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Review on the Correlation between Natriuretic Peptide Levels and Heart Failure

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Abstract
Many studies have evaluated the diagnostic characteristics of BNP and NT-proBNP. Study populations have included patients with acute decompensated HF who present to the emergency room or patients with symptoms and signs of HF who are evaluated by primary care physicians. These studies have examined the performance of BNP and NT- proBNP in patients with various comorbidities and at different cut points. However, questions about issues such as optimal cut points still persist regarding the diagnostic capability of BNP and NT-proBNP. Consequently, a systematic review is needed to better understand the diagnostic capability of BNP and NT-proBNP.Clinically, HF is a syndrome with typical symptoms (e.g., breathlessness and fatigue) and signs (e.g., elevated jugular venous pressure and pulmonary crackles). Patients with HF may have either reduced or preserved left ventricular ejection fraction (LVEF). The diagnosis of HF can be difficult since the clinical features of the condition are not always sensitive or specific. No gold standard investigation exists to diagnose HF. The use of BNP or NT-proBNP in the diagnosis, prognosis, or treatment for HF requires knowledge of the variation in peptide levels over serial measurements. Currently, the evidence is uncertain concerning how much of a difference in BNP or NT-proBNP concentration is clinically important.

Key Words: *BNP, Heart Failure, Prognosis*

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The challenge of diagnosing HF emphasizes the importance of evaluating whether other investigations may help diagnose the condition. Furthermore, the characteristics of these other investigations should be examined for their prognostic utility and their usefulness in guiding HF therapy. The natriuretic peptides, i.e., B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), may be useful to help with diagnosis, prognosis, and management of HF. BNP and NTproBNP are secreted into the blood- stream by cardiac myocytes in response to increased ventricular wall stress, hypertrophy, and volume overload. BNP and NT-proBNP levels are increased in persons with HF, and low levels rule out HF. Thus, these peptides have emerged as promising markers for HF[1].

Assessment of prognosis is important to promote better counseling of HF patients with regard to future therapies, including cardiac transplantation. Research suggests that BNP and NT-proBNP may provide incremental prognostic information beyond what is available from the clinical data such as New York Heart Association (NYHA) class, LVEF, and comorbidities[2]. A systematic review is required to better understand whether BNP and NT-proB- NP provide prognostic information for patients with acute decompensated HF and chronic stable HF.

The management of HF is essentially directed by an algorithm for medical therapy. Many times, patients are not fully optimized on therapy because clinicians believe, based on the clinical findings, that further optimization is unnecessary. This could result in under treatment for HF patients. Since BNP and NT-proBNP concentrations have been found to decrease with the escalation of therapy, sequential measurement of these markers may be a useful means of guiding HF treatment. To date, individual studies have not definitively demonstrated whether BNP or NT- proBNP test values can guide HF therapy. A systematic review of this issue would provide information to assess strategies to better optimize the management of HF patients.

The use of BNP or NT-proBNP in the diagnosis, prognosis, or treatment for HF requires knowledge of the variation in peptide levels over serial measurements. Currently, the evidence is uncertain concerning how much of a difference in BNP or NT-proBNP concentration is clinically important.

Given the many outstanding issues involved in using BNP and NT-proBNP for diagnosing, prognosticating, and treating HF, the following questions are to be addressed[3]:

• Question 1: In patients presenting to the emergency department or urgent care facilities with signs or symptoms suggestive of heart failure (HF):

- What is the test performance of BNP and NT- proBNP for HF?
- What are the optimal decision cutpoints for BNP and NT-proBNP to diagnose and exclude HF?
- What determinants affect the test performance of BNP and NT-proBNP (e.g., age, gender, and comorbidity)?

• Question 2: In patients presenting to a primary care physician with risk factors, signs, or symptoms suggestive of HF:

- What is the test performance of BNP and NT- proBNP for HF?
- What are the optimal decision cutpoints for BNP and NT-proBNP to diagnose and exclude HF?
- What determinants affect the test performance of BNP and NT-proBNP (e.g., age, gender, and comorbidity)?

•Question 3: In HF populations, is BNP or NT- proBNP measured at admission, discharge, or change between admission and discharge, an independent predictor of morbidity and mortality outcomes?
•Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge, add incremental predictive information to established risk factors for morbidity and mortality outcomes?
• Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?
•Question 6: In patients with HF, does BNP- assisted therapy or intensified therapy compared to usual care, improve outcomes?

For persons presenting to emergency departments or urgent care settings with signs and symptoms of HF, BNP and NT-proBNP have good diagnostic performance to rule out, but lesser performance to rule in, HF compared to the reference standard of global assessment using patients' medical records. Comorbidities, including age, renal function, and BMI [(BMI) body mass index for BNP only], have important effects on the performance of the tests. The studies do not agree on appropriate cutpoints.

Both BNP and NT-proBNP have good diagnostic performance in primary care settings to identify persons who are at risk of developing HF, or who have few symptoms and less severe signs of HF. Using manufacturers' suggested cutpoints, BNP can effectively rule out the presence of HF in primary care settings. In the case of NT-proBNP, limited evidence is available to determine whether manu- facturers' suggested cutpoints are effective[4].

The published literature shows that BNP and NT- proBNP are associated with all-cause mortality and com- posite outcomes in both decompensated and chronic stable HF populations. Other mortality outcomes (e.g., cardiac and sudden cardiac) demonstrated less convincing associations in chronic stable populations, and were less often evaluated in decompensated populations. In six studies of patients undergoing resynchronization therapy, BNP and NT-proBNP were shown to be independent predictors of all-cause and cardiovascular mortality and morbidity.

In persons with decompensated HF, the literature search yielded limited yet consistent evidence that BNP and NT- proBNP added incremental value to other prognostic factors when predicting all-cause and cardiovascular mortality in the short (3 and 6 months) and longer terms (22 months to 6.8 years); the included studies did not evaluate morbidity or composite outcomes[5]. No included studies assessed the incremental value of BNP in populations with chronic stable HF. NT-proBNP added incremental value to predicting all-cause mortality, cardiovascular mortality, and composite outcomes at 1- to 3 year intervals in chronic stable HF populations.

Studies involving the general population reported associations between NT-proBNP and morbidity (i.e., onset of HF or atrial fibrillation) and mortality (i.e., all cause, cardiovascular, and sudden cardiac). No included studies examined BNP in the general population[6].

Nine studies assessed the benefits of BNP- or NT-proB- NP-guided therapy over usual care. Outcomes included all- cause mortality, hospitalizations, clinic visits, days alive, and quality of life. Results were equivocal, with some studies showing benefits and others showing no benefits. All-cause mortality, evaluated in seven studies, was lower in the groups receiving guided therapy; however, the results in only two of the seven studies were statistically significant[7].

Across all of the different topics in series of research papers, no evidence was found to suggest that BNP should be favored over NT-proBNP, or vice versa. It is also noted that no studies looked at the incremental value of BNP in populations with chronic stable HF and no studies examined the ability of BNP to serve as an independent predictor of morbidity and mortality in general populations. Age tended to show positive associations with the concentrations of both peptides, while BMI and renal function showed negative associations. No statistically significant associations were apparent for sex and ethnicity. However, only a limited number of studies examined the potential confounding effects of these and other covariates. Future

studies should be expressly designed and adequately powered to investigate the effects of age, sex, ethnicity, BMI, renal function, and comorbidities on BNP and NT- proBNP cutpoints. Researchers should agree on a standard set of covariates to be evaluated in future work, especially in nonrandomized studies, which form the bulk of published reports in this area[8].

Often authors selected arbitrary cutpoints based on information from their own datasets (e.g., they established cutpoints using the median or mean peptide concentration values in their samples). Although values above the cutpoints indicated a greater likelihood of HF diagnosis, or poorer prognosis, the totality of evidence did not suggest an optimal cutpoint or BNP or NT-proBNP. Risk of bias was generally low in the included studies[9]. The most problematic areas of bias concerned the studies' failure to consider all of the confounders that we pre-specified as important (i.e., age, BMI, and renal function), as well as the studies' reliance on the use of composite outcomes.

Although follow-up intervals were not part of the criteria that we used to assess the risk of bias, many of the included studies did not justify their selection of follow-up intervals. We recommend future studies establish clinically meaningful follow-up intervals. Furthermore, the included studies utilized a wide assortment of outcomes that diminished our ability to make generalizable inferences across articles. Researchers should standardize outcome assessment by specifying a set of mandatory outcomes to evaluate in future studies of BNP and NT- proBNP. Standardization should include uniform definitions and measures of these outcomes.

The assessment of strength of evidence suggests that future studies will be unlikely to change our findings with respect to the sensitivity of using BNP or NT-proBNP tests to diagnose HF in emergency room or primary care set- tings. However, further research may change the review's findings with regard to the specificity of this testing. For BNP- or NT-proBNP-assisted therapy, the strength of evidence is low and future research may well change the findings of this review.

Although no assessment was made on the strength of evidence for the prognosis key questions, the findings consistently show that both peptides have prognostic ability. The literature lacks practical guidance on how to employ BNP or NT- proBNP for prognostic purposes; the development of clinical protocols is required in this area.

In a nutshell, BNP and NT-proBNP are useful diagnostic clinical tools to exclude HF. They also have a strong association with prognosis in persons with HF, but the clinical utility of any potential prognostic ability has not yet been established. Further work is required to set cut- points and develop protocols for the use of these peptides in standard clinical practice settings. Additional research is required to establish the utility of BNP- or NT-proBNP- guided treatment in HF. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are promising markers for heart failure diagnosis, prognosis, and treatment. A total of 72 studies showed a relationship between B-type natriuretic peptides and a determinant[10]. These determinants have the potential to affect accurate diagnosis, prognosis and the ability to monitor treatment effectively. For demographic determinants, age was the most frequently reported determinant and in 13 of 15 studies was positively correlated with both BNP and NT-proBNP. Few functional measures were evaluated. Of these weight, but not BMI, showed a negative relationship with B-type natriuretic peptides and these two studies had no, or very few, patients who were obese.

In general, evidence available on 21 cardiac diseases was associated with an increase in the B-type natriuretic peptides. However, there were differences among diseases within the broad category of cardiac ischemia. The evidence available on 11 non-cardiac diseases and B-type natriuretic peptide levels was mixed; the non-cardiac causes of dyspnea, diabetic nephropathy, and stroke were all associated with higher levels of B-type natriuretic peptides. There were 29 biochemical and hematological markers where an association with the B-type natriuretic peptides was made. Markers of myocardial damage, including Tn-I,Tn- T,myoglobin, and CK-MB, were mostly positively associated with B-type natriuretic peptide levels. There were 23 measures from 14 studies reported for heart function[11]. Most of the hemodynamic, electrocardiographic and echocardiographic measures were compared to BNP and a few were compared to NT-proBNP. Both positive and negative associations were found. There were 14 studies, including nine different drug treatments, with data on the effect of drug therapy. All showed a decrease in, or no effect on, B-type natriuretic peptide levels.

There were a total of 27 studies eligible for evaluation of the clinical performance of BNP and NT-proBNP and not all of these reported performance characteristics or were suitable for meta- analysis. The 12 studies evaluating BNP utilized several cut point values ranging from 50 to 400 pg/mL and reported sensitivities from 60 to 100 percent, specificities from 27 to 99 percent, and areas under the curve (AUC) of 0.67 to 0.99. The three studies evaluating NT-proBNP utilized values ranging from 254 to 4567 pg/mL and reported sensitivities from 74 to 98 percent, specificities from 47 to 93 percent, and AUC values of 0.89 to 0.96.

There were a total of six studies eligible for review in specialized clinics, though diagnostic performance data could be abstracted in only three. All studies evaluated BNP except two which compared both BNP and NT-proBNP. These two studies evaluated BNP using the same method, had similar cut points (135 and 142 pg/mL) and gave similar sensitivities (72 and 73 percent), specificities (73 and 77 percent), AUC (0.79 and

0.83), respectively.Although different methods and cut points were used for NT-proBNP measurement, the diagnostic performance data were similar to each other and to the BNP data. The cut points were 695 and 4127 pg/mL, with corresponding sensitivities of 85 and 70 percent, specificities of 73 and 77 percent, AUC of 0.82 and 0.79. There were no studies with patients with symptoms suggestive of HF or with known HF presenting in long term care settings. From the all settings combined, 15 studies had sufficient data for meta-analysis. The cut points across all settings ranged from 10 to 200 pg/mL (mean = 95 pg/mL) for BNP and 125 to 1691 pg/mL (mean = 642 pg/mL) for NT-proBNP. Sensitivities for BNP and NT-proBNP ranged from 50 to 99 percent and 83 to 99 percent, respectively. Specificities for BNP and NT- proBNP ranged from 19 to 97 percent and 46 to 89 percent, respectively. There were 108 studies eligible for evaluating the ability of BNP or NT-proBNP levels to predict cardiac events. Both B-type natriuretic peptides were found to be independent predictors of mortality and other cardiac composite endpoints in patients, but few evaluated NT-proBNP and even fewer evaluated both. Thus there is limited evidence to suggest that either of these B- type natriuretic peptides is a better prognostic marker of mortality or cardiac events than the other[12].The prognostic value of BNP or NT-proBNP for mortality and cardiac events was examined in 12 studies of individuals with risk factors for CAD. These studies differed in terms of the age and gender of their participants, methods of diagnosing risk factors for CAD, lengths of follow up, and outcomes. Multiple regression analyses consistently showed that the level of BNP or NT-proBNP was positively associated with the outcome. The 38 studies evaluating CAD patients varied with respect to the age and gender of participants, sample size, length of follow up, and outcomes. However, consistent positive associations were found between the level of BNP or NT-proBNP and the outcome of interest. For BNP the range of risk estimate is 2.00 to 3.00 and for NT-proBNP it is 1.50 to 3.00. For both these B-type natriuretic peptides, the small number of studies prevents any differential prediction in persons with or without prior cardiac related surgery. A number of these studies demonstrated a relationship between the change in BNP or NT- proBNP and either mortality, morbidity or other clinical parameters. Although promising, the findings have not been uniform and the majority of studies were of poor methodological quality; overall this suggests limited evidence that BNP or NT-proBNP may be useful to monitor therapy in HF patients. Numerous factors have been found to be associated with the levels of B-type natriuretic peptides[13]. However, the value of these associations for clinical use is not clear and future research should explore these associations, particularly as a function of HF severity.In all settings (ED, specialized clinics, and primary care) both BNP and NT-proBNP have high sensitivity and lower specificity. This would suggest that these measurements could serve as a test for ruling out cardiac dysfunction. Measurement of B-type natriuretic peptide levels adds independent information relative to traditional diagnostic measures for this condition. Large multicentre trials (especially in ED with complex clinical patients) that allow for multivariate analyses to evaluate variables that contribute to low specificity should be undertaken in the future[14].

BNP and NT-proBNP have been shown to be independent predictors of mortality and other cardiac composite endpoints for populations with risk of CAD, diagnosed CAD, and diagnosed HF. There were few studies which evaluated B-type natriuretic peptides in populations without known heart failure. All but a single study suggest these are not sufficiently accurate to be an effective screening test for unrecognized left ventricular dysfunction[15]. Future research should explore the relative merits of B-type natriuretic peptides compared to and combined with other markers of cardiac dysfunction to predict future outcomes. There is insufficient evidence to demonstrate that BNP and NT-proBNP levels show change in response to therapies to manage stable chronic HF patient. Future research could include large randomized trials to show whether therapy guided by changes in B-type natriuretic peptides affect outcome.

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