curve of 0.83-0.88 for the 65 years of older group and 0.83-0.85 in the cohort with a high number of risk factors.

NT-proBNP is also useful in ruling out HF in primary care patients with suspected HF [105]. Omland *et al.* showed that elevated BNP levels were associated with increased risk of HF in patients with stable coronary artery disease, while NT-proBNP was associated with increased risk of heart failure as well as cardiovascular death and stroke [76]. More comparison studies with current automated BNP and NT-proBNP assays are needed to determine their relative usefulness in this context.

MONITORING AND GUIDING HEART FAILURE MANAGEMENT

BNP and NT-proBNP may also be valuable in guiding therapeutic treatment for HF [9, 34, 106]. As discussed, BNP may be more sensitive to hemodynamic changes *in vivo* [19, 56]. More research needs to be done to understand whether this impacts the relative effectiveness of BNP to monitor changes in patient prognosis following therapeutic intervention. For example, measurement of BNP may more accurately reflect recent changes in the production of BNP. Alternatively it could be overly sensitive in patients with wide swings in filling pressures. It has been shown that the disease modifying therapies in heart failure that reduce hospitalization and mortality also reduce natriuretic peptide levels chronically over time; these include: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone-receptor antagonists, and biventricular pacing [107-110]. Thus, the concept that natriuretic peptide levels, analogous to glycohemoglobin in diabetes management, could be a treatment target for office physicians is worthy of randomized trials.

Data from the Strategies for Tailoring Advanced HF Regimens (STARS-BNP) clinical trial showed that monitoring patient BNP levels can augment proper titration of certain drug therapies to improve patient outcomes [111]. This study included 220 patients in the NYHA function class II-III. Only 24% patients who received BNP guided therapy died or were readmitted to the hospital during a 15-month period compared to 52% of patients that underwent unguided therapy. In the same study, it was found that event-free sur-

vival was 84.3% in the BNP-guided group vs. 73.3% in the unguided group. In addition, HF related hospitalization dropped from 44% to 20% as a result of BNP-guided therapeutic modifications.

In a single-center trial of 73 patients with HF and ejection fraction < 40%, Inomata *et al.* randomized patients to a BNP-guided strategy to a target BNP < 200 pg/mL versus usual care. The combined endpoint death or hospitalization occurred in 22% vs. 55%, $p = 0.037$ over 25 months [112]. The Strategies for Tailoring Advance Heart Failure Regimens in the outpatient setting: BNP vs the clinical congestion score (STARBRITE) clinical trial pilot study assessed 130 patients with more advanced HF (NYHA class III-IV) [113]. In contrast to the STARS study, the pilot study found no significant change in the endpoint of readmission or death between patients that received BNP guided or unguided therapy. Thus, further research is needed to understand whether BNP guided therapy is advisable in patients with more progressive disease.

A randomized trial by Troughton *et al.* evaluated the role of NT-proBNP in guiding outpatient therapeutic intervention in class 2-4 HF patients with an ejection fraction < 40% [106]. The percent of patients that experienced a cardiovascular event within 6 months was 27% in the NT-proBNP guided group vs. 53% in the cohort that lacked NT-proBNP monitoring. Thus, NT-proBNP guided therapy also positively impacts patient outcome. Several large clinical trials, the BATTLESCARRED study, the PROTECT study and the TIME-CHF study are being undertaken to understand how NT-proBNP guided therapy impacts mortality and hospital admission rates in HF patients [114-116]. Head-to-head comparisons of current BNP and NT-proBNP for guiding patient therapy would be highly useful in the future.

USEFULNESS OF CURRENT BNP AND NT-PROBNP ASSAYS IN PATIENTS RECEIVING NESIRITIDE THERAPY

Recombinant BNP itself (nesiritide or Natricor) is used therapeutically in HF patient to ameliorate acute symptoms such as dyspnea and reduced cardiac output [117,118]. Treatment with these recombinant forms of BNP results in an inhibition of the renin-angiotensin system and aldosterone release, which promotes diuretic and vasodilatory effects. Endogenous BNP and NT-proBNP levels have been successfully measured in patients following treatment with nesiritide (recombinant hBNP) [119]. It has been shown that NT-proBNP does not respond dynamically over the course of a nesiritide infusion, probably because of its longer half-life [119]. Nesiritide has an extremely short half-life of 18 minutes [118]. Thus, although it has been argued that NT-proBNP may be advantageous because nesiritide may obscure BNP levels, it is unlikely due to the half-life of the treatment. Measurement of BNP levels as soon as 2 hours after treatment should largely measure endogenously produced BNP; however, this needs to be tested. This represents an area where further study is needed to understand the relative usefulness of these assays in this cohort of HF patients.

BNP AND NT-PROBNP ASSAYS IN ACUTE CORONARY SYNDROMES

Measurement of circulating natriuretic peptides, BNP and NT-proBNP has found a secure place in the diagnosis, prog-

nosis, and management of patients with heart failure. The natriuretic peptides have also been evaluated in the setting of acute coronary syndromes (ACS), primarily on the initial or baseline blood sample and have been found to be prognostic for in-hospital and short-term (6 month, 1 year) outcomes. The most recent ACC/AHA guidelines for the management of non-ST segment elevation ACS cite the use of natriuretic peptide management as a Class IIb indication: "Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. (Level of Evidence: B)" [129].

In the setting of stable angina, Omland *et al.* [130] showed that in patients with angiographically documented stable coronary artery disease, plasma BNP level was independently related to long-term survival. In their study, BNP level > 87pg/ml (> 80th percentile) was associated with a survival rate of a little bit lower than 80% at 8 years compared to 90% at 8 years for patients with BNP < 87pg/ml. Richards *et al.* in a review [131], compared BNP and NT-proBNP in stable ischemic heart disease and concluded that, in this population, both natriuretic peptides correlated closely ($r=0.9$, $p<0.001$), were powerful indicators of left ventricular function and independent predictors of clinical outcomes. Both peptides were similarly and independently influenced by gender, age, renal function and had the same performance in detecting left ventricular dysfunction.

In unstable angina and non-ST-segment elevation myocardial infarction, BNP and NT-proBNP levels have been shown to have similar prognostic value. Cameron *et al.* compared both peptides in emergency department in patients presenting with suspected ACS [132]. Despite the level of NT-proBNP being quantitatively higher than BNP, they were closely correlated ($r=0.89$, $p<0.0001$) across subgroups of patients with coronary artery disease, hypertension, hypercholesterolemia, diabetes, all of which can influence vascular function and potentially left ventricular wall tension. The higher level of NT-pro BNP (median of 185 ng/ml compared to 15 ng/ml for BNP) might be explained by its prolonged half-life and greater reliance on glomerular filtration function for elimination.

De Lemos *et al.* studied the value of BNP in patients with unstable angina and non-ST-segment elevation myocardial infarction and showed that a single measurement of BNP obtained within 40 hours of the onset of ischemic symptoms can be used for risk stratification in ACS. In the same study, it was shown that BNP can be elevated, even in the absence of myocardial infarction [133]. Patient's exceeding the threshold of 80 pg/ml, approximating the level of neurohormonal activation in heart failure (100 pg/ml), had an increased risk of 10-month mortality (OR = 5.8) compared to patients with BNP < 80 pg/ml [133]. Other authors found the same threshold as useful to identify patients at risk for heart failure and death at 6 months after ACS [134].

BNP itself also adds incremental prognostic information to other biomarkers including troponin I and CRP in patients with non-ST-segment elevation myocardial infarction. Sabatine in a review showed that patients with one, two or three elevated biomarkers had respectively 2.1, 3.1 and 3.7 fold increases in the risk of death, myocardial infarction, and congestive heart failure at 6 months [135].

NT-proBNP has also been assessed in non-ST-segment elevation myocardial infarction and unstable angina and has been found to improve early risk stratification. NT-proBNP can be elevated in patients with normal troponin considered at low risk, allowing discrimination of patients at higher risk in this population. The NT-proBNP level range obtained on admission associated with risk of death in ACS is between 400 and 1000 pg/ml [136-139]. Weber *et al.* showed that a level > 474 pg/ml on admission adds incremental prognostic value in patients admitted for ACS without an elevation in troponin [136].

In ST-segment elevation myocardial infarction, Mega *et al.* demonstrated that a BNP level of more than 80 pg/ml at initial presentation identified patients at higher risk of death (seven fold higher) [139]. In the same study, increased concentration of BNP at initial presentation of patients with ST-segment elevation myocardial infarction was associated with impaired reperfusion and fibrinolysis [140]. In ST-segment elevation myocardial infarction patients, BNP level has been associated with underlying severity of coronary artery disease and degree of ischemic myocardium. Palazzuoli *et al.* studied 88 patients with non-ST-segment elevation myocardial infarction and preserved ejection fraction, and found that BNP levels were significantly higher in patients with three-vessel disease compared to patients with two or one vessel disease. Patients with left anterior descending artery stenosis had a higher BNP levels compared to patients with stenoses in other vessels [140]. This concept of the association between BNP and ischemia related increased in wall tension is supported by studies showing that there is an increase in BNP level after exercise thallium stress testing with significant ischemia and after transient ischemia induced by PCI [141].

The prognostic significance of large increase in BNP level has not been thoroughly studied in the literature. In most of the studies, the cut point of BNP level associated with worse prognosis is 80ng/ml.

In a retrospective study done on 91 patients admitted with ST-segment elevation myocardial infarction, with BNP levels obtained within 24 hours of the patients admission, markedly elevated BNP levels (median, 25th percentile and 75th percentile of the BNP value were 366, 142 and 1011 pg/ml, respectively) predicted LAD and multivessel disease, reduced ejection fraction, diastolic dysfunction, and hemodynamic compromise including cardiogenic shock and the need for intra-aortic balloon counterpulsation early during hospitalization. In the same study, despite prompt angiography and primary PCI, substantial elevations of BNP was a prognostic marker of in-hospital mortality due to cardiovascular causes after ST-segment elevation myocardial infarction. These data suggest that, BNP level might predict not only the infarct size but also may portend cardiogenic shock in patients with ST-segment elevation myocardial infarction. [142].

Overall, BNP and NT-proBNP have a comparable prognostic value in stable angina, unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. The threshold value of BNP is lower than NT-proBNP most likely secondary to the size of the molecule, half-life and mode of elimination, which is different. Early neurohormonal activation in myocardial

ischemia secondary to wall tension, or temporary or permanent left ventricular dysfunction secondary to ischemia, might explain why both peptides are elevated in ACS. Whether measurements one or both peptides on admission in patients with ACS, including patients considered otherwise at low risk without elevations of troponin, to assist in management decisions remains to be determined.

CONCLUSIONS

Testing for BNP or NT-proBNP has a significant impact on patient care and outcome in high-risk groups and in patients with suspected HF. The development of assays on automated instruments to test for these markers is a valuable tool for physicians and it is estimated that 70% of hospitals now have the capability to test for these markers [9]. Accurate diagnosis of HF and/or the ability to rule out suspected HF requires the use of BNP/NT-proBNP markers and clinical expertise, which together have been shown to greatly improve the accuracy of diagnosis in suspected HF patients. Prompt and appropriate use of therapeutic interventions can have a positive impact on patient quality of life and accurate markers of HF such as BNP and NT-proBNP are valuable for diagnosis and monitoring of HF patients in the ED and in high-risk populations.

In general, both markers are sensitive and specific markers of HF, which provide valuable prognostic information, improve patient care, and may be used to screen high-risk populations. BNP assays have the advantage of utilizing a single cutoff value for any age group. Thus, simpler, teachable algorithms are possible with BNP and not NT-proBNP. NT-proBNP levels are more significantly affected in elderly patients or in those with renal dysfunction, and thus, have lesser utility. In addition, a recent meta-analysis suggests that even with modified cutoff values BNP may be a superior diagnostic tool in elderly patients (44). In addition, although both markers have been shown to improve patient outcomes when used to guide admission decisions and/or therapy, head-to-head comparisons should be done to directly compare the usefulness of these assays in the longitudinal management of heart failure.

Measurement of natriuretic peptides in the setting of ACS identifies patients at high risk for short-term outcomes including the development of HF, rehospitalization, and death. This application is germane to patients with unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. The elevation of BNP and NT-proBNP appears to reflect the area of ischemic myocardium at risk, severity of coronary disease, and impending LV dysfunction.

It should be noted that levels of both peptides are found to be lower in normals and in those with HF among the obese. This may be related to enhanced clearance of the peptides. Malavazos and colleagues have described a relationship between epicardial fat and increased levels of NT-proBNP that suggest either myocardial triglyceride content or the paracrine effect of adipokines may be related to increased wall tension, left ventricular hypertrophy, and production of natriuretic peptides [143]. Clearly more research is needed in this area.

Finally, the use of natriuretic peptides can be seen as a major advance in the diagnosis, prognosis, screening, and

management of CVD. Future studies that use these markers in treatment pathways to improve outcomes are anticipated.

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