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Q&A

Natriuretic Peptides in Heart Failure

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Heart failure is a major global health problem affecting 23 million people worldwide. As more cardiac patients survive and live longer with this progressive disease, heart failure is a condition for which the prevalence will grow. Based solely on clinical presentation, heart failure can be difficult to diagnose since its presentation is complex, with signs and symptoms that are nonspecific and may not always be present. B-type natriuretic peptide (BNP)[7] and N-terminal proBNP (NT-proBNP) are well established, clinically validated biomarkers that have been shown to improve the diagnostic accuracy for heart failure and provide prognostic information for risk stratification. The widespread clinical use of these biomarkers for more than a decade is reflected by their incorporation into national and international medical guidelines for heart failure, at the highest classification for recommendation.

BNP is a cardiac hormone secreted by cardiomyocytes into the circulation in response to states of volume expansion and pressure overload, as is the case in heart failure. BNP's diuretic, natriuretic, and vasodilatory actions, and its protective effects on endothelial function and vascular remodeling, act to relieve the adverse consequences of heart failure. During the synthesis and processing of BNP, its 108 amino acid biologically inactive precursor, proBNP, is proteolytically cleaved to form the 32 amino acid peptide BNP and the 76 amino acid peptide NT-proBNP. While BNP is physiologically active, NT-proBNP is biologically inert. Due to its secretion at a 1:1 ratio to BNP and its longer half-life (90–120 min vs 20 min for BNP), the measurement of NT-proBNP has proven to have an essentially equivalent clinical performance to BNP as a biomarker for heart failure.

In recent years, the simplistic model for the processing of BNPs has undergone a dramatic shift, with a better understanding of the complexity of their post-translational modification and secretion. ProBNP is now known to undergo *O*-linked glycosylation at multiple amino acid residues within its N-terminal and central portions to give rise to glycosylated forms of NT-proBNP. In addition, proBNP itself has been shown to be present in the circulation of healthy individuals and to increase considerably in heart failure patients. Furthermore, once in circulation, BNP, NT-proBNP, and proBNP are subject to proteolytic cleavage at both their N- and C-terminal ends, giving rise to yet more molecular forms of these peptides.

In this Q&A, 4 experts discuss the clinical utility of BNP testing for the diagnosis, prognosis, and guided therapy of heart failure, and the implications of the multiplicity of molecular forms of BNP, NT-proBNP, and proBNP on the measurement of these peptides and on the pathophysiology of heart failure.

How are BNPs used in the clinical diagnosis of heart failure? In what clinical circumstances do

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[7] Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; ACC/AHA, American College of Cardiology/American Heart Association; GUIDE IT, Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment study; STOP-HF, Screening to Prevent Heart Failure study; PONTIAC, NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease study; PROTECT, Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy study.

BNP and NT-proBNP provide the greatest diagnostic utility?

James L. Januzzi, Jr.: The heaviest use of the natriuretic peptides has been in the context of acutely decompensated heart failure. The tests are often used to evaluate dyspnea to correctly identify or exclude the diagnosis of decompensated heart failure as the cause of shortness of breath. They are also useful in this setting to establish the severity of heart failure, based on their concentrations, which are also very important from a prognostic setting.

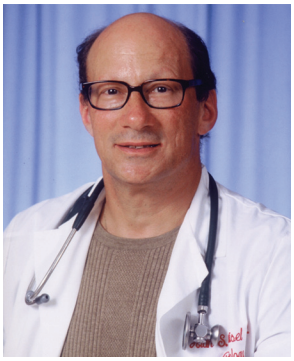
These uses have all been shown in prospective trials to be of substantial value to the clinician. In studies where patients were randomized to routine BNP or NT-proBNP measurement vs blinded BNP or NT-proBNP measurement, those patients evaluated with the biomarkers had more secure diagnosis, shorter hospital lengths of stay, and less money spent on their care. This informs the current support in the recent American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines for heart failure, where BNP and NT-proBNP received a class I, level of evidence A for diagnosis and prognosis in acute heart failure.

Clearly, a role for both peptides also exists in chronic heart failure. They retain similar value for the diagnosis or exclusion of heart failure as well as prognosis. Additionally, there has been an emerging interest in using both BNP and NT-proBNP to monitor the progress of heart failure therapy, and even use them as targets for therapy.

The basis for using BNP or NT-proBNP in the management/therapy of patients with heart failure is predicated on the observation that their values frequently change in response to heart failure decompensation and recompensation (rising and then falling), and therapies used to treat heart failure typically lead to parallel reductions in BNP or NT-proBNP as the patient improves. The more reduction in BNP or NT-proBNP after a therapy change, the better the prognosis.

Indeed, in the hospital, it has been shown that robust reduction in either BNP or NT-proBNP in the course of acute heart failure treatment is associated with superior outcomes compared to a less significant (for example $<30\%$) drop in the peptides. Those patients with inadequate reduction have higher rehospitalization and death rates, and therefore many clinicians have started using a robust reduction in BNP or NT-proBNP as a criterion for safe hospital discharge.

In the physician's office, there has been a major focus on the use of BNP or NT-proBNP to "guide" the care of patients with heart failure. In this regard, both peptides have been studied as an addition to standard clinical judgment for the care of patients with ambulatory heart failure. In these studies, therapies were adjusted to achieve clinical goals, but also to reduce the natriuretic peptide below a target value. In trials where low targets were selected and met, biomarker guidance was typically superior to clinical judgment alone. Pivotal studies are currently examining this approach.



Alan Maisel: Natriuretic peptides should be used in all patients with dyspnea. These peptides have excellent sensitivity and specificity, depending on the cut points one uses. Natriuretic peptides are not used by themselves but as adjuncts to history, physical exam, and other laboratory tests. Of course, the greatest utility would be in those patients for whom the doctor is unable to come to a conclusion as to whether or not heart failure is present.

Allan S. Jaffe: It is clear that the greatest diagnostic utility for natriuretic peptides occurs in individuals in whom there is ambivalence about the diagnosis of heart failure. One of the issues in the field, however, is that different physician groups may have different degrees of expertise, and so natriuretic peptide measurement may be more helpful for those without vast experience in heart failure and be less important for those who are more familiar with this patient group. Thus, I would argue that the use of natriuretic peptides in the emergency room or in general internist offices may be different than for cardiologists and, beyond that, heart failure specialists, at least for this indication.

Aldo Clerico: According to all of the most recent guidelines, the greatest diagnostic utility provided by the measurement of B-type natriuretic peptides is high accuracy in ruling out the diagnosis of heart failure in a patient presenting with dyspnea. The measurement of BNP or NT-proBNP usually shows a very high clinical sensitivity and negative predictive value (both >90%). However, to achieve the maximum clinical sensitivity (and therefore the best ability to correctly exclude heart failure), the cutoff value should be corrected for sex, age, and body mass index. Furthermore, although some international guidelines (i.e., those of the National Institute for Health and Clinical Excellence and the European Cardiology Society) suggest the use of a single cutoff value for all BNP immunoassays, recent studies have demonstrated that some BNP methods provide values that are about half of the others, suggesting that the cutoff values are method dependent. BNPs are not very useful for ruling-in heart failure due to their relatively low specificity and positive predictive value. In fact, the circulating concentrations of BNP and NT-proBNP may also be increased in several physiological (i.e., pregnancy and high-intensity physical exercise) and pathologic conditions (i.e., renal, liver, metabolic, endocrinological, neoplastic, and inflammatory diseases) and in response to some pharmacological agents (i.e., glucocorticoids, female sex steroid hormones, antineoplastics, and β-adrenergic agonists), drug abuse (i.e., amphetamine and alcohol), or poisoning (especially by carbon monoxide).

While clinical studies have demonstrated that BNP and NT-proBNP have relatively equivalent performances as biomarkers for heart failure, are there instances where one of these biomarkers would be preferred over the other?

James L. Januzzi, Jr.: Honestly, I do not envision the differences to be significant enough to mandate that one be preferred over the other. Studies have shown substantial equivalence in most groups, and even in groups where the performance of the peptides is hampered there is relatively equal influence on BNP or NT-proBNP. Where there are relatively few data in terms of comparative value, however, is in the guidance of outpatient heart failure care. In this setting, few studies have been done with BNP, so a clear need is present in this regard. Fortunately, studies are planned that should hopefully address this issue.

Allan S. Jaffe: I cannot think of a situation where there are large differences in clinical performance, with the possible exception of amyloid heart disease, for which I am unaware of the data with BNP but would suspect it would work just as well as NT-proBNP. However, because the concentrations of NT-proBNP can be so high at times, especially in patients with end-stage renal disease, clinicians are unsure of how to interpret the values; with time, I think, this is something clinicians learn to cope with. The only other relevant difference that can be important is that BNP is more prone to degradation if samples are not processed expeditiously or when they are stored.

Aldo Clerico: BNP is the active hormone while NT-proBNP is an inactive peptide that shows better analytical characteristics than BNP. These include lower in vivo and in vitro degradation, higher circulating concentrations, lower biological variability, and the ability to measure in specimens collected with various tube types (EDTA or heparinized plasma and serum). From a theoretical point of view, the measurement of BNP should be preferred in all physiological or pathophysiological studies when the goal is the assessment of the "true" degree of activation of the cardiac endocrine system. Unfortunately, all of the commercially available BNP immunoassays are markedly interfered with by some inactive B-type related peptide, particularly the precursor proBNP, which is probably the predominant circulating form of B-type natriuretic peptide in patients with heart failure. These interferences may greatly affect the analytical specificity of immunoassays for active peptide BNP. For these reasons, BNP and NT-proBNP usually show very similar results in patients with heart failure when assayed with commercially available methods, which are subject to interference by the precursor proBNP.

The prognostic values of BNP and NT-proBNP have been well demonstrated. How best can the prognostic information provided by measurement of BNPs be used? Do you feel that the prognostic information provided by BNP and NT-proBNP has been underutilized?

James L. Januzzi, Jr.: There is no question that the prognostic information from BNP or NT-proBNP may be the strongest application for either peptide and, in this regard, there is no question that they are underused. Both biomarkers have been unequivocally shown to predict outcome across a wide range of patient types, with incremental value from serial measurement. They

are now the gold standard for biomarker-based prognosis, clinically and in research studies.

Alan Maisel: In the emergency department, patients with high concentrations need to be admitted while those with very low concentrations can be discharged after treatment. At the time of discharge, high natriuretic peptide concentrations predict early readmission. Stable concentrations during outpatient treatment represent good prognosis. Outpatients with high concentrations should be targeted with an increased medical regimen. Yes, this is still an area that is very underutilized.

Allan S. Jaffe: There is no doubt that on a statistical basis highly increased concentrations of natriuretic peptides are associated with adverse outcomes. The issue is what can or should be done about that. From my perspective, the lack of a proven treatment strategy is what has led to the underutilization of natriuretic peptides for risk stratification. From that perspective, having a baseline concentration to refer to is very helpful both to anticipate problems when concentrations are rising and to make sure that, after treatment, concentrations have returned toward baseline. I believe that in the long run the value of using natriuretic peptides to titrate therapies will be proven, but in my view the supporting data at present are not adequately robust.

Aldo Clerico: In my opinion, the prognostic information provided by BNP/NT-proBNP assays is underutilized by clinicians. Several studies indicated that serial measurements in the same patient enable clinicians to more accurately assess the response to treatment and provide more prognostic information than a single measurement. Indeed, patients with acute heart failure who have significantly decreased BNP/NT-proBNP values (>30%) after treatment usually show fewer adverse events and have lower mortality rates. However, serial measurements are not currently performed in patients with heart failure because they incur additional costs and discomfort to patients and require a particular interpretation by clinicians. I hope that future guidelines will give this important point more attention.

The observation that BNP and NT-proBNP concentrations are lowered as a result of treatment for heart failure has led to efforts to guide therapy using these measurements. What are the advantages of BNP- or NT-proBNP–guided therapy and what do you believe needs to be demonstrated before their routine use?

James L. Januzzi, Jr.: Together with the substantial value of BNP and NT-proBNP to prognosticate and their ability to monitor heart failure care, it is natural to assume that BNP and NT-proBNP would be useful to "guide" heart failure care.

The reason that the opportunity exists to add biomarkers to standard clinical care includes the fact that the ability to judge the adequacy of heart failure therapeutics may be challenging, even for the experienced physician. Additionally, there is the strong possibility that BNP or NT-proBNP are direct barometers reflecting the pathophysiology of heart failure, wherein therapies that are adjusted to reduce their values are essentially driving to the core of the abnormal biology present in each patient. Of course, there is resistance in the heart failure community, where the belief is that each patient with heart failure should be treated to the maximal degree with each and every therapy available. The reality is that this goal is rarely met and, as such, patients go undertreated. The use of biomarkers in this setting also provides an objective assessment of risk, so that the highest-risk patients can be identified.

The studies that have addressed BNP- or NT-proBNP–guided care have been generally small and underpowered, although many have suggested substantial benefit from the approach as long as certain provisos are met. A low target must be selected, and this target is crucial. If a patient is treated with a goal BNP or NT-proBNP value that is too high, then the treatment will be inadequate. Those clinicians choosing a lower target value (e.g., BNP of 100 ng/L; NT-proBNP of 1000 ng/L) have been more often successful in reducing cardiovascular events when compared to clinicians who use standard management. Therapies must be adjusted to achieve that goal. Studies with low rates of therapy adjustment to achieve target BNP or NT-proBNP concentrations were not successful, but the strategy went untested! There is no such a thing as a "stable" patient with a markedly increased BNP or NT-proBNP concentration, no matter how clinically stable the patient may appear. The target must be reached: it is important to reduce BNP or NT-proBNP concentration in the course of heart failure treatment or the prognosis of the patient is not improved.

As stated earlier, a multicenter, randomized National Heart, Lung and Blood Institute trial, the Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment study (GUIDE IT), is currently under way to evaluate NT-proBNP–guided care, while studies focusing on BNP are currently planned.

Beyond their use in patients with ESTABLISHED heart failure, the recent St Vincent's Screening to Prevent Heart Failure (STOP-HF) and NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC) studies demonstrated that a BNP- or NT-proBNP– (respectively) driven strategy for "at risk" pa-

tients was superior to clinical judgment for reducing incident heart failure. This exciting finding could have even greater impacts on the care of patients if these markers could be applied in patients even before heart failure has developed.

Alan Maisel: Either marker can be used to guide therapy. Randomized trials must demonstrate reduced admissions and death. Trials should attempt to drive down the natriuretic peptide concentrations to low concentrations. Actions must be taken as a result of these concentrations. Finger-stick home BNP monitoring will also allow the doctor to monitor rising natriuretic peptide concentrations.

Allan S. Jaffe: It is very difficult to discern when patients with heart failure are starting to decompensate or when, after treatment, they have returned to baseline because so much of the evaluation of symptoms is subjective. Thus, objective measures are needed and natriuretic peptides can provide that objective information. I believe the mixed results of the studies reflect less aggressive treatment than is needed to cause major changes in natriuretic peptide values and thus, outcomes. Multiple publications have touted changes that are much less than one might expect from the biological variation data. Our own data suggest that much larger changes are needed to influence outcomes. Such a conclusion is also consistent with the Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) data from Januzzi and colleagues.

Aldo Clerico: In our institution, clinicians have been routinely using the measurement of natriuretic peptides to guide therapy in patients with heart failure since the 1990s. The BNP-guided therapy allows a tailored administration of drugs according to both the activation of endocrine cardiac function as well as electrolyte and fluid balance of patients. Patients who do not respond to standard pharmacological treatment with a substantial decrease of BNP or NT-proBNP concentrations should be clinically reevaluated for possible presence of comorbidities and/or considered for alternative and more aggressive treatments. I think that some well-designed clinical trials are needed to definitively demonstrate the subset of heart failure patients that may benefit (or not) from BNP-guided therapy. Indeed, it is theoretically conceivable that a cardiovascular biomarker assay could be more useful in the early stage of heart failure, when patients are usually responsive to treatment, than in stage D of heart failure, a point at which they are refractory to standard pharmacological treatment and require specialized interventions. Patients who respond to treatment are usually younger (<70 years) and without relevant comorbidities. In addition, when designing such a trial, researchers should consider as an end point the baseline, euvolemic "dry" BNP concentration rather than a fixed concentration, given the high variability of BNP concentrations among stable patients. In some patients, a very good clinical stability is achieved in the presence of relatively increased BNP or NT-proBNP concentrations. In these patients, an aggressive therapy (e.g., diuretics) with the aim of further reducing natriuretic peptide concentrations may have detrimental results.

Recent evidence has shown that the processing and secretion of BNPs is complex. Multiple variably glycosylated and proteolytically cleaved forms of BNP and NT-proBNP as well as intact proBNP are present in the circulation of healthy individuals and heart failure patients. Given that all current immunoassays cross-react with proBNP and that immunoassays for NT-proBNP do not effectively measure glycosylated forms, do you feel there is a need for next generation assays with a greater specificity?

Alan Maisel: Only if the following can be demonstrated: An altered form is more prevalent in acute heart failure. An altered form might better separate heart failure with preserved ejection fraction from heart failure with reduced ejection fraction. An altered form might be used to screen asymptomatic patients for disease.

Allan S. Jaffe: Present assays simply reflect how strongly this compensatory system is being stressed. The results do not provide any information concerning the functional consequences of such stimulation. In the long run, it likely would be valuable to know how much active natriuretic peptide is present and eventually to even know which forms are present. The latter has the potential to allow for targeted approaches to reduce the less active forms and to improve the functional consequences of in vivo stimulation. It may also eventually provide insights into what drugs might be necessary in individual patients to either improve processing of the natriuretic peptides or to replace them.

Aldo Clerico: The NT-proBNP assay by Roche Diagnostics is not affected by glycosylated proBNP, while the commercially available methods for BNP are affected, although at different degrees of cross-reactivity. At present, the pathophysiological relevance of the glycosylated compared to nonglycosylated forms of BNPs is not well understood. Therefore, further studies are needed to better evaluate the physiological and/or clinical role of glycosylated forms of BNPs and to recommend the clinical use of immunoassays specific for glycosylated or nonglycosylated forms of BNPs.

Do you feel there is a clinical value in measuring proBNP as a biomarker for heart failure and how do you think it can be integrated into current measurements for BNP or NT-proBNP?

James L. Januzzi, Jr.: There are conflicting data in this regard. Some individuals have suggested the ratio of proBNP/BNP or proBNP/NT-proBNP to be more informative regarding prognosis than just BNP or NT-proBNP alone. That said, most studies do not indicate that there is a clear need, and given the huge amount of data existing that support BNP or NT-proBNP alone, it is hard to envision a change in direction at this point.

Alan Maisel: If a ratio of proBNP to one of the others can be shown to reflect acuity of disease, then yes. Unfortunately, with some of the assays there are multiple binding sites of antibodies and much cross-reactivity.

Allan S. Jaffe: In the few studies available, the assay for proBNP seems to provide comparable information to the other natriuretic peptides but the sampling at present is small. However, this assay is a good start on the way to trying to unravel the issues described earlier in regard to the specific forms that are present in any given patient. In our experience doing these separations with mass spectrometry, we could not find a consistent pattern, but we studied only 70 patients. One analysis has suggested that the ratio of proBNP and BNP may contain important prognostic information. However, in our data sets, such an approach has not been revealing.

Aldo Clerico: There is a need for next generation assays with greater specificity for both the active peptide BNP and the precursor proBNP. From an analytical point of view, proBNP has some theoretical advantages as a biomarker (i.e., more stable molecule, higher molecular weight, lower biological variability) compared to the active hormone BNP. As a future perspective, the simultaneous measurement in the same plasma sample with 2 methods, one specific for the intact precursor proBNP and the other for the active peptide BNP, could allow a more accurate estimation of both production/secretion of B-type related peptides from cardiomyocytes and overall activity of the cardiac endocrine function compared to the single measurement of either peptide. Information obtained by contemporaneous measurement of proBNP and BNP with specific assays should likely extend our present understanding of pathophysiological mechanisms linking disease progression and cardiac endocrine dysfunction. A recent study in ambulatory patients with chronic systolic heart failure showed that the combined assessment of conventional BNP and proBNP immunoassays provides additional information in determining the risk of adverse clinical outcomes, particularly in patients with low BNP concentrations. However, clinical studies will be necessary to determine and compare the diagnostic and prognostic accuracy of specific assays for the different B-type related peptides, BNP, NT-proBNP, and intact proBNP, when used alone or in combination.

It has been suggested that the increased release of biologically inactive proBNP in heart failure may reflect impaired processing of BNPs. Are there possible implications for the failing endocrine function of the heart on the pathophysiology of heart failure?

James L. Januzzi, Jr.: Yes, indeed. In contrast to my ambivalence about the potential role of proBNP as a diagnostic or prognostic tool, there may be value informed by its measurement regarding the actual biology of heart failure. proBNP is released in very small amounts in healthy individuals, and its production starts to rise only as heart failure progresses. In this regard, the loss of biologically active BNP comes at a time when the heart can least sustain such a loss. Thus, understanding why proBNP cleavage is lost would be a large advance, as would be developing strategies to augment its cleavage, with an effort to clinically favor patients with very advanced heart failure.

Alan Maisel: There are definite implications for heart–endocrine interactions in the pathophysiology of heart failure. We just don't yet know if inactive proBNP in heart failure may reflect impaired processing of BNPs, and if so, what the clinical implications might be. NT-proBNP is the inactive moiety that is already measured in practice.

Allan S. Jaffe: There certainly is evidence to suggest that heart failure is characterized by dysfunction of the natriuretic peptide system. Whether it is primary or secondary is not clear as yet but we do know it occurs. However, measurement of the circulating convertases like corin has not been terribly illuminating to date.

Aldo Clerico: A blunted natriuretic response after pharmacological doses of cardiac natriuretic hormones has been observed in experimental models and in patients with chronic heart failure, suggesting a resistance to the biological effects of these cardiac hormones. Resistance to the biological action of cardiac natriuretic peptides can be attributed to different mechanisms, acting at prereceptor, receptor, and postreceptor levels. Considering the possible causes of resistance at the prereceptor level, recent findings suggest that, in patients with heart failure, there may be insufficient posttranslational maturation of biosynthetic precursors of the

BNP system. The soluble form of corin, a transmembrane serine protease able to cleave proBNP, is also capable of processing the circulating intact precursor of natriuretic hormones, indicating that the precursor proBNP may be a circulating prohormone. The peripheral processing of circulating proBNP could likely be submitted to regulatory rules, which might be impaired in patients with heart failure, opening new perspectives in the treatment of heart failure. Related to this hypothesis, some studies using quantitative mass spectral analysis reported very low circulating concentrations (or even the absence) of the active peptide BNP in patients with severe heart failure. Therefore, a novel pharmacological target may be enzymes (such as corin) that regulate the maturation of the prohormone proBNP into the active hormone (i.e., BNP).

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