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Testing for BNP and NT-proBNP in the Diagnosis and Prognosis of Heart Failure

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives: The purpose of this systematic review was to evaluate BNP and NT-proBNP to: (a) identify determinants, (b) establish their diagnostic performance in heart failure (HF) patients, (c) determine their predictive ability with respect to mortality and other cardiac endpoints, and (d) determine their value in monitoring HF treatment.

Data Sources: MEDLINE®, EMBASE, CINAHL, Cochrane Central and AMED from 1989 to February 2005 were searched for primary studies.

Review Methods: Standard systematic review methodology, including meta-analysis, was employed. All study designs were included. Eligibility criteria included English-only studies and restricted the number of test methods to maximize generalizability. Outcomes for prognosis were limited to mortality and specific cardiac events. Further specific criteria were developed for each research question.

Results: Determinants: There were 103 determinants identified including age, gender, disease, treatment, as well as biochemical and physiological measures. Few studies reported independent associations and of those that did age, female gender and creatinine levels were positively associated with BNP and NT-proBNP. **Diagnosis**: Pooled sensitivity and specificity values were 94 and 66 percent for BNP and 92 and 65 percent for NT-proBNP; there was minimal difference among settings (emergency, specialized clinics, and primary care). B-type natriuretic peptides also added independent diagnostic information above traditional measures for HF. **Prognosis**: Both BNP and NT-proBNP were found to be independent predictors of mortality and other cardiac composite endpoints in patients with risk of coronary artery disease (CAD) (risk estimate range = 1.10 to 5.40), diagnosed CAD (risk estimate range = 1.50 to 3.00), and diagnosed HF patients (risk estimate range = 2.11 to 9.35). With respect to screening, the AUC values (range = 0.57 to 0.88) suggested poor performance. **Monitoring Treatment**: Studies showed therapy reduced BNP and NT-proBNP, however, relationship to outcome was limited and not consistent.

Conclusions: Determinants: The importance of the identified determinants for clinical use is not clear. **Diagnosis:** In all settings both BNP and NT-proBNP show good diagnostic properties as a rule out test for HF. **Prognosis:** BNP and NT-proBNP are consistent independent predictors of mortality and other cardiac composite endpoints for populations with risk of CAD, diagnosed CAD, and diagnosed HF. There is insufficient evidence to determine the value of B-type natriuretic peptides for screening of HF. **Monitoring Treatment:** There is insufficient evidence to demonstrate that BNP and NT-proBNP levels show change in response to therapies to manage stable chronic HF patients.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/bnp/bnp.pdf**.**

Executive Summary

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are promising markers for heart failure diagnosis, prognosis, and treatment.[1,2] This systematic review addresses these four main questions:

1. What are the determinants of both BNP and NT-proBNP measurement?
2. With respect to the diagnosis of heart failure:
   a. What are the clinical performance characteristics of both BNP and NT-proBNP measurement in patients with symptoms suggestive of heart failure (HF) or with known HF
      i. presenting to the emergency department (ED)
      ii. in a specialized clinic or outpatient setting
      iii. presenting to a primary care setting
      iv. presenting in long term care setting
      v. all settings combined
   b. Does measurement of BNP or NT-proBNP add independent diagnostic information to the traditional diagnostic measures of HF in patients with symptoms suggestive of HF?
3. Do BNP or NT-proBNP levels predict cardiac events in populations:
   a. Specific populations
      i. at risk for coronary artery disease (CAD)
      ii. with diagnosed CAD
      iii. with diagnosed HF
   b. What are the screening characteristics of BNP or NT-proBNP in general asymptomatic populations?
4. Can BNP or NT-proBNP measurement be used to monitor response to therapy?

Methods

Two search strategies were undertaken, one for the main report and a smaller review of reviews for Question 2b. MEDLINE®, EMBASE, CINAHL, Cochrane Central and AMED (Allied and Complementary Medicine) were searched from 1989 to February 2005. Hand searching was not undertaken. For Question 2b, which compared other diagnostic tests relative to BNP and NT-proBNP, a review of reviews was undertaken in MEDLINE® and EMBASE only, from January 2000 to September 2005.

Only English language studies and those that measured BNP in blood by methods predominately available for use in clinical laboratories were eligible. There were no restrictions on study design. Outcomes for prognosis were restricted to mortality and other cardiac events.

Standard systematic review methodology was employed for the screening of studies to meet eligibility criteria and included two reviewers. Further specific criteria were developed for each research question. Both qualitative and quantitative (meta-analysis) summary of the results were undertaken.

Results and Discussion

The search yielded 4338 citations, from which 1733 proceeded to full text screening. After the final eligibility screening, data were abstracted from a total of 144 studies.

What Are the Determinants of Both BNP and NT-proBNP?

A total of 72 studies showed a relationship between B-type natriuretic peptides and a determinant. 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.[3-15] Few functional measures were evaluated. Of these weight,[8] but not BMI,[9,10] showed a negative relationship with B-type natriuretic peptides and these two studies had no,[9] or very few,[10] 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,[16-18] diabetic nephropathy,[15] and stroke[8] 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,[3,19,20] Tn-T,[8,14,16,21-26] myoglobin,[21] and CK-MB,[21,27-29] were mostly positively associated with B-type natriuretic peptide levels. There were 23 measures from 14 studies reported for heart function.[4,8-12,14,15,29-34] 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.[31,35-47] All showed a decrease in, or no effect on, B-type natriuretic peptide levels.

What Are the Clinical Performance Characteristics of Both BNP and NT-proBNP Measurement in Patients with Symptoms Suggestive of HF or with Known HF?

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. We meta-analyzed studies within specific settings and also across all study settings where sufficient data were available to calculate sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-), diagnostic odds ratio (DOR) and summary ROC curves. Since there is no guideline for meta-analyzing studies that present results with single and multiple cut points the lowest cut point was chosen in studies with multiple cut points to maximize sensitivity. Summary estimates for studies within setting and across all settings were calculated.

Presenting to emergency department. Fourteen articles[7,16-18,48-57] were selected for data abstraction. 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. In addition, the LR+ ranged from 0.69 to 70 and the LR- from 0 to 0.44. DOR values ranged from 13 to 1635 and based on the meta-analysis of eight studies the summary estimate was 81 (95 percent CI: 29 to 219).

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. The LR+ ranged from 1.85 to 13.43 and the LR- from 0.03 to 0.29. DOR values ranged from 17 to 291 with a summary estimate of 60 (95 percent CI: 9 to 407).

Most studies of the studies scored high on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) items indicating lack of bias.

Specialized clinic or outpatient setting. There were a total of six studies eligible for review in specialized clinics,[11,58-62] though diagnostic performance data could be abstracted in only three. All studies evaluated BNP except two[58,60] 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), LR+ (2.7 and 3.17) and LR- (0.38 and 0.35), 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, LR+ of 3.19 and 2.59 and LR- of 0.2 and 0.41.

Methodological quality was high on the QUADAS for these studies.

***Primary care setting*.** There were a total of seven papers[34,63-68] from this setting and data could be abstracted from only five. Two studies evaluated BNP with cut points ranging from 10 to 115 pg/mL and reported sensitivities from 66 to 92 percent, specificities from 18 to 88 percent, AUC from 0.70 to 0.88, LR+ from 1.12 to 5.7, and LR- from 0 to 0.27. Meta-analysis gave a summary DOR of 2 (95 percent CI: 1 to 6).

The three studies evaluating NT-proBNP with cut points from 67 to 338 pg/mL and reported sensitivities from 67 to 100 percent, specificities from 18 to 84 percent, AUC from 0.70 to 0.93, LR+ from 1.22 to 5.7, and LR- from 0 to 0.27. Meta-analysis gave a summary DOR 17 (95 percent CI: 9 to 32).

These studies generally rated well on the QUADAS.

Long term care setting. There were no studies with patients with symptoms suggestive of HF or with known HF presenting in long term care settings.

All 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.

We observed significant heterogeneity when the data were meta-analyzed and the sources were subsequently explored. The Moses-Littenberg regression model was not significant indicating that cut point was not a factor in explaining heterogeneity. The meta-analysis indicated the diagnostic parameters remain similar even when results from all settings are combined. The summary estimate of sensitivity was high for both BNP (94 percent; 95 percent CI: 32 to 97) and NT-proBNP (92 percent; 95 percent CI: 87 to 97), whereas the summary

estimate for specificity was low for BNP (66 percent; 95 percent CI: 52 to 79) and NT-proBNP (65 percent; 95 percent CI: 51 to 78). The LR- summary estimates for BNP (0.10; 95 percent CI: 0.05 to 0.22) and NT-proBNP (0.14; 95 percent CI: 0.09 to 0.23) were much better than the summary estimates for LR+ for both BNP (2.92; 95 percent CI: 2.09 to 4.09) and NT-proBNP (2.67; 95 percent CI: 1.98 to 3.59).

The summary ROC curves for BNP and NT-proBNP both tended to curve strongly towards the upper left hand corner, signifying high accuracy. Furthermore, the AUC values were 0.86 for both BNP and NT-proBNP, suggesting that regardless of the clinical setting, the cut point chosen, or the test used, measurement of B-type natriuretic peptides is useful in the diagnosis of HF.

Further analysis of heterogeneity was possible to do in six studies from the ED setting that measured BNP by one method with a cut point of 100 (± 5) pg/mL. Even with this uniformity, specificity remained wide (28 to 94 percent). Given that the inclusion and exclusion criteria were not the same in these studies, and are themselves possible determinants of BNP, this heterogeneity is not unexpected.

Overall, there is not clear evidence to suggest the superiority of either BNP or NT-proBNP when all settings are considered.

Does Measurement of BNP or NT-proBNP Add Independent Diagnostic Information to the Traditional Diagnostic Measures of HF in Patients with Suggestive HF?

We first examined the subset of primary papers from Question 2a that performed multivariate logistic regression analysis to determine whether or not BNP or NT-proBNP measurement provided independent information in the diagnosis of HF. Odds ratios for the B-type natriuretic peptides ranged from 9 to 220 and were generally as high as or higher than, other diagnostic variables. This suggests that measurement of the B-type natriuretic peptide does provide information independent from the traditional diagnostic measures.

Secondly, we examined existing systematic reviews of the diagnosis of HF. These reviews considered many diagnostic tests for HF, both alone and in combination. The DOR ranged from 11 to 569 for BNP and 15 to 230 for NT-proBNP.

These data suggest measurement of the BNP or NT-proBNP are as good as, or better than traditional diagnostic measures for ruling out HF.

Do BNP or NT-proBNP Levels Predict Cardiac Events in Populations at Risk of CAD, with Diagnosed CAD and HF?

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.

At risk of CAD. The prognostic value of BNP or NT-proBNP for mortality and cardiac events was examined in 12 studies[4,9,9,10,15,24,69-74] 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 (adjusted measures of risk 1.10 to 5.40) with the outcome.

With diagnosed CAD. The 38 studies[3,8,13,14,19-22,27-29,33,75-100] 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.

With diagnosed HF. There were 58 studies eligible for evaluating BNP or NT-proBNP levels in predicting cardiac events in HF patients. The majority of the 38 studies[12,23,25,30,32,36,41,48,101-130] found baseline BNP levels to be independent predictors of mortality across various cut points and six studies evaluated both BNP and NT-proBNP tests. The adjusted hazard ratio (HR) showed a 2.5 to a 7.2 fold increase relative to those subjects with lower levels of BNP. Baseline BNP values were independent predictors of composite outcomes with HR estimates from 1.7 to 3.2. Studies comparing baseline and predischarge BNP levels suggest differences in the prediction of mortality. More research is required to establish the relative contribution of these two measurements of BNP. Primarily single studies evaluated the combined use of baseline BNP levels with other markers of cardiac dysfunction (e.g., troponin I and T, or percent VO2 max) as predictors of mortality and composite outcomes. Although the findings may suggest that the combined markers increase the ability to predict future outcomes, more research is needed to establish their relative benefit.

The majority of the 18 NT-proBNP studies[26,35,41,103,112,125,126,128,131-140] found this marker to be a significant independent predictor of death or composite endpoints at various cut points. The adjusted risk estimates varied from 2.17 to 9.35 for mortality outcomes, and 2.11 to 5.96 for cardiac composite outcomes.

What Are the Screening Performance Characteristics of the BNP or NT-proBNP in General Asymptomatic Populations?

A screening test was defined as being used to detect preclinical cardiac dysfunction, systolic or diastolic, in the general population. There were eight studies[5,74,122,141-145] in populations without established or overt disease; two studies had no sensitivity or specificity data.[74,122] BNP generally shows poor screening test characteristics for both the detection of moderate to severe LVSD and of diastolic dysfunction. It is even less accurate for the detection of milder degrees of systolic dysfunction. There was a single NT-proBNP study[145] and it showed the screening highest for those with LVEF > 40, and over 70 years of age.

Can BNP or NT-proBNP Measurement Be Used To Monitor Response to Therapy?

There were 18 studies meeting the eligibility criteria.[31,37-47,110,146-150] The studies included chronic HF patients with at least three B-type natriuretic peptide measurements over time. Only

half these studies reported the change in BNP or NT-proBNP and related the change to other outcomes including cardiac function, exercise capacity, symptoms or clinical events.

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.

Conclusions

Determinants

Numerous factors have been found to be associated with the levels of B-type natriuretic peptides. 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.

Diagnostic Properties for HF

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.

Prognosis

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. 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.

Monitoring Treatment

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.

EVIDENCE REPORT

Chapter 1. Introduction

B-type Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have emerged as promising markers for heart failure (HF) diagnosis, prognosis, and treatment. BNP is produced from heart muscle cells, mainly in the left ventricular myocardium but also in the atrial myocardium, as a pro-hormone and released into the cardiovascular system in response to ventricular dilation and pressure overload. Regulation of BNP is at the level of gene expression; there is no storage of BNP in cardiomyocytes. The pro-hormone ($proBNP_{1-108}$) is split inside the myocyte by the protease furin and secreted as the physiologically active C-terminal fragment BNP_{77-108} (BNP_{1-32} or BNP) and the inactive NT-$proBNP_{1-76}$ fragment. BNP exhibits several physiologic functions including vasodilation, promotion of natriuresis and diuresis, inhibition of the sympathetic nervous system and several hormone systems such as the renin-angiotensin-aldosterone system, as well as inhibitory and beneficial effects on the physiological mechanisms associated with the cardiovascular system.[151] BNP has a half-life of 22 minutes,[152] whereas NT-proBNP has a longer half-life estimated to be 1 to 2 hours.[153] The major clearance mechanisms for BNP are endocytosis through the natriuretic peptide receptor C and by enzymatic degradation by neutral endopeptidase, while for NT-proBNP it is through the reticuloendothelial system and renal clearance. For more information on the biochemistry and physiology of B-type natriuretic peptides the reader is referred to recent reviews on this subject.[154,155] In this report BNP and NT-proBNP will be referred to as the B-type natriuretic peptides unless it is pertinent to refer to one of these specifically.

Heart Failure

Heart failure is a complex clinical syndrome that occurs when there is alteration in the function or structure of the heart that reduces its capability to supply adequate blood flow throughout the body. It is an important clinical problem with significant morbidity, mortality, and socioeconomic impact. Approximately 5 million patients in the United States of America have HF, and a first time diagnosis will occur in over 550,000 patients annually.[156] The prevalence is 1.8 percent but rises to 10 percent after age 75. Heart failure is the leading cause of hospitalization in people over 65 years. The natural history of HF is poor, and within 5 years of diagnosis 60 percent of men and 49 percent of women will die of the disease.

Given that HF is a complex clinical syndrome, diagnosis relies on clinical judgments with respect to generic symptoms reflecting cardiac problems. The clinical symptoms in the early stages of HF are non-specific and although a key symptom is dyspnea, it may be difficult to identify the cause. Similar symptoms are found in the elderly or obese patients with respiratory disease,[157] and syndromes associated with edema and fatigue. Imaging diagnostics such as chest x-rays, echocardiography, radionuclide angiogram (RNA), magnetic resonance imaging (MRI) and computed tomography (CT) are used as objective criteria to diagnosis and monitor patients. Several guidelines for diagnosis and management of HF have been produced including those from the American College of Cardiology/American Heart Association,[156] the Canadian Cardiology Society,[158] the European Society of Cardiology, [159] and the modified Framingham

Clinical Criteria for Heart Failure[160]. Early diagnosis of HF and prompt treatment (e.g., angiotensin-converting enzyme (ACE) inhibitors , diuretics, and beta blockers) leads to a better prognosis and quality of life.[161]

Determinants of B-type Natriuretic Peptides

As B-type natriuretic peptides are involved in several physiological processes their concentrations will be influenced by factors that affect these processes. Increasing age is associated with a decline in cardiac function and endocrine diseases such as hyperthyroidism increase blood pressure. Drugs such as ACE inhibitors that affect the renin-angiotensin-aldosterone system, or that reduce the effects of catecholamines such as beta blockers, as well as those like diuretics that increase fluid loss, will alter the level of B-type natriuretic peptides. These are just a few examples of variables that may be important when interpreting B-type natriuretic peptide levels. Analytical factors such as sample collection procedure, test method, interference and sample stability can also falsely alter concentrations.[155] Given the potential importance of B-type natriuretic peptides there was interest in gathering the evidence on determinants that are associated with changes in B-type natriuretic peptide levels.[162] These determinants have the potential to confound the accurate interpretation related to diagnosis, prognosis and the ability to monitor treatment effectively.[151]

Diagnosis of Heart Failure Using B-type Natriuretic Peptides

Evaluation of the diagnostic properties of the B-type natriuretic peptides are important if they are to be fully understand both in terms of both strengths and weaknesses for use in HF. The quality of any biochemical test is dependent upon the biological properties of the analyte, the test method used, the diagnostic threshold chosen and the skill and knowledge of those interpreting the test result. The characteristics of the population that presents for testing, including the prevalence and severity of the disease, are also important. This is particularly true in situations where the severity of the disease affects the magnitude of the test response, such as in HF. The diagnostic characteristics of a test, including sensitivity, specificity, negative and positive likelihood ratio, are likely to vary by the setting where patients present for care. The acuity of symptoms in patients who are evaluated in an emergency department setting, for instance, are likely to be quite different than those who are seen in primary care settings or in a specialized clinic. Furthermore, when interpreting the results of a diagnostic test, it is important to know whether or not the information obtained is independent from, and of added value to, information obtained by other tests.

Prognostic Utility of B-type Natriuretic Peptides

There are high rates of mortality and acute decomposition events requiring hospitalization in HF patients. This demonstrates the need for a good prognostic indicator so that treatments can be optimized. Identification of patients who may be at higher risk for readmission could result in these patients being treated more aggressively. B-type natriuretic peptides could be used to more quickly identify patients who are at higher risk for developing cardiovascular events. Again, as for HF patients, these at risk patients may benefit from accelerated therapy. It is not clear,

however, whether or not B-type natriuretic peptides measurements provide an added benefit to current methods of assessment of patients who may be at high risk for cardiovascular events.

Several studies have reported that elevated B-type natriuretic peptide levels are inversely related to the prognosis in patients with coronary artery disease (CAD), HF and possibly other subgroups. Higher levels of B-type natriuretic peptides, or levels that do not decrease despite an intervention, suggest a poorer prognosis overall.[163] The ability of the B-type natriuretic peptides tests to function as a prognostic marker for subsequent cardiac events is important to consider. As a prognostic marker B-type natriuretic peptides could have great value in identifying subjects by level of risk for subsequent cardiac events and in identifying those most amenable to interventions for arresting further progression to more serious disease.

The use of B-type natriuretic peptides as a screening test could assist in reducing morbidity associated with subsequent heart dysfunction development. However, its use would also have to take into consideration the efficacy and acceptability of the current therapies for HF, and the degree to which the natural history of the disease is understood.

Treatment Monitoring Using B-type Natriuretic Peptides

Therapeutic strategies range from drugs to invasive and costly methods such as cardioverter-defibrillators and heart transplantation. The pace and type of therapy given is, for the most part, clinically guided. It would be of benefit to have more objective guides to monitor therapy. B-type natriuretic peptides may be helpful in this regard as they have been shown to predict morbidity and mortality in HF patients.

There has been some evidence that suggests the potential usefulness of sequential BNP or NT-proBNP measurements in monitoring patients with HF.[148,149] B-type natriuretic concentrations decrease when patients with HF are treated, and lower BNP concentrations are associated with fewer cardiovascular events. It remains unclear, however, both if monitoring BNP levels can reduce those levels more quickly by prompting the use of more aggressive therapy and, what the target levels should be. It might be possible to improve current drug therapy by tailoring it to the patient if clearer measures of the effect of the therapy were known. Some patients may benefit from dosages higher than the guidelines indicate, or conversely, lower doses may be sufficient in other patients thereby reducing the risk of side effects. Moreover, it is not clear if the utility of the B-type natriuretic peptides measurement varies with the type of intervention used to manage HF. It was therefore of interest to search the literature for information on the utility of sequential BNP or NT-proBNP measurements in monitoring treatment in stable HF patients.

Scope and Purposes of the Systematic Review

This systematic review addresses 4 main questions as follows:

1. What are the determinants of both BNP and NT-proBNP measurement?
2. With respect to the diagnosis of heart failure:
    a. What are the clinical performance characteristics of both BNP and NT-proBNP measurement in patients with symptoms suggestive of heart failure (HF) or with known HF
        i. presenting to the emergency department (ED)
        ii. in a specialized clinic or outpatient setting
        iii. presenting to a primary care setting
        iv. presenting in long term care setting
        v. all settings combined
    b. Does measurement of BNP or NT-proBNP add independent diagnostic information to the traditional diagnostic measures of HF in patients with symptoms suggestive of HF?
3. Do BNP or NT-proBNP levels predict cardiac events in populations:
    a. Specific populations
        i. at risk for coronary artery disease (CAD)
        ii. with diagnosed CAD
        iii. with diagnosed HF
    b. What are the screening characteristics of BNP or NT-proBNP in general asymptomatic populations?
4. Can BNP or NT-proBNP measurement be used to monitor response to therapy?

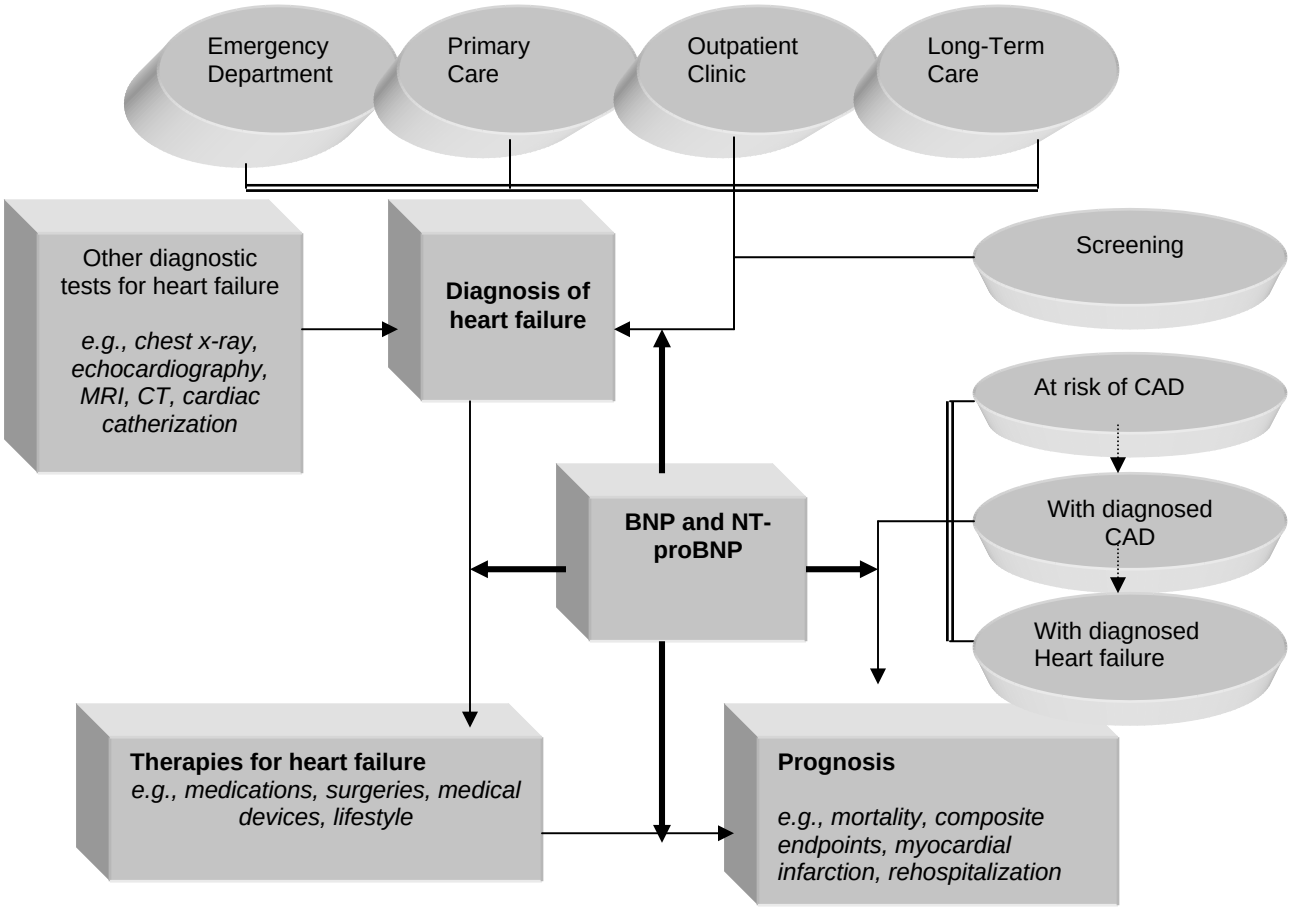
This systematic review will serve to identify both the strength of the evidence and gaps in existing research to facilitate future research priorities.

Chapter 2. Methods

Analytic Framework

An analytic framework is a schematic representation of the strategy for organizing topics for review and guiding literature searches. Figure 1 illustrates the inter-relationship among the questions being asked in this systematic review. The key areas addressed were diagnosis of heart failure (HF) using B-type natriuretic peptide tests, the prognostic value of B-type natriuretic peptide levels, and guiding treatment of HF patients using B-type natriuretic peptide measurements. The B-type natriuretic peptides included BNP and NT-proBNP and in the figure they are illustrated as the central component for the key areas. Four settings were chosen to evaluate the diagnostic ability of B-type natriuretic peptides for HF. They included the emergency department, primary care, outpatient clinics and long term care. Patients with coronary artery disease (CAD) risk factors, diagnosed CAD or HF were chosen to evaluate whether B-type natriuretic peptides levels are useful prognostic indicators. In addition the general population was used to determine whether B-type natriuretic peptides could be used for screening. Monitoring of B-type natriuretic peptides with respect to outcome was used to assess the effect of therapy in patients with HF. Furthermore, determinants that affect B-type natriuretic peptide levels independent of HF were extracted for each of the key areas, but not shown as part of the analytic framework.

Figure 1: Analytic Framework



The methodological chapter has been divided into two sections: (1) General Methods and (2) Question Specific Methods. The first section will describe methods that were general in nature and were applicable to almost all of the research questions in this review. The second section will describe the specific methodological decisions that were relevant to each research question.

General Methods

Refinement of the Topic and the Research Questions

The first step during the topic assessment and refinement process was to organize a teleconference with partner organizations. The Task Order Officer (TOO) invited topic experts and the McMaster multidisciplinary research team to define the magnitude of the topic to be addressed and to refine/clarify the preliminary research questions for this evidence report. An international Technical Expert Panel (TEP) was assembled to provide high-level content expertise on this topic (Appendix E) and to participate in conference calls on an as-needed basis throughout the data refinement and extraction phase.

Search Strategy

Two search strategies were undertaken, one for the main report (Appendix A) and a second one for the review of reviews (Appendix A) for Question 2b. The bibliographic databases searched included MEDLINE®, EMBASE, CINAHL, Cochrane Central and AMED (Allied and Complementary Medicine) from 1989 to February 2005. Hand searching was not undertaken for this systematic review.

For Question 2b, which compared other diagnostic tests relative to BNP and NT-proBNP, a review of reviews was undertaken in MEDLINE® and EMBASE from January 2000 to September 2005. The start date of 2000 was chosen in order to identify only the most recent reviews.

Eligibility Criteria

A list of eligibility criteria was developed in Systematic Review Software (SRS) for the purposes of this systematic review. Details of the eligibility criteria can be found in Appendix B.

Publication

Criteria for publication inclusion. Language: Only English language studies were eligible. The number of non-English studies that were excluded equaled approximately 6 percent of all possible citations (268/4342). Publication Date: 1989 to February 2005. Our search started in 1989, as this was the first year an assay for BNP was reported.

Criteria for publication exclusion. Narrative and systematic reviews (except for Question 2b), editorials, letters, comments, opinions, abstracts and unpublished studies were excluded.

Assay method

Measurement of BNP or NT-proBNP. This systematic review included only those studies that measured BNP by methods that were available commercially for diagnostic use in a clinical setting up to February 2005 (Table 1). However, for NT-proBNP methods, three methods were included that were not commercially available for use in clinical settings for the purposes of diagnosis (see Table 2). One of these methods was the early generation assay to the Roche NT-proBNP method (ELISA method). The other two methods (Biomedica and Christchurch) were included because of their frequent use and because comparison studies have been done with the Roche NT-proBNP method.[147,164] The purpose of these restrictions was to ensure that results from this systematic review were not unduly affected by the test method used. The goal was to reduce the variability and thus uncertainty in the analysis of our results and for them to be directly applicable for clinical use (since these will be the methods clinical laboratories will use). One limitation with this approach is the possible exclusion of studies with important information not available in any of the included studies. Also, the strength of some findings may be weakened due to a smaller number of studies reporting similar findings but using different test methods. Tables 1 and 2 provide the details of the assays used in this review to measure BNP or NT-proBNP.

Table 1: Details of BNP test characteristics.

Table row #	Company Name	Test / Instrument Name	Date Available
1	Shionogi & Co. Ltd, Osaka, Japan	Shionoira-IRMA	1993
2	Biosite, Inc., San Diego, CA, United States	Triage® B-Type Natriuretic Peptide (BNP)	Nov. 2002
3	Bayer Diagnostics Corporation, Tarrytown, NY, United States	ADVIA Centaur® B-Type Natriuretic Peptide (BNP)	June 2003
4	Beckman Coulter Inc, Fullerton CA, United States	Access	Oct 2003
5	Abbott Laboratories. Abbott Park, IL, United States	Abbott AxSYM ® B-Type Natriuretic Peptide (BNP)	Feb 2004

Table 2: Details of NT-proBNP test characteristics.

Table row #	Company Name / Reference	Test / Instrument Name	Date Available
6	Christchurch, New Zealand referenced to: Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive aminoterminal probrain natriuretic peptide (NT-proBNP): A new marker for cardiac impairment. Clin Endocrinol 1997; 47:287-296	NT-proBNP	1997
7	Roche Diagnostics GmbH, Tutzing, Germany, referenced to: Karl J, Borgya A, Gallusser A, Huber E, Krueger K, Rollinger W, Schenk J. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl. 1999; 230:177-81	NT-proBNP	1999
8	Biomedica, Vienna, Austria	NT-proBNP ELISA	2001[a]
9	Roche Diagnostics Corporation, Indianapolis, IN, United States	Elecsys® NT-proBNP Immunoassay	Nov. 2002
10	Dade Behring, Inc., Newark, DE, United States	Dimension® NT-proBNP (PBNP)	July 2004

a. For research purposes only.

Number of measurements of BNP or NT-proBNP. For Question 4, BNP or NT-proBNP was to be measured at a minimum of 3 time points. This restriction was not applied to any other question in this review.

Population

Criteria for population inclusion. Any population including any subjects aged greater than or equal to 18 years of age.

Criteria for population exclusion. All studies conducted on animals or on human samples other than blood (e.g., urine) or cell cultures were excluded from this review.

Study designs

Criteria for study designs inclusion. All study designs (randomized controlled trials (RCTs), observational, case control, cohort studies) for primary data were included. In addition, systematic reviews were included to address Question 2b.

Data Collection and Reliability of Study Selection

A team of trained research assistants evaluated the title, abstract and full text screening. Standardized forms and a guide explaining the criteria were developed. Two reviewers were required to achieve consensus on the identification, selection, validity and abstraction of articles and information. Disagreements that were not resolved by consensus were settled by one or more members of the local expert team.

Quality Assessment of Included Studies

To assess the quality of primary studies we utilized standardized rating scales with acceptable reliability and validity. The specific scale to be used was dependent on the study design and the research question. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)[165] was selected to evaluate studies chosen for the research question addressing diagnostic accuracy of the BNP or NT-proBNP test. The QUADAS was developed specifically to take into account biases unique to the design of diagnostic studies. Quality items were considered individually rather than as a composite score as recommended by the developers of this tool.[166] The Jadad scale was used for studies that were RCTs.[167] For non-randomized study designs the only two criteria selected for evaluation were consecutive sampling and blinding to the outcome.[168] For quality assessment of systematic reviews, the Screening and Test Evaluation Program (STEP) checklist was used.[169] Appendix B shows the instruments used to evaluate quality.

Summarizing Our Findings: Descriptive and Analytic Approaches

Both descriptive and quantitative approaches were used to summarize study characteristics and outcomes. Multiple publications on the same study cohort were grouped together and treated as a single study for statistical analysis. Standardized summary tables explicating important study population and BNP or NT-proBNP test characteristics, as well as study results, were created. Results for BNP and NT-proBNP measurements were reported using the units pg/mL.

Conversions were made to pg/mL, using the factor 1 pmol/L = 3.46 pg/mL for BNP and 1 pmol/L = 8.457 pg/mL for NT-proBNP.

Meta-analysis was only carried out for Question 2a. Meta-analysis for the remaining questions was not considered for several reasons including lack of data, too few studies and significant clinical heterogeneity. Quality scores were not used for weighting data in any of the analyses; rather, the inverse of the variance was used to weight studies.

For each primary study included in Question 2a, we calculated the following measures of test results accuracy: sensitivities, specificities, likelihood ratios (positive LR^+ and negative LR^-) and diagnostic odds ratios (DOR). For those papers where the actual numbers of true and false positive and negative results (TP, FP, TN, FN) were presented, or where enough information was given to allow us to calculate and estimate these numbers, we recalculated the sensitivities, specificities and calculated the LR+, LR- and DOR with the accompanying 95 percent confidence intervals (CI).

These measures were calculated across different cut points and by study setting (emergency, outpatient, primary care and long term care settings) for BNP and NT-proBNP separately. Overall estimates of the diagnostic accuracy of the test were obtained by pooling the sensitivities, specificities and LRs obtained from each primary study. These different analyses were assessed for publication bias (graphical as well as statistical). We used sensitivity analysis to examine the influence of one study at a time and Galbraith plots for assessing heterogeneity across studies.

Our initial analyses considered the level of heterogeneity across the individual studies that were included in the meta-analysis. The Cochrane's Q test was used as a measure of heterogeneity in all the meta-analyses and the I^2 as a measure of inconsistency. We observed some heterogeneity in many of our meta-analyses and as a result, analyses using the random effects models were selected. Subgroup analysis and stratification were carried out to further explore the causes. As a part of these, meta-regression methods were employed to study the effects of a few covariates on the respective diagnostic test measures. Due to the number of studies available, we were only able to carry out univariate meta-regressions in most cases. We also assessed the correlation between sensitivities and specificities. However, no significant correlations were observed. All statistical analyses were carried out using Stata/SE 8.0 for Windows (Stata Corporation) and Meta Package.

Pooled estimates were also calculated for DORs and summary receiver operator characteristic (SROC) curves were created in our analyses to assess the effect of different cut points. A DOR is a simple measure used when combining sensitivities and specificities from different studies. It is easy to calculate and less sensitive to diagnostic thresholds.[170] The DOR makes use of the sensitivity and specificity pair by comparing the odds of one to the other. It compares the odds of positive test results in the trial participants with the outcome of interest, to the odds for positive test results for those without the outcome of interest (Equation 1).

Equation 1: DOR

$$DOR = \frac{sensitivity/(1-sensitivity)}{(1-specificity)/(specificity)}$$

The standard error of the log DOR is approximately given by: $\sqrt{1/TP + 1/FN + 1/TN + 1/FP}$

Where TP is true positive, FP is false positive, TN is true negative and FN is false negative. Appropriate adjustments are made in cases of zero counts.

An alternative formulation of the DOR is given in Equation 2:

Equation 2: Alternative calculation for DOR.

$$\mathbf{DOR} = \frac{\textit{sensitivity}/(1-\textit{specificity})}{(1-\textit{sensitivity})/(\textit{specificity})} = \frac{LR^{+}}{LR^{-}}$$

Where the LRs are the positive and negative likelihood ratios.

Using this definition, a DOR is a measure of the spread between the two LRs. The SROC curve mimics the receiver operator characteristic (ROC) curve and is a way to measure the diagnostic accuracy across different studies. It is based on logit transformation of the data, which plots D, the difference between the logit of the true-positive rates (TPR, sensitivity) and the logit of the false-positive rates (FPR, 1 - specificity) on the *y* axis against their sum S on the *x* axis i.e., D = logit TPR – logit FPR against S = logit TPR + logit FPR. The *y* axis (D) is equivalent to the log (DOR), and the *x* axis (S) is a way to measure how the test characteristics vary with respect to the thresholds of the diagnostic tests. A regression equation (D = α + ß * S) derived from the SROC curve analysis can be used to assess the heterogeneity among study results.[171]. It is possible to get spurious SROC plots based on regression analysis when individual studies have homogeneity in their results since regression analysis with small variations in both the independent and dependent variables can result in misleading results.

Question Specific Methods

Population Criteria for Each Question

Question 1: criteria for population inclusion. All studies that were eligible for Questions 2, 3 and 4 were considered for Question 1. For Question 1, all determinants associated with B-type natriuretic peptides were abstracted except for the well-known relationship to systolic HF or severity of HF, and echocardiographic parameters associated with systolic dysfunction. Both categorical determinants (e.g., gender, disease status, drug therapy) and determinants with continuous scale (e.g., creatinine, weight, left ventricular mass) were included, however, determinants were excluded if the continuous scale was categorized into a categorical variable (i.e., above and below a cut point value). Drug therapy data were included if the therapy was compared to baseline or a placebo group. Data on all determinants that were analyzed using univariate or multivariate regression approaches were abstracted; however, if both analyses were available, the multivariate took primacy in the results. If data were given for multiple time points the admission time was chosen unless otherwise specified in the evidence tables (Evidence Table 1, Appendix C). Although these restrictions decreased the number of abstractable pieces of data, it also reduced the classification error.

Question 2a: criteria for population inclusion. A study was also eligible if it considered one of the following symptoms or signs as a marker for HF: anginal pain, anginal syndrome, ankle swelling, bilateral leg edema, breathlessness, cardiac dysfunction, cardiac insufficiency, cardiomegaly on chest x-ray, diastolic distensibility, diastolic dysfunction, diastolic dysfunction

on cardiac catheterization, diastolic stiffness, dyspnea, ejection fraction (EF), elevated jugular venous pressure, fatigue, fluid retention, hepatomegaly, left ventricular (LV) relaxation, filling, LV systolic function (or dysfunction), nocturnal cough, orthopnea, palpitation, paroxysmal nocturnal dyspnea, peripheral edema, pleural effusion, pulmonary congestion, pulmonary rales, tachycardia (heart rate ≥ 120 beats/min), third heart sound, ventricular dysfunction, weight loss.

Question 2a: criteria for population exclusion. For emergency of primary care settings only, studies were excluded if the population had subjects with known HF, and samples that only included subjects with any of the following: heart transplantation, obesity clinic patients, hypertrophic cardiomyopathy, mitral valve regurgitation patients. Inpatient hospital or community settings were excluded.

Question 2b: criteria for population inclusion. Primary studies with traditional diagnostic tests of HF included the following: chest x-ray, echocardiography, myocardial radionuclide angiogram (MRNA), dobutamine echo, cardiac catheter, magnetic resonance imaging (MRI), computerized tomography (CT), and pulmonary/vascular measures.

Question 3a: criteria for population inclusion. All patients with: i) at risk of CAD; ii) with diagnosed CAD; iii) with diagnosed HF. The citation was required to use at least one of the following terms to indicate HF: i) HF; ii) congestive HF; iii) New York Heart Association (NYHA) criteria, NYHA functional class, American College of Cardiology (ACC), American Heart Association (AHA), Canadian Cardiovascular Society (CCS), Modified Framingham Clinical Criteria for diagnosis of Heart Failure, and European Study Group on Diastolic Heart Failure; iv) cardiac dysfunction.

Question 3a: criteria for population exclusion. Studies were excluded if the population had any of the following health conditions: heart transplant, stenosis, renal disease, pulmonary embolism, cardiomyopathy, tumour, amyloid, leukemia, atrial fibrillation after pacemaker implant, respiratory disease, pulmonary hypertension, ischemic stroke, sepsis, perimyocarditis, intensive care unit patients.

Question 3b: criteria for population inclusion. General populations with no known cardiac dysfunction.

Question 4: criteria for population inclusion. Studies evaluating treatments for HF had to have identified the subjects using one of the following criteria: ACC / AHA, NYHA, CCS, Modified Framingham Clinical Criteria for the Diagnosis of Heart Failure, European Study Group on Diastolic Heart Failure.

Question 4: criteria for population exclusion. Studies were excluded if the patients' HF was not stable.

Intervention for Each Question

Selection of interventions was not relevant for research Questions 1, 2 and 3.

Question 4: criteria for intervention inclusion. Treatments for HF could include any of the following:

- ***Medications***: angiotensin converting enzyme (ACE) inhibitors; angiotensin receptor blocker therapy; beta blockers; cardiac glycosides; diuretics; nitrates; spironolactone

- ***Surgeries, Procedures and Medical Devices***: balloon valvuloplasty catheter; enhanced counterpulsation; heart valve replacement surgery; automatic implantable cardiac defibrillator; cardiac resynchronization therapy; intra-aortic balloon pump insertion; prosthetic heart valve; ventricular assist device; valvuloplasty (balloon or surgical).

- ***Healthy Lifestyles***: Exercise; maintain a healthy weight; eat a healthy diet; control blood pressure; control blood cholesterol; prevent and manage diabetes mellitus; quit smoking; manage stress.

Outcome Criteria for Each Question

Question 2a and 2b outcomes criteria for outcomes inclusion. Any measure of the degree or presence of HF was accepted, including: clinical diagnosis, left ventricular ejection fraction (LVEF), change in NYHA class, left ventricular end-diastolic pressure, left ventricular end-diastolic dimension, left ventricular end-systolic dimension, end-diastolic thicknesses of the inter-ventricular septum.

Question 3a and 3b outcomes criteria for outcomes inclusion. Admission to hospital for any of the following outcomes: angina requiring a minimum 24 hour hospitalization (acute coronary syndrome), angiographic percutaneous coronary interventions (including terms angioplasty, bypass surgery, coronary artery bypass graft, cardiac revascularization, percutaneous transluminal coronary angioplasty, stent), atrial fibrillation (arrhythmias), cerebrovascular event (e.g., stroke), composite endpoint, congestive heart failure (CHF), isolated diastolic ventricular dysfunction, mortality (all cause), myocardial infarction (MI).

Question 4 outcomes. criteria for outcomes inclusion. No a priori outcomes were identified for inclusion.

Criteria for outcomes exclusion. Non-cardiac events

Peer Review Process

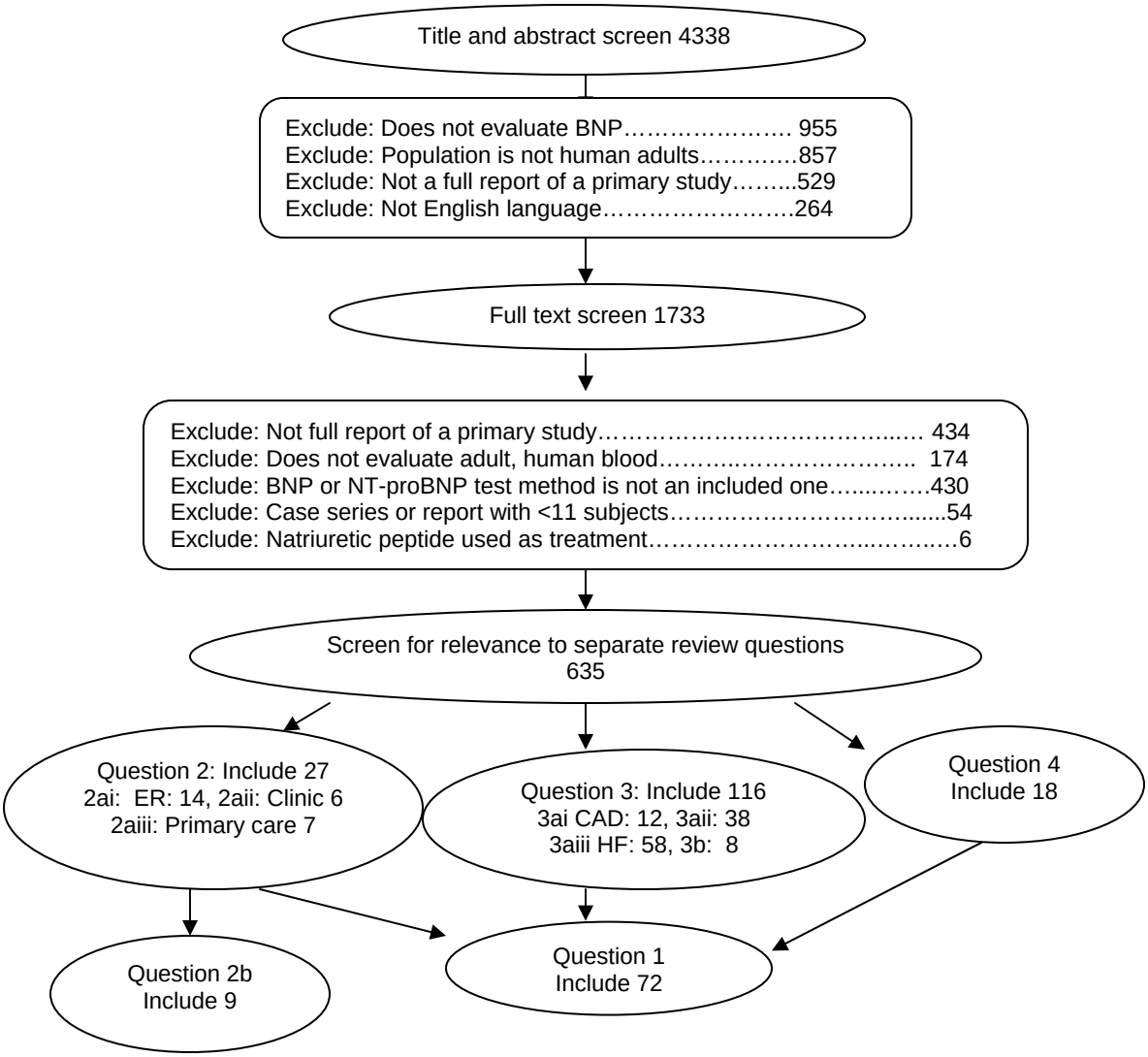
A list of potential peer reviewers was assembled at the outset of the study from a number of sources including our technical expert panel (TEP), our partners, the McMaster research team, and the AHRQ. During the course of the project, additional names were added to this list by the McMaster Center and AHRQ. Thirteen content experts have reviewed this report (see Appendix E) and their comments and suggestions have been incorporated where possible.

Chapter 3. Results

The search yielded 4338 citations in total. From these 1733 citations proceeded to full text screening. Criteria for each specific research question were applied to these 1733 citations that yielded 4 subsets of papers to be further screened: one for each of the research questions (Figure 2). A total of 264 citations (6 percent) were eliminated because of non-English language of publication (6 percent) at the title and abstract phase. The final number of eligible papers varied as a function of the specific research question. A total of 30 studies were eligible for Question 2; the results of the review of reviews for Question 2b are detailed later in the results. For question 3, a total of 150 citations were eligible, and from these 110 are evaluated for this report. Forty of the citations for Question 3 reflected very specialized populations that did not necessarily reflect cardiac dysfunction. Finally for Question 4, a total of 18 studies were abstracted and evaluated.

The results of the systematic review are presented in this chapter according to the four research questions: determinants, diagnostic performance, prognosis and monitoring of treatment.

Figure 2. Flow diagram showing the numbers of articles processed at each level



Question 1: What Are the Determinants of Both BNP and NT-proBNP?

Study Characteristics

There were 144 studies included for all the clinical questions in this systematic review (Appendix C - Reference List of Included Articles). Of these, 72 studies showed a relationship between B-type natriuretic peptides and a biological determinant. In general, most determinants showed a positive association with B-type natriuretic peptides in this review. The determinants were categorized according to type of measurement (i.e., demographic, biochemical or physiological), disease and treatment. The determinant was considered to show a significant effect on B-type natriuretic peptide levels if the p-value was less than 0.05. Table 3 lists the details of the associations found and is presented according to the determinant category, effect (increase, none, and decrease) and test type (BNP and NT-proBNP).

Demographic Characteristics

Age was the most frequently reported determinant and in 13 of 15 studies was positively correlated with both BNP and NT-proBNP.[3-15] There were two studies that did not show a relationship with age,[31,34] but these studies had the smallest number of patients (n = 21 and 36, respectively) as compared to the other studies (range = 85 to 6809). One study reported no difference between African Americans and Caucasians.[49] The association of B-type natriuretic peptides with gender was examined in 11 studies, with an almost equal number reporting either a higher level (n=5), or no difference in males (n = 6). There were no obvious similarities among studies with respect to observed association and patient population. However, larger studies were more likely than smaller studies to report a higher B-type natriuretic peptide level in females compared to males. Two studies looked at current smoking and reported no association.[8,85]

Cardiac Disease

In general, all cardiac diseases (n = 21) were associated with an increase in the B-type natriuretic peptides. These included diastolic dysfunction,[5,11,16,33,34,65] cardiac decompensation,[26] acute right HF,[57] and cardiac pulmonary edema (CPE).[57] Acute right HF without cardiac pulmonary decompensation was not related to BNP concentration. Cardiac decompensation, however, was related to an increase in NT-proBNP. Patients with CPE had higher levels of BNP than patients with obstructive lung disease. Patients with diastolic dysfunction had elevated B-type natriuretic peptide levels but not as elevated as patients with systolic dysfunction.[11,16,172]

There were differences among diseases within the broad category of cardiac ischemia. Patients with acute coronary syndrome (ACS) had elevated NT-proBNP levels,[85] but there was no difference between patients with and without ischemic heart disease unless the patients had cardiovascular risk factors.[4,116] Acute myocardial infarction (MI)[4,8,29] or historical MI[14,85] were associated with increased levels of B-type natriuretic peptides. Stable angina was not associated with a difference in B-type natriuretic peptides in one study[4] that included hypertensive patients, but was positively associated in patients with Non ST-elevation myocardial infarction (NSTEMI) ACS.[57] Patients with left anterior descending (LAD) coronary artery lesions had elevated BNP and those with proximal lesions had higher levels than those with mid-lesions.[95] Multi-vessel

disease was associated with higher NT-proBNP levels.[85] Also NT-proBNP levels were positively associated with patients who had previous revascularization.[8] There was no difference between patients with dilated cardiomyopathy and old MI.[124] Arrhythmia[65] was associated with elevated levels of B-type natriuretic peptides; however, there was no difference between atrial fibrillation and sinus rhythm[115] valvular disease[65] and all severities of aortic stenosis[6] were positively associated with B-type natriuretic peptides levels.

Non-cardiac Diseases

The effect of non-cardiac diseases (n = 11) on B-type natriuretic peptide levels was mixed. Non-cardiac causes of dyspnea,[16-18] diabetic nephropathy,[15] and stroke[8] were all associated with higher levels of B-type natriuretic peptides. Lung disease compared to HF,[56] or HF plus lung disease,[65] had lower BNP and NT-proBNP levels respectively. Diabetic retinopathy[15] and cerebrovascular disease (including stroke and transient ischemic attack)[4,8] did not show association with B-type natriuretic peptide levels. For diabetes, one study showed a positive association with NT-proBNP[8] but in three studies[4,14,85] there was no association. Four of five studies that evaluated hypertension[8,10,34,89] showed a positive association with B-type natriuretic peptides. The one study[85] that did not show a difference used a statistical test for the difference in medians whereas the other studies used mean difference tests or regression analysis. Duration of hypertension was also not associated with BNP levels.[10] There was no difference in NT-proBNP levels between patients with peripheral vascular disease as compared to patients without risk factors for cardiovascular disease (CVD).[4] Two studies reported hyperlipidemia as a determinant. One of these studies showed an inverse relationship with NT-proBNP levels[85] using the Wilcoxon rank sum test, whereas the other study showed no relationship[8] using multiple linear regression analysis.

Biochemical and Hematological Markers

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,[3,19,20] Tn-T,[8,14,16,21-26] myoglobin,[21] and CK-MB,[21,27-29] were mostly positively associated with B-type natriuretic peptide levels. One study did not show a statistically significant correlation with CK-MB.[27] This study included only ST-segment elevation myocardial infarction (STEMI) patients, whereas the other studies excluded STEMI patients, or included MI patients admitted to the coronary care unit. No significant association was found in one study with Tn-I.[20] This study included only NSTEMI and unstable angina patients in contrast to the other studies that included STEMI and ACS patients. Total creatine kinase showed no significant association with BNP but this may be because no patients in this study had elevated levels of this marker.[26] Furthermore, the cardiac hormones ANP,[12,13,25,84] NT-proANP,[13,20,41,74,84,144,144] and second messenger cGMP,[12,84] were positively associated with B-type natriuretic peptide levels. However, relaxin, also a cardiac hormone, showed no association with NT-proBNP.[136] Several markers of inflammation including C-reactive protein,[8,14,21] interleukin-6,[22] the ST2 receptor protein[90] and osteoprotegerin[98] were positively associated with B-type natriuretic peptide levels. The association with lymphocytes was patient group specific.[105] There was no statistically significant association between BNP and lymphocytes observed in the patient group with hypertensive heart disease, mitral stenosis, atrial fibrillation and hypertrophic cardiomyopathy, but a negative association was observed in a group composed of patients with ischemic heart disease, dilated

cardiomyopathy aortic stenosis, aortic regurgitation and mitral regurgitation. There was a mixed association with markers of the renin-angiotensin-aldosterone system (RAAS). Plasma renin activity[106] was inversely associated with BNP, whereas andromedullin[84] and aldosterone[106] showed no significant relationship with NT-proBNP and BNP, respectively. The ACE genotype DD,[81] endothelin-1,[106] big endothelin-1,[41,106] epinephrine[84] and norepinephrine[12,25,39,41,84,106] were all positively associated with the B-type natriuretic peptides. Creatinine, an indirect marker of renal function, increased in five of eight studies with increasing levels of B-type natriuretic peptides.[8,9,13,29,34,36,76,100] The reason why two studies[29,34] did not show a correlation with creatinine is unknown; however, these two studies had the smallest sample size (n = 64 and 36, respectively) compared to the other studies (n = 84 to 6809). There was also no significant relationship observed between total protein[9] and BNP. Fasting glucose[15] and HbA1c[9,15] tests for diabetes showed no significant relationship with B-type natriuretic peptides, but random glucose[135] was positively associated with BNP. Cholesterol,[9,15] a marker of HF, showed no significant relationship with BNP or NT-proBNP. However, hemoglobin,[15] a marker of anemia, was negatively associated with NT-proBNP.

Functional and Physiologic Measure

Two measures of renal function, glomerular filtration rate[15] and creatinine clearance,[122] showed an inverse relationship with B-type natriuretic peptides. Weight,[8] but not BMI,[9,10] showed a negative relationship with B-type natriuretic peptides. Exercise testing also showed that a decrease in physical endurance was related to higher B-type natriuretic peptide levels.[116] Two studies which evaluated BMI as a determinant had no,[9] or very few,[10] patients who were obese.

Hemodynamic, Electrocardiographic and Echocardiographic Measures

There were 23 measures from 14 studies reported for heart function.[4,8-12,14,15,29-34] Most of the hemodynamic, electrocardiographic and echocardiographic measures were compared to BNP and a few were compared to NT-proBNP. Nine were positively associated with the B-type natriuretic peptides whereas eight showed no association. I-123 – metaiodobenzylquanidine (MIBG) activity,[30] was negatively associated with B-type natriuretic peptides. Deceleration time of early mitral inflow was also negatively associated with BNP (the lower the deceleration time, the higher the plasma BNP).[32] Heart rate and systolic blood pressure were the only two measurements that showed discrepant effects on B-type natriuretic levels. Heart rate was associated with both an increase[8,12,31] and no change[9,34] in B-type natriuretic peptides. Of the two studies that did not show an association, one included only hypertensive patients[34] and in the other, the association was in elderly subjects (> 80 years).[9] Systolic blood pressure was either positively[4,15] associated with NT-proBNP, or showed no association with BNP.[10,31] In one of these studies[31] the association changed to positive after the patients were treated with a beta blocker.

Drug Treatment

There were 14 studies, including nine different drug treatments, with data on the effect of drug treatment.[31,35-47] The effect of these drugs was a decrease or no effect on B-type natriuretic peptide levels. Studies involving therapy with amiodarone,[37] atenolol,[41] enalapril[40,42] and valsartan[39,43,45,46] all showed a decrease in B-type natriuretic peptides. Studies that assessed B-type natriuretic peptide levels after therapy with perindopril[47] or metoprolol[44] showed no difference compared to baseline. There was no dose dependent change in B-type natriuretic peptide levels with lisinopril[36] or furosemide.[36] The effect of carvedilol therapy on B-type natriuretic peptide levels, compared to baseline or a placebo group, showed either a decrease,[31,36,47] or no change.[35,44] There were two studies[38,44] that treated patients with beta blockers but did not differentiate between the two drugs (carvedilol or metoprolol). One study reported a decrease in NT-proBNP concentration[38] whereas the other study reported no change in BNP concentration[44] after treatment.

Non-drug Treatment

There was only one study in this group of papers that reported a non-drug therapy. In this study the concentration of BNP decreased after implantation of a left ventricular device.[150]

Question 2a: What Are the Clinical Performance Characteristics of Both BNP and NT-proBNP Measurement in Patients with Symptoms Suggestive of HF or with Known HF?

Question 2ai: Emergency Department

Sample and Design Characteristics of Studies

Fourteen articles met all of the inclusion criteria and were selected for data abstraction.[7,16-18,48-57] Of the 14 selected studies, four were from the Breathing Not Properly Multinational Study.[18] The data from the sub-studies[49,51,54] were excluded from the meta- analyses. This study and seven others examined only BNP.[17,48,50,52,55-57] Two other studies examined only NT-proBNP, [16,53] and one study examined variations of both BNP and NT-proBNP.[7] The included studies were published over a period of four years (2001 – 2004) with the majority published in 2002 and 2004 (Table 4). The patients enrolled in all studies presented to emergency departments with shortness of breath and were over 18 years of age. One study[57] limited enrolment to patients over 65 years of age while another[16] limited enrolment to patients between 44 and 88 years of age.

Diagnosis of HF in studies. All studies except two[52,53] selected for data abstraction employed a cohort design and a reference standard agreed upon by consensus of at least two physicians (mostly cardiologists). Two studies based the diagnosis on the opinion of a single cardiologist[48,52] and the third only stated that the definitive diagnosis was based on the

Framingham criteria and echocardiography results.[53] The adjudicating physicians each arrived at a diagnosis of HF based on their interpretation of all available clinical data, often including echocardiography results. The Boston Criteria were employed in the diagnosis in one study[52] and the Framingham criteria in three studies,[18,53,55] one of which also applied the National Health and Nutrition Examination Survey (NHANES).[18]

Diagnostic properties. Table 4 presents the results to answer the question "What are the clinical performance characteristics of both BNP and NT-proBNP measurement in patients with symptoms suggestive of HF or with known HF presenting to an emergency department?"

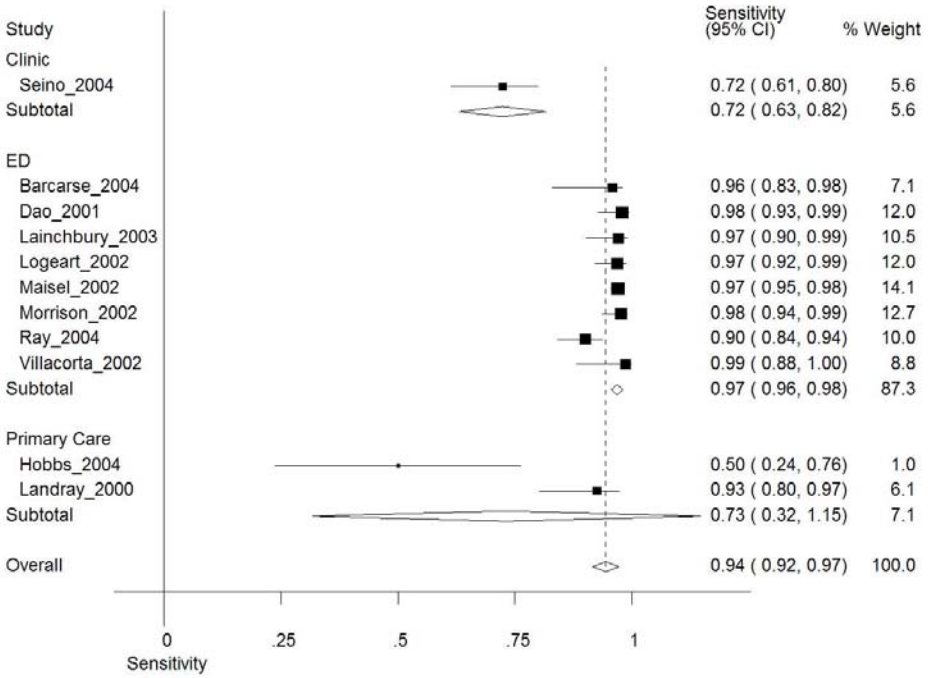
The 12 studies evaluating BNP utilized several cut point values ranging from 50 to 400 pg/mL and reported sensitivities from 60 percent to 100 percent, specificities from 27 to 99 percent, and areas under the curve (AUC) of 0.67 to 0.99.[7,17,18,48-52,54-57] In addition, the reported positive likelihood ratio (LR+) ranged from 0.69 to 70 and the negative likelihood ratio (LR-) ranged from 0.00 to 0.44 (Table 4). The three studies evaluating NT-proBNP utilized several values ranging from 254 to 4567 pg/mL and reported sensitivities from 74 percent to 98.6 percent, specificities from 47 to 93 percent, and AUC values of 0.89 to 0.96. It was possible to do meta-analysis on eight studies for BNP[7,17,18,48,52,55-57] and three studies for NT-proBNP.[7,16,53] To maximize sensitivity the lowest cut point was used if multiple cut point data were given. The data are summarized in Table 7 and Figures 3 and 4. The sensitivities of the BNP studies were similar with a summary sensitivity of 97 percent and a CI of 96 to 98 percent. In contrast, the specificity data was very heterogeneous with a summary estimate of 70 percent and a CI ranging from 56 to 85 percent (see Appendix C, Table 13-15 for results of tests for heterogeneity with regards to setting). The corresponding likelihood ratios (LRs) showed that the LR- (0.06, 95 percent CI: 0.03 to 0.10) was better than the LR+ (3.63, 95 percent CI: 2.49 to 5.31) in terms of diagnostic value. The diagnostic odds ratio (DOR) for BNP ranged from 13 to 1635 with a summary estimate of 81 (95 percent CI: 29 to 219). With the exception of the pooled sensitivity estimates (Figure 3a) for BNP in the ED, all other combined estimates (for specificity, LR+, LR-, and DOR) had positive tests for heterogeneity; as such our confidence in these pooled estimates is decreased.

For NT-proBNP the summary estimates were similar to BNP in that the sensitivity (95 percent, 95 percent CI: 90 to 101) was much higher than the specificity (72 percent, 95 percent CI: 53 to 90). The LR- (0.07, 95 percent CI: 0.02 to 0.27) was also better than the LR+ (3.35, 95 percent CI: 1.75 to 6.41). The DOR from these three studies assessing NT-proBNP ranged from 17 to 291 with a summary estimate of 60 (94 percent CI: 9 to 407). All pooled estimates of NT-proBNP diagnostic accuracy measures were significant for heterogeneity for ED studies.

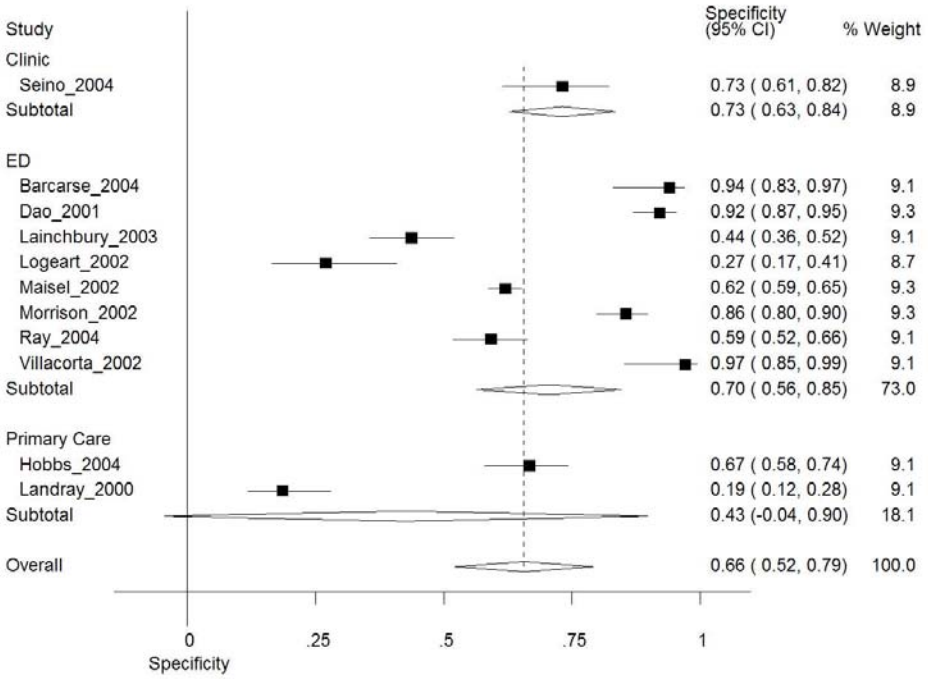
There were six studies that provided diagnostic information at a BNP cut point of 100 (±5) pg/mL.[7,17,18,55-57] The meta-analysis on these studies shows a similar pattern to that described for varying cut points (Figure 5); with the exception of LR-, all other diagnostic pooled estimates were positive for heterogeneity. The sensitivity summary estimation is 95 percent (95 percent CI: 91 to 96) with a lower and broader specificity summary estimation (67 percent, 95 percent CI: 53 to 80). The LR+ was 3.4 (95 percent CI: 2.14 to 5.42) and the LR- was 0.11 (95 percent CI: 0.08 to 0.15), which is higher than the lowest cut point summary estimate. The overall DOR for this group of studies was reduced to 38 but the 95 percent CI was tighter (17 to 85) compared to the lowest cut point summary estimate.

Figure 3. Forest plots for BNP in all settings using the lowest cut point provided in each study: a) sensitivity, b) specificity, c) LR+, d) LR-, e) DOR.

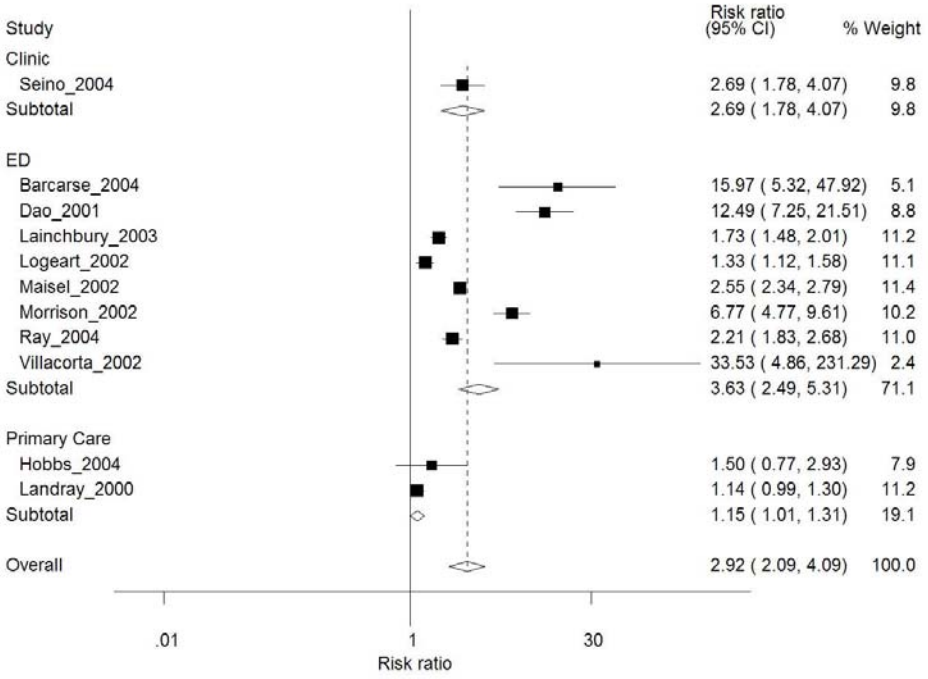
3a. Summary Sensitivity, Random Effects



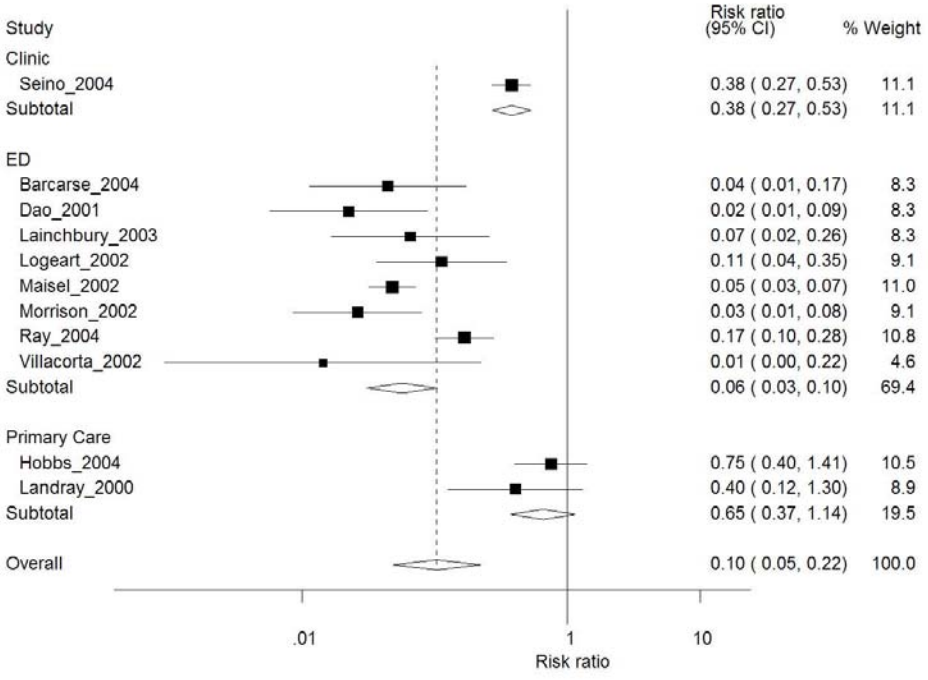
3b. Summary Specificity, Random Effects



3c. Summary LR+, Random Effects



3d. Summary LR-, Random Effects



3e. Summary Diagnostic Odds Ratio, Random Effects

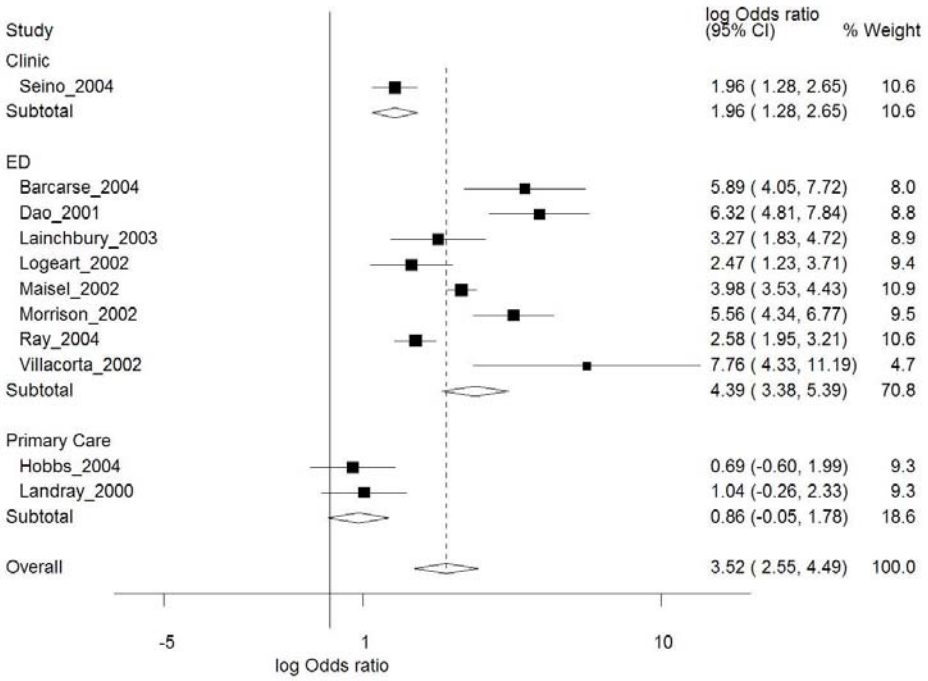
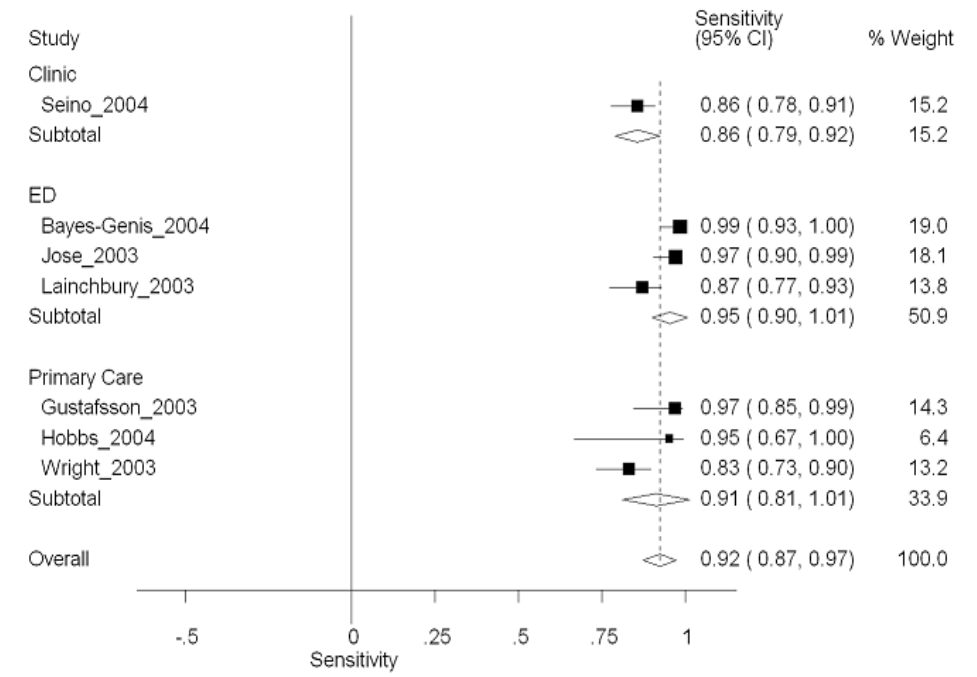
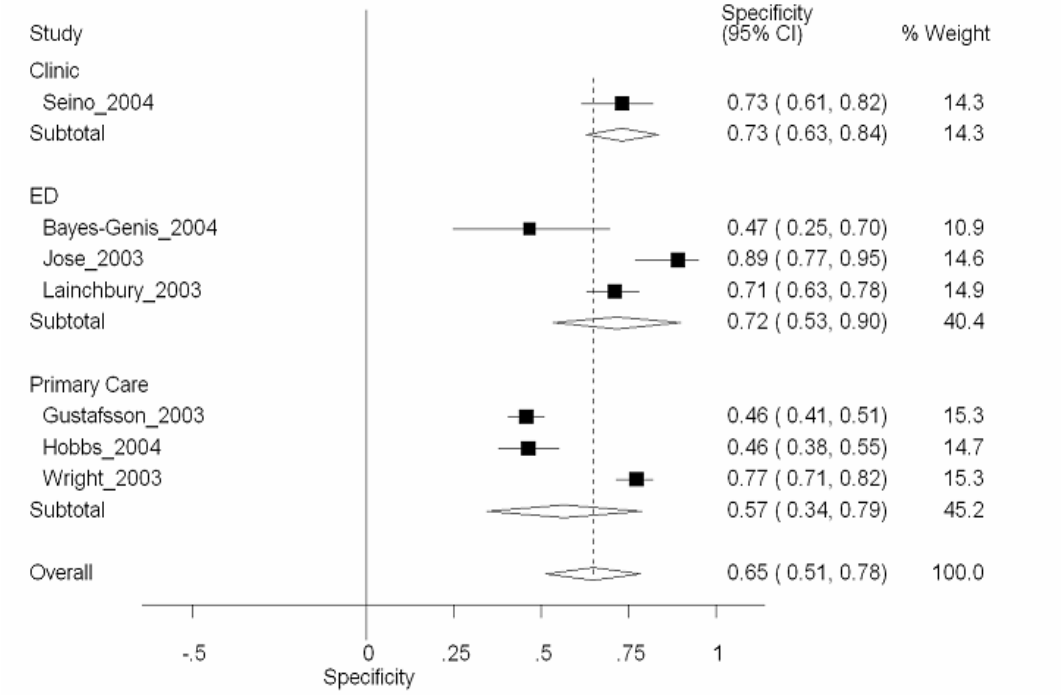


Figure 4. Forest plots for NT-proBNP in all settings using the lowest cut point provided in each study: a) sensitivity, b) specificity, c) LR+, d) LR-, e) DOR.

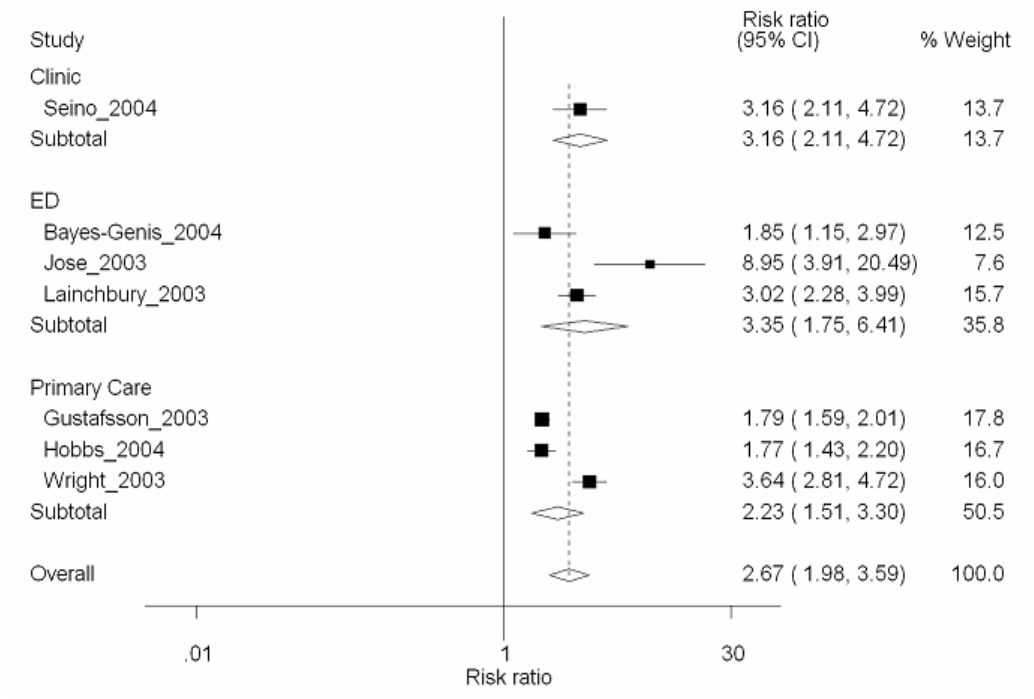
4a. Summary Sensitivity, Random Effects



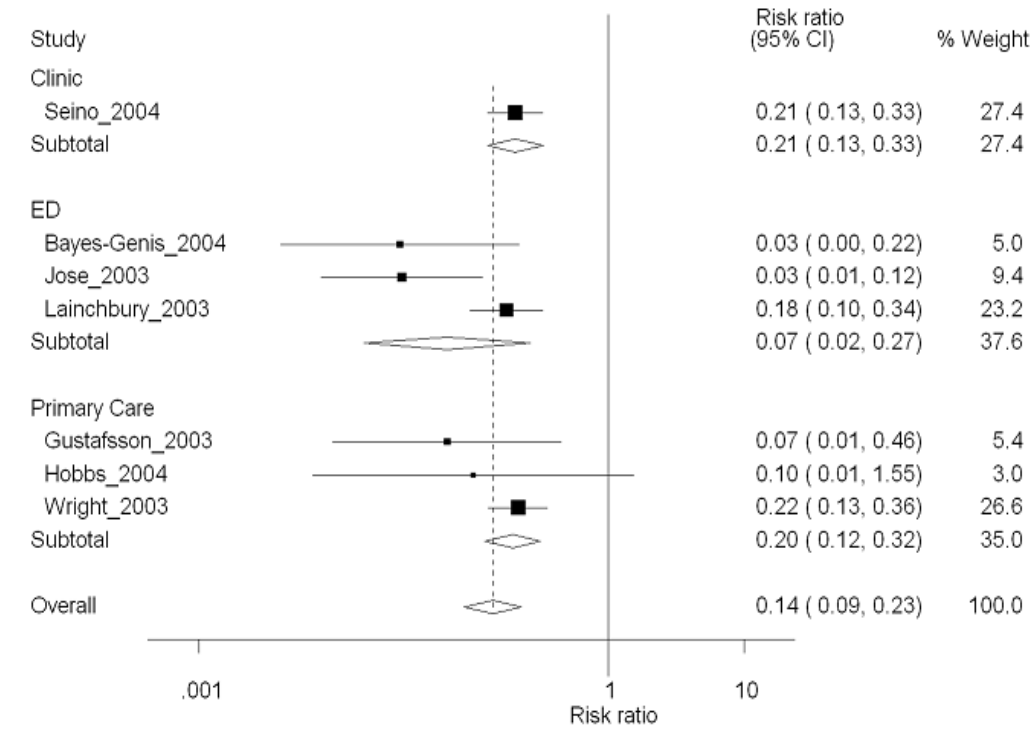
4b. Summary Specificity, Random Effects



4c. Summary LR+, Random Effects



4d. Summary LR-, Random Effects



4e. Summary Diagnostic Odds Ratio, Random Effects

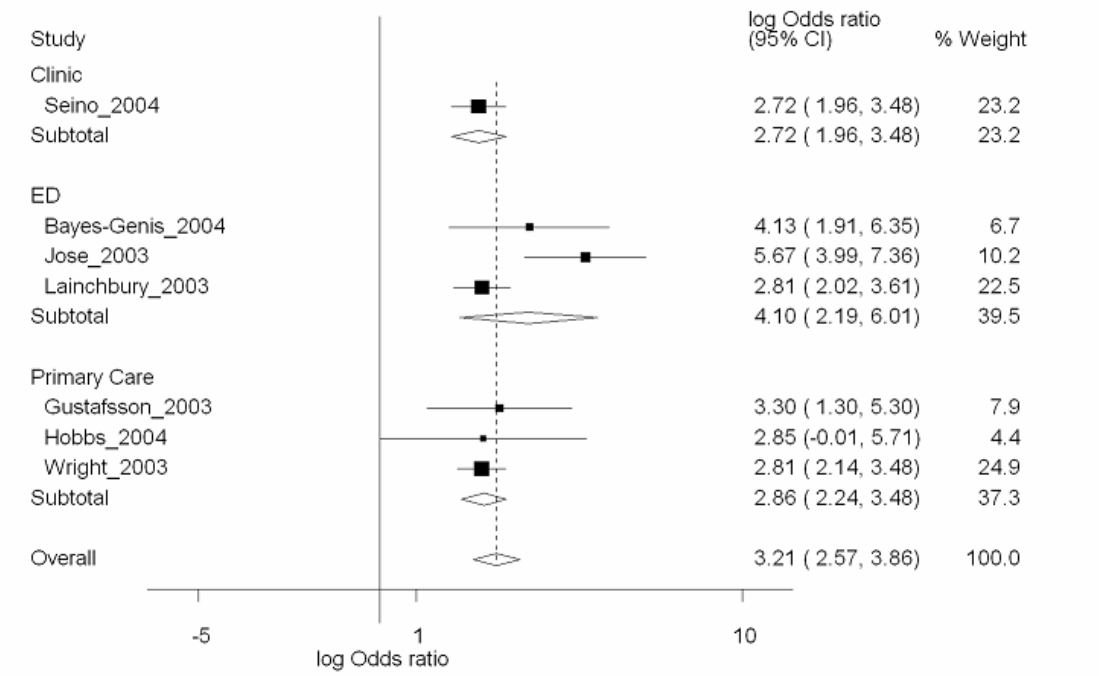
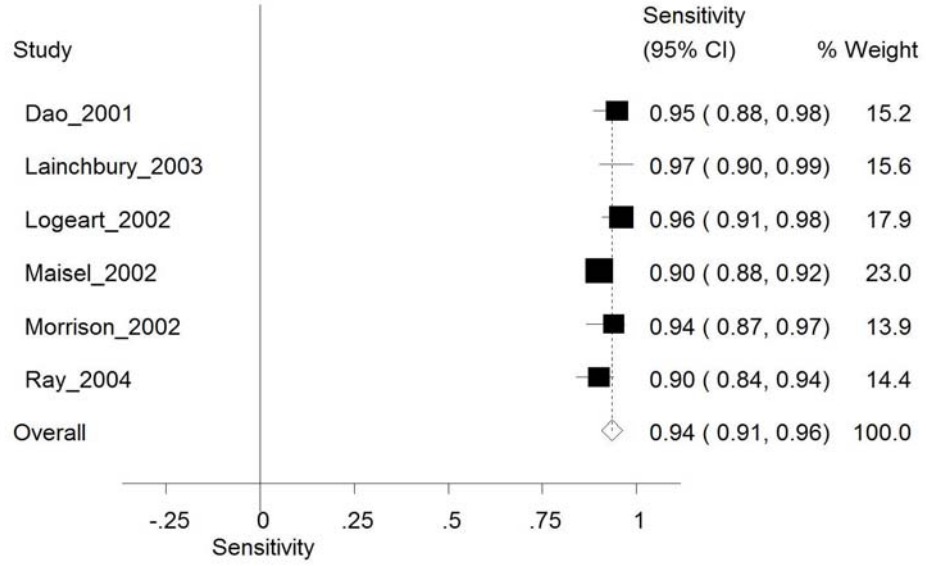
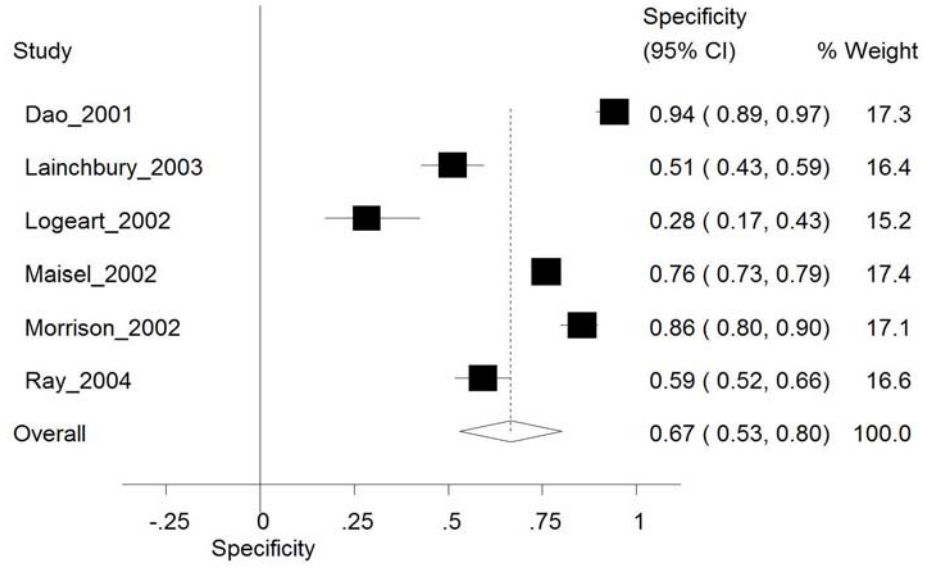


Figure 5. Forest plots for BNP in the ED using a cut point of 100 (±5) pg/mL: a) sensitivity, b) specificity, c) LR+, d) LR-, e) DOR.

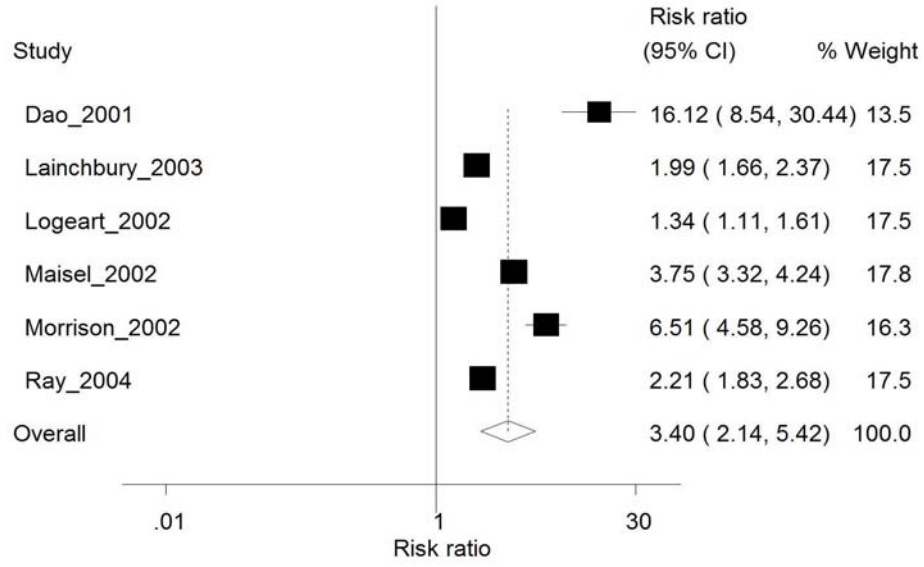
5a. Summary Sensitivity, Random Effects



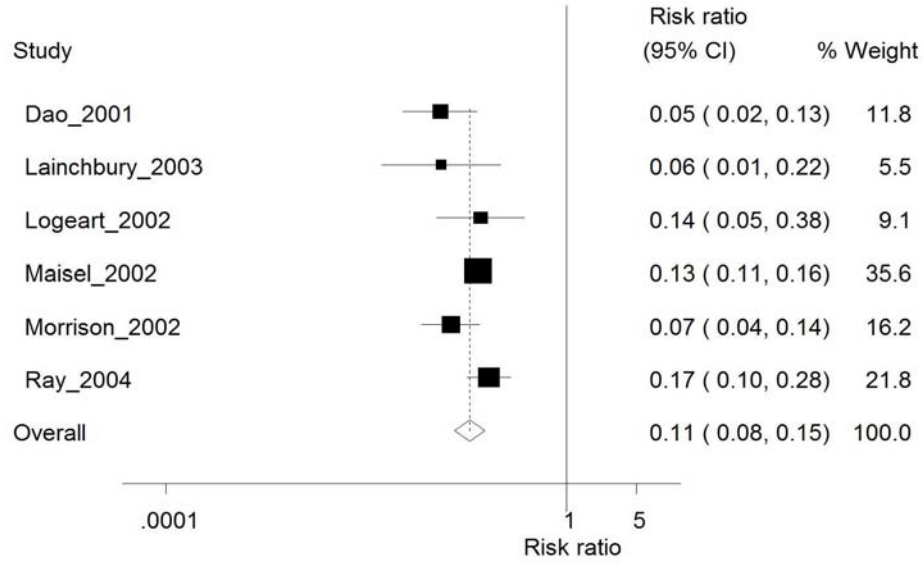
5b. Summary Specificity, Random Effects



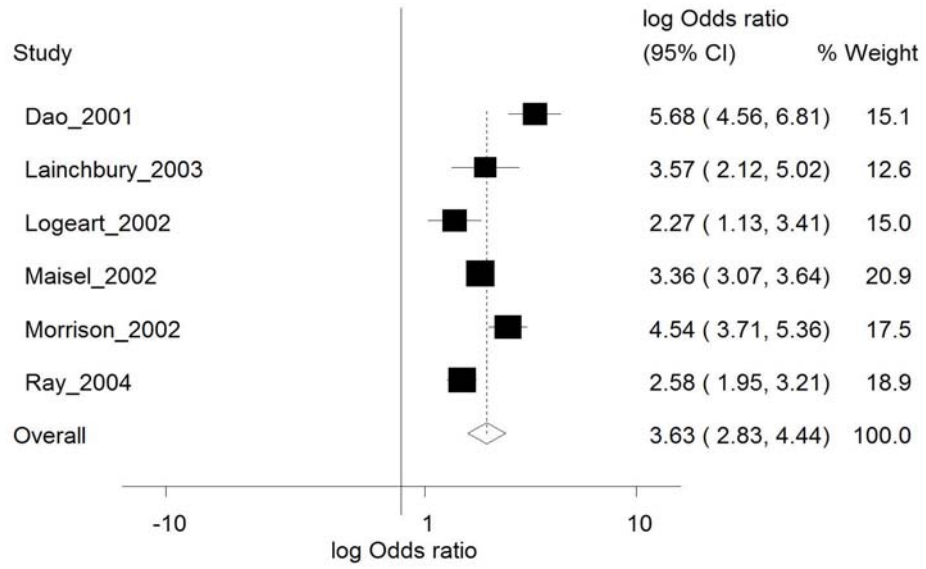
5c. Summary LR+, Random Effects



5d. Summary LR-, Random Effects



5e. Summary Diagnostic Odds Ratio, Random Effects



Quality assessment of studies. Results from the application of the QUADAS Question 14, quality assessment tool are as follows (see also Appendix C Evidence Figures, Figure 1): one (9.1 percent) of the studies clearly addressed the issue of disease progression bias (QUADAS Question 4); the reference standard was independent of the index test result (QUADAS Question 7) in 10 (90.9 percent) of the studies; the reference standard was described in sufficient detail (QUADAS Question 9) in seven (63.6 percent) of the studies; interpretation of the peptide marker (BNP or NT-proBNP) measurement was clearly without knowledge of the reference test results (QUADAS Question 10) in one (9.1 percent) of the studies; interpretation of the reference test results was clearly without knowledge of the B-type natriuretic peptide marker results (QUADAS Question 11) in seven (63.6 percent) of the studies; none (100 percent) of the studies stated whether or not the clinical data was available when the B-type natriuretic peptide test results were interpreted as would be the case when the test is used in practice (QUADAS Question 12); one (9.1 percent) of the studies reported uninterpretable or intermediate test results (QUADAS Question 13) and; withdrawals were not explained in two (18.2 percent) of the studies (QUADAS Question 14). Overall, the quality of these studies was good.

Question 2aii: Specialized Clinic or Outpatient Setting

Sample and Design Characteristics of Studies

There were a total of six papers eligible for review published between 1997 and 2004.[11,58-62] All studies evaluated BNP with the exception of two[58,60] which compared both BNP and NT-proBNP. The studies were conducted in Austria, Japan, Portugal and USA. Two studies were based on patients referred to a HF clinic[11,59] and the remaining, to outpatient settings.[58,60-62] All studies provided evaluation on BNP and two compared BNP and NT-proBNP.[58,60] Three of these papers provided data on sensitivity, specificity, and ROC curves for BNP or NT-proBNP [11,58,60].

Three of these papers did not provide ROC characteristics or sensitivity or specificity data; instead, only correlation data for BNP or NT-proBNP with different variables of cardiac structure, function and symptoms were provided.

Diagnosis of HF in studies. Three studies[58,60,62] used echocardiography as the reference standard, one study used echocardiography plus clinical criteria[11] and two studies[59,61] used the NYHA classification.

Diagnostic properties. Hammerer-Lercher et al.[60] directly compared the diagnostic values of NT-proBNP with BNP in 57 patients with stable chronic HF. In the analysis of normal (echocardiographic ejection fraction (EF) ≤ to 48 percent or radionuclide angiographic EF ≤ to 55 percent) versus impaired (echocardiographic EF < 48 percent or radionuclide angiographic EF < 55 percent) LVEF the AUC for BNP was 0.75 (SE ± 0.06), and for NT-proBNP was 0.67 (SE ± 0.07) (Table 5). In the analysis of LVEF less than 40 percent versus greater than or equal to 40 percent, the AUC for BNP was 0.83 (SE ± 0.06), and for NT-proBNP was 0.79 (SE ± 0.07). Positive and negative LRs were 3.17 and 0.35, respectively for BNP and 2.59 and 0.41, respectively for NT-proBNP. NT-proBNP did not differ significantly from BNP in either of the analyses. The optimal discriminator values were 142 pg/mL for BNP, and 4127 pg/mL for NT-proBNP for the detection of LVEF less than 40 percent compared to greater than or equal to 40 percent. For these discriminators the sensitivity was 73 percent for BNP, and 70 percent for NT-proBNP. The specificities were 77 percent for BNP, and 73 percent for NT-proBNP.

Bettencourt et al.[11] studied 100 patients with symptoms suggestive of HF referred to a HF clinic. These patients had suspected or not previously investigated HF. Since healthy controls were included in this study, this suggested the potential for spectrum bias, although it was not clear if the control data was used in the estimates of diagnostic accuracy. For a cut point value of 39.7 pg/mL, the positive predictive value was 95.5 percent. For the diagnosis of HF regardless of LVEF, the AUC was 0.92 (95 percent CI: 0.86 to 0.99; $p < 0.0001$). The accuracy of BNP for the detection of systolic dysfunction was slightly less with an AUC of 0.78 (95 percent CI: 0.69 to 0.88; $p < 0.0001$). The BNP performance for detection of diastolic dysfunction expressed by the AUC was 0.89 (95 percent CI: 0.78 to1.00; $p < 0.0001$) for the patients without systolic dysfunction. Multiple regression analysis demonstrated that age, left ventricular mass index, and LVEF were independently associated with BNP.

Seino et al.[58] compared BNP and NT-proBNP relative to LVEF less than 40 percent and less than 50 percent in patients with HF. Their data indicate that detection of LVEF less than 50 percent was slightly greater for NT-proBNP than BNP (AUC 0.820 and 0.794, respectively). The reverse was true for LVEF less than 40 percent, with BNP having slightly greater AUC (0.770) compared to NT-proBNP (0.754). The optimum cut point values were determined to be 135 pg/mL for BNP and 695 pg/mL for NT-proBNP. There were four papers11,59,61,62 that examined the relationship between BNP only and other HF variables but did not provide any data about the sensitivity, specificity or accuracy of these measurements. In general, it was demonstrated that BNP was related to cardiac function measured either as LVEF[62] or left ventricular end diastolic pressure.[61] One study[59] examined 41 HF patients and found BNP was related to the NYHA class.

There was only one study[58] that contained sufficient information to conduct meta-analysis by clinic setting alone. Therefore, no overall estimates for the individual clinic setting are possible. However, this one study was used to conduct meta-analysis for all sites combined (Figure 3 and 4). The results of this analysis are described elsewhere.

Quality assessment of studies. Results from the application of the QUADAS Question 14 quality assessment tool are as follows (see also Appendix C Evidence Figures - Figure 2): three (50.0 percent) of the studies clearly addressed the issue of spectrum bias(QUADAS Question 1); the selection criteria were only described in four (66.7 percent) of the studies (QUADAS Question 2) and in remaining two (33.3 percent) of the studies it was difficult to assess the selection criteria; four (66.7 percent) of the studies described if the reference standard was likely to correctly classify the HF (QUADAS Question 3); three (50 percent) of the studies clearly described the issue of disease progression (QUADAS Question 4); the reference standard was described in sufficient detail (QUADAS Question 9) in five (83.3 percent) of the studies; interpretation of the peptide marker (BNP or NT-proBNP) measurement was clearly made without knowledge of the reference test results (QUADAS Question 10) in five (83.3 percent) of the studies; interpretation of the reference test results was clearly made without knowledge of the B-type natriuretic peptide marker results (QUADAS Question 11) in all of the studies; five (83.3 percent) of the studies stated whether or not the clinical data was available when the B-type natriuretic peptide test results were interpreted as would be the case when the test is used in practice (QUADAS Question 12); one (16.7 percent) of the studies reported uninterpretable or intermediate test results (QUADAS Question 13); and withdrawals were explained in five (83.3 percent) of the studies (QUADAS Question 14). Overall, the quality of these studies was good.

Question 2aiii: Primary Care

Sample and Design Characteristics of Studies

There were seven papers eligible for review that selected patients from a primary care setting. Five of these studies were cross-sectional in design[34,65-68] and one was a RCT[64]. There was one study that selected patients randomly and identified a high risk cohort group.[63]

Two of the studies restricted their recruitment by age; one to 40 years of age and above,[64] and one to more than 45 years of age.[63] One study presented data stratified by gender.[65] The RCT[64] examined the effect of BNP measurement on diagnostic accuracy in primary care. All patients had BNP measured, but the groups were randomized as to whether or not the primary care physician received the results. Nevertheless, this paper is useful because the BNP concentrations can be compared against the reference standard of HF (expert diagnosis) in both arms of the study.

Two studies[34,67] either did not provide estimates of the diagnostic performance of the BNP test, or presented the data in a manner such that these diagnostic characteristics could not be calculated.

Diagnosis of HF in studies. Four studies used evaluation of left ventricular systolic function by echocardiogram as the reference standard for HF.[63,65,67,68] Three used LVEF of less than or equal to 40 percent,[63,67,68] one used LVEF less than or equal to 45 percent,[65] and one[34] did not state the reference cut point. Another study used x-ray or echocardiogram with evidence of pulmonary edema or cardiomegaly as the reference cut point.[66] The European Society of Cardiology criteria were used as the reference standard for the RCT study.[64]

Diagnostic properties. Table 6 presents the results to answer the question, "What are the clinical performance characteristics of both BNP and NT-proBNP measurement in patients with symptoms suggestive of HF or with known HF presenting to a primary care physician?" Three papers evaluated only BNP,[34,66,67] three evaluated only NT-proBNP,[64,65,68] and one evaluated

both.[63] Two of seven failed to indicate the cut point for BNP or NT-proBNP used. Two studies presented data for more than one cut point.[65,66] The range in cut points were 10 to 115 pg/mL for BNP and 67 to 338 pg/mL for NT-proBNP. Where possible, sensitivities, specificities, and LRs, either reported or calculated, are presented. Area under the ROC curve is presented when reported. Sensitivity ranged from 66 to 92 percent for BNP and 80 to 100 percent for NT-proBNP. Specificity ranged from 18 to 88 percent for BNP and 18 to 84 percent for NT-proBNP. For BNP, LR+ ranged from 1.12 to 6.71 and LR- ranged from 0.022 to 0.75. For NT-proBNP the LR+ ranged from 1.22 to 5.7 and the LR- ranged from 0 to 0.27.

Meta-analysis was done on two studies[63,66] for BNP and three studies for NT-proBNP.[63-65] To maximize sensitivity the lowest cut point was used if data for multiple cut points were given. The data for the meta-analysis are summarized in Table 7 and the results presented in Figures 3 and 4. Since there were few studies available, the accompanying pooled summary statistics must be interpreted with caution. However, looking at the three studies for NT-proBNP the DOR summary estimate was 17 (95 percent CI: 9 to 32) whereas it was only 2 (95 percent CI: 1 to 6) for BNP. Furthermore, in the Hobbs study[63]where both BNP and NT-proBNP were measured, the DOR was about eight times higher (2 and 17 for BNP and NT-proBNP, respectively). Tests for heterogeneity were not significant for either of the B-type natriuretic peptides for the pooled LR- or DOR.

Quality assessment of studies. Results from the application of the QUADAS Question 14 quality assessment tool are as follows (see also Appendix C Evidence Figures - Figure 3): six (85.7 percent) of the studies clearly addressed the issue of spectrum bias(QUADAS Question 1); the selection criteria were only described in six (85.7 percent) of the studies (QUADAS Question 2); all of the studies described if the reference standard was likely to classify the HF properly (QUADAS Question 3); five (71.4 percent) of the studies clearly described the issue of disease progression (QUADAS Question 4); the reference standard was described in sufficient detail (QUADAS Question 9) in six (85.7 percent) of the studies; interpretation of the peptide marker (BNP or NT-proBNP) measurement was clearly without knowledge of the reference test results (QUADAS Question 10) in all of the studies; interpretation of the reference test results was clearly without knowledge of the B-type natriuretic peptide marker results (QUADAS Question 11) in all of the studies; six (85.7 percent) of the studies stated whether or not the clinical data was available when the B-type natriuretic peptide test results were interpreted as would be the case when the test is used in practice (QUADAS Question 12); five (71.4 percent) studies reported uninterpretable or intermediate test results (QUADAS Question 13) and; withdrawals were explained in five (71.4 percent) studies (QUADAS Question 14). Overall, the quality of these studies was good.

Question 2aiv: Long Term Care Setting

No papers were identified in the screening process that examined the question "What are the clinical performance characteristics of both BNP and NT-proBNP measurement in patients with symptoms suggestive of HF or with known HF presenting in long term care settings?"

Question 2av: All Settings Combined

Meta-Analysis

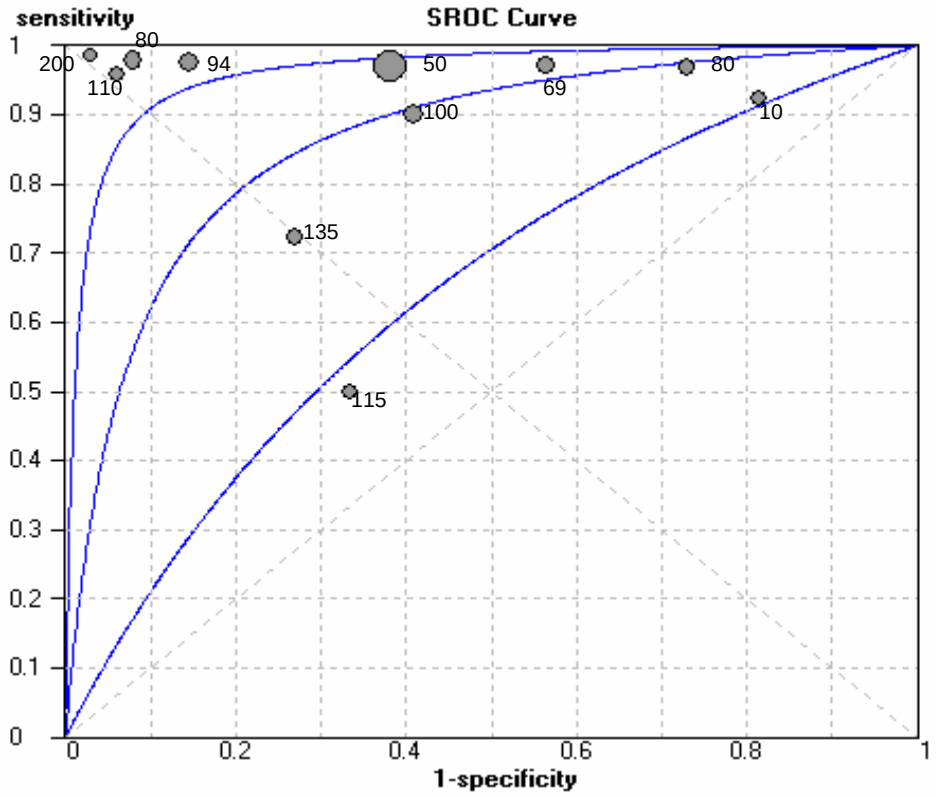
We chose studies for meta-analysis from Questions 2ai, 2aii and 2aiii where sufficient information was presented to allow calculation of sensitivity, specificity, LRs and DOR for as many diagnostic cut points as were presented (Table 7). Using this information, we developed summary estimates of these parameters (Figures 3, 4 and 5) as well as summary receiver operator characteristic (SROC) curves (Figure 6). In the pooling these data, we observed significant heterogeneity. As a result, we tried to explore the sources of the heterogeneity using meta-regressions and stratifications. We evaluated potential sources of heterogeneity for B-type natriuretics by stratifying groups according to the following factors: a) study setting (clinic, emergency department, and primary care), b) study design (cross-sectional, prospective cohort, randomized trials, and diagnostic types), c) sample size (greater than or equal to 500 and less than 500), d) comparison to reference standard (LVEF, compared to other signs and symptoms, and HF defined by clinical criteria), and e) cut points (exactly 100 pg/mL, greater than 100 pg/mL, and less than 100 pg/mL). Across the 5 different metrics of diagnostic accuracy (sensitivity, specificity, LR+, LR-, DOR), many of these were observed to be positive for heterogeneity, suggesting that no single factor helped to explain the variation between studies (Appendix C, Tables 13-26 detail the results of the heterogeneity tests by factors). The small number of studies within each of the various categories was also a limiting factor in exploring the relative contribution of these covariates to the observed heterogeneity.

We also used the Moses-Littenberg regression model to develop a summary ROC curve and test for the presence of a threshold effect. Using both weighted and unweighted regressions, the slope parameter was small and not statistically significant (BNP p = 0.4183, NT-proBNP p = 0.3430), thus indicating the lack of a threshold effect. These data show that despite the various cut points and patient cohorts studied there was fairly high concordance among the studies.

Figure 6 presents the summary ROC curves for BNP and NT-proBNP. In both cases the curve tends strongly towards the upper left hand corner. The cut points 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. The areas under the curves, however, are 0.86 for both BNP and NT-proBNP, suggesting that regardless of the clinical setting, the cut point chosen, or the test used, measurement of B-type natriuretic peptides are useful in the diagnosis of HF. The standard error (SE) for the BNP AUC was slightly higher than for the NT-proBNP AUC (0.068 compared to 0.034, respectively). There are two noted outliers in the BNP SROC with respect to sensitivity that can account for this. One is from the clinic setting[58] and the other is from the primary care setting.[63] Although there were two studies from the primary care setting in the SROC, the study that appeared as an outlier selected patients who were at high risk for HF (prevalence = 7.5 percent) compared to the other study which selected patients suspected of having HF (prevalence = 32 percent).[66]

Figure 6. Summary ROC curves for a) BNP and b) NT-proBNP from all settings using the lowest cut point provided in each study.

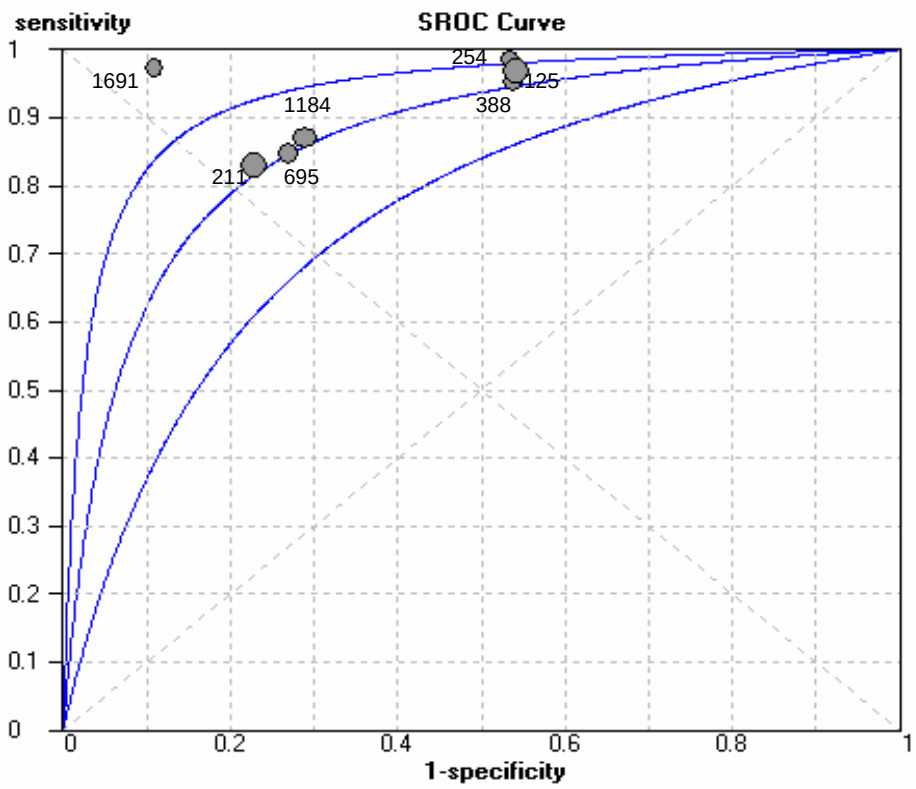
6a. Summary-ROC curves for BNP



Symmetric SROC
AUC= 0.8623
SE(AUC)= 0.0679
Q*= 0.7930
SE(Q*)= 0.06581

The lines on this graph represent the best-fit curve and 95 percent CIs around it. Each number on the graph indicates the various cut point in pg/mL

6b. Summary ROC curves for NT-proBNP



Symmetric SROC
AUC= 0.8634
SE(AUC)= 0.0340
Q*= 0.7940
SE(Q*)= 0.0331

The lines on this graph represent the best-fit curve and 95 percent CIs around it. Each number on the graph indicates the various cut point in pg/mL.

Question 2b: Does Measurement of BNP or NT-proBNP Add Independent Diagnostic Information to the Traditional Diagnostic Measures of HF in Patients with Suggestive HF?

Study Characteristics

To address this question, data were abstracted from studies included in Question 2a. These included evaluation of multivariate analysis to quantify the independent contribution of the B-type natriuretic peptides for the diagnosis of HF.

For the review of reviews a total of 145 reviews were evaluated for relevance by examining the titles and abstracts and 13 reviews were retrieved for full text screening.[151,163,173-183] One additional review was obtained by the local expert panel,[184] bringing the total to fourteen. However, only nine reviews met our inclusion criteria for data abstraction.

Multivariate Analyses

It is recognized that clinicians request more than a single test, which are typically not independent of each other. Thus, methods that adjust for multiple tests such as, multivariate

regression analysis, may assist in evaluating the independence of all the tests used within the same study. These analyses also provide estimates of the independent ability to "predict" the probability of the disease of interest while controlling for other tests. Limitations of multivariate analyses include sample sizes and the number of variables included in the model.[185]

Studies from Questions 2ai, 2aii and 2iii that performed multiple linear regression or multiple logistic regression to assess the value of B-type natriuretic peptides for the diagnosis of HF were brought forward into Question 2b. Nine papers from 2ai (emergency department) met this requirement. Eight of these studies used BNP[17,18,49,51,54-57] and one used NT-proBNP[53] for HF diagnosis. Four of the BNP studies were from the Breathing Not Properly Cohort.[18,49,51,54] There were no studies from 2aii (specialized or outpatient clinic) or 2aiii (primary care) with multivariate analysis data.

The diagnostic measures considered in this section included: clinical signs and symptoms (dyspnea, edema, rales, orthopnea, increased jugular venous pressure (JVP), S_3 heart sound and murmurs); other objective diagnostic measures (chest X-ray echocardiography, myocardial radionuclide angiogram, cardiac catheterization, MRI, CT scan); and composite scoring systems (NHANES score, Framingham score, NYHA class, and clinical judgment). In eight studies the NHANES and Framingham composite scoring systems and LVEF less than 40 percent were used as the reference standard to establish the diagnosis of HF.[17,18,51,53-57]

Two papers[49,54] used clinical judgment as a composite measure, five[18,51,53,56,57] used edema, four[17,18,53,55] used increased JVP, four[18,53,55,57] used rales, three[17,53,56] used orthopnea, and two used gallops or murmurs[53,56] as variables in the regression analysis. X-ray measures included four papers on pulmonary venous hypertension,[18,55,56,186] three papers on cardiomegaly,[51,53,55] and two on x-ray edema.[17,51] Seven of the papers report the results of multiple logistic regression as odds ratios (ORs) or exponential β, two use chi square, and one used diagnostic accuracy.

Table 8 presents the results of the data abstraction for this section. In cases where the results are expressed as ORs with 95 percent CI, BNP appears to add significant information to the diagnosis of HF that is independent of other diagnostic measures. The ORs associated with BNP ranged from 12.3 (95 percent CI: 7.4 to 20.4) to 221 (95 percent CI: 24.6 to 1983.1), and were usually larger than the other diagnostic measures in the study. The single paper reporting the results of NT-proBNP[53] gave an OR of 8.9 (95 percent CI: 3.9 to 20.5)

Those publications that reported the results as chi-square or diagnostic accuracy, also suggest that BNP measurement adds significant information to the diagnosis. This suggests that BNP and NT-proBNP measurement can add independent diagnostic information beyond that which is available from the traditional diagnostic measures.

Comparison of Estimates of DOR and SROC for Different Tests for HF Based on the Review of Reviews

Review characteristics. A total of 14 reviews evaluated some aspect of tests used for HF. Table 9 describes the characteristics of these reviews. Of these 14, nine[151,173,174,177,179,181-184] contained information that was useful and pertinent to this review. Five studies were excluded from further analysis. Three[163,176,178] were systematic reviews, but did not examine the diagnosis of heart failure. The remaining two[175,180] were not systematic reviews.

Two reviews[174,184] considered patients in all settings, one[182] considered only emergency department patients, one[177] primary care only, one[183] considered both primary care and emergency department patients, and three[151,173,179] did not specifically state a clinical setting.

One review[181] selected studies "on the basis of quality and relevance to primary care". Three reviews[182-184] have examined the value of BNP and NT-proBNP measurement in the diagnosis of HF compared to other diagnostic measures. One review [174] examined BNP alone, and one[151] examined BNP and "related peptides" alone. One review[177] examined the 12-lead electrocardiogram (ECG) only, and one[181]examined the clinical exam, x-ray and ECG. Neither of these studies provided a comparison to B-type natriuretic peptides, but both present useful supporting evidence for the discussion.

The National Health Service Quality Improvement Scotland Technology Assessment Report #6[183] examined the role of B-type natriuretic peptide measurement and ECG in primary care. They concluded that BNP or NT-proBNP is superior to machine-read ECGs, but equivalent to an accurate physician-interpreted ECG in deciding which patients to refer to echocardiography. A systematic review of the 12-lead ECG for the evaluation of suspected HF[177] concludes that this is an inadequate tool to screen for those patients that require echocardiography.

Doust et al.[184] prepared a systematic review for the National Institute for Clinical Studies in Melbourne Australia. The results of this review are difficult to interpret because no pooled estimates of the data are presented. Nevertheless, they conclude that most signs and symptoms lack both the sensitivity and specificity required for the diagnosis of HF. Tachycardia at rest, elevated JVP, displaced apex beat, and added heart sounds are the most specific. A normal ECG will rule out HF, but may require specialist interpretation. An abnormal chest x-ray is useful only when accompanied by an abnormal ECG. They further conclude that B-type natriuretic peptide measurement is the most valuable tool in ruling out HF, because of its high negative predictive value.

Wang et al.[182] reviewed papers that assessed the diagnosis of HF in patients presenting to the ED with dyspnea. The features that increased the probability of HF were S3 gallop, chest x-ray showing pulmonary venous congestion and an ECG showing atrial fibrillation. Those that decreased the probability were an absence of rales, a normal response to the Valsalva maneuver, absence of cardiomegaly or edema on x-ray and a normal ECG. A serum BNP less than 100 pg/mL proved to be the most useful tool in ruling out HF (LR- .011, 95 percent CI: 0.07 to 0.16).

Table 10 outlines the diagnostic tests examined and the performance characteristics in each of the reviews. To compare the performance of diagnostic tests between reviews, we chose to use the DOR. This performance characteristic is the single most useful measure of diagnostic performance and the most easily comparable between studies and reviews, partly because it is relatively insensitive to the decision threshold chosen in each study. In cases where the DOR was not presented, we estimated the DOR from the sensitivity and specificity or positive and negative LR.

Three reviews[151,173,174] considered only BNP or NT-proBNP without comparison to other tests. In these studies the DOR or the estimated DOR for BNP ranged from 31 to 569. The single review that examined NT-proBNP has an estimated DOR of 230. BNP and NT-proBNP were compared to other diagnostic tests in three other reviews.[182-184] In these reviews the DOR for BNP ranged from 10 to 498, and the single review comparing NT-proBNP to other tests had a DOR of 14.

B-type Natriuretic Peptides Compared to Other Diagnostic Measures

In our assessment of the primary research studies of the diagnostic properties of BNP and NT-proBNP, we looked for papers that compared the B-type natriuretic peptides against a number of reference measures. Therefore, in our examination of reviews, we also looked for

studies that measured the independent contribution of these peptides against these reference measures. No reviews compared the diagnostic performance characteristics of BNP or NT-proBNP against myocardial radionuclide angiography, cardiac catheterization, MRI, or CT scan.

Three reviews[182-184] compared BNP to abnormal ECG and one[177] examined ECG abnormalities alone. The estimated DOR ranged from 3 to 223 whereas the DOR for BNP in the same studies ranged from 10 to 498. The DOR for an abnormal ECG exceeded the DOR for BNP in only one case[183] (12.4 vs. 10.4), but the 95 percent CIs were overlapping. Similarly the DOR for NT-proBNP was similar to that for an abnormal ECG (14.9 vs. 12.4). One systematic review[181] describes an abnormal ECG as having a high sensitivity but poor specificity and useful for confirmation of diagnosis only but no numerical values were provided.

Two parameters of the chest x-ray (evidence of pulmonary venous hypertension and evidence of cardiomegaly), had diagnostic importance and were examined in three studies.[181,182,184] The estimated DOR for these two tests were 3 to 28 for pulmonary venous hypertension and 2 to 10 for cardiomegaly. Again this is less than the DOR of BNP in the same studies.

Any abnormality in the clinical exam, history of paroxysmal nocturnal dyspnea, S3 gallop, and increased JVP were the components of the clinical exam that had diagnostic usefulness. Three reviews[182-184] compared these parameters to BNP. In all cases the estimated DOR for these tests was less than the estimated DOR for BNP.

Quality Assessment of Reviews

The quality of the reviews was assessed by the STEP Questionnaire.[169] The quality of reviews varied from good to poor. Three reviews[173,182,183] were obviously of higher quality than the rest. These reviews clearly stated the main question, the clinical population and the main comparators. Inclusion and exclusion criteria were plainly stated and it is unlikely that relevant studies were missed. Assessments were made by at least two reviewers and the results were presented clearly. Meta-analysis was performed where appropriate. Two reviews[177,184] were of good quality, but the results were presented in a less clear manner. Five further reviews[151,174,175,180,181] were of lesser quality.

Question 3a: Do BNP or NT-proBNP Levels Predict Cardiac Events in Populations at Risk of CAD, with Diagnosed CAD and HF?

A total of 150 studies were eligible for evaluating the prognostic ability of BNP or NT-proBNP levels in HF patients to predict cardiac events of interest for this review. For the purposes of this review we have limited the findings to four major groups and these include, people at risk of CAD, those diagnosed CAD or HF, and general populations for screening. A small group (n = 40) of studies included populations in ICU, with pulmonary embolism, stroke, or renal failure; the data from these specialized groups will not be presented here.

Question 3ai: At risk of CAD

Design and Sample Characteristics of Studies

The prognostic value of BNP or NT-proBNP was examined in 12 studies of people with risk factors for CAD, ten were prospective cohorts,[9,10,15,24,69-74] one was a RCT,[4] and one was cross-sectional.[6] Sample sizes ranged from 111[9] to 3346.[74] Most study participants were between 50 and 75 years of age, although eight studies included patients over 50 years.[6,10,15,24,69,71,73,74] Four studies included participants under 75 years of age.[9,10,24,71] The widest age range, (19 to 105 years) was from an Irish study[71] in an emergency room. In one study,[70] only the mean age of participants was reported so it was not possible to assess the age range of the sample. The percentage of males in the studies ranged from 21 percent[9] to 96 percent.[69] Follow up averaged 8 to 9 years in two studies[15,70] and 8 to 12 days in another.[71] Excluding the cross-sectional study,[6] and another study for which the follow up time was reported as "until discharge,"[72] follow up time ranged from approximately 1 to 5 years.[4,9,10,24,69,73,74]

CAD Risk Factors

Study participants were recruited in an emergency room or when admitted to a cardiac care unit. CAD risk factors included diabetes,[15,69,70,74] suspicion of cardiac dysfunction,[69] ACS or chest pain,[24] suspected heart disease,[9,71,74] cardiac arrest with cardiac cause,[72] hypertension,[4,10,74] prior MI,[74] aortic stenosis or aortic valve replacement,[6] left atrial enlargement or left ventricular hypertrophy,[74] significant heart disease upon admission, or a cardiac event within 90 days of admission.[73]

CAD risk factors were assessed using a mixture of electrocardiography, chest x-ray, clinical examination, LVEF, or NYHA classification criteria. Diabetes was assessed by clinical criteria such as persistent macroalbuminuria (> 300 mg/24 hours) in at least two out of three consecutive 24-hour urine collections, with the presence of diabetic retinopathy and the absence of other kidney or urinary tract disease. Hypertension was defined as systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg.

BNP and NT-proBNP Tests and Threshold Values

BNP was measured using the Triage BNP method in two studies,[69,71] and the Shionoria-IRMA method in four studies.[9,10,72,74] NT-proBNP was measured using the Elecsys method in six studies.[4,6,15,24,70,73]

BNP or NT-proBNP cut point values were not uniform; six studies[6,9,24,69,71,73] reported multiple and six[6,24,70,71,73,74] reported single cut points. Cut points were chosen based on median or percentile levels of fasting plasma NT-proBNP[4,70] or plasma BNP,[9,74] mean BNP,[10] ROC curves,[6,72,73] information from the test package insert,[71] or miscellaneous external sources.[15] In two studies, the selection of cut points was arbitrary or unexplained.[24,69]

Definition of Outcomes

Death was a primary outcome in 10 studies,[4,9,10,15,24,69-71,73,74] although in four [4,10,70,73] it was part of a composite outcome including other cardiovascular events (e.g., non-fatal MI). Death was limited to cardiovascular events in four studies[4,10,70,73] and included all-cause mortality in six studies.[9,15,24,69,71,74] Deaths were ascertained using public records (e.g., death certificates) in four studies,[15,24,69,73] while in three there was mention of "clinical assessment" of cardiovascular outcomes (including death).[4,10,74] Assessment of death was not described in three studies.[9,24,71]

The two studies with non-death outcomes were the only studies that enrolled patients with prior surgeries. In the first study,[72] 27 to 40 percent of patients had an intra-aortic balloon counterpulsation or a coronary revascularization. The outcomes ranged from survival to hospital discharge. In the second study,[6] 12 percent of patients had coronary artery bypass graft (CABG) and 9 percent had percutaneous coronary intervention. The outcome was the severity of aortic stenosis. Outcomes other than death were measured by clinical tests such as the mean transvalvular pressure gradient[6] or LVEF.[73]

Four studies had secondary outcomes, including non-cardiac causes of death[69] and cardiovascular mortality plus hospitalization for HF.[70] One study[74] had three secondary outcomes: MI, heart disease, and atrial fibrillation. The fourth study[72] had four secondary outcomes: return of spontaneous circulation, hospital admission, 24-hour survival, and favorable neurologic outcome after discharge.

Adjusted Results – Multiple Regression Analysis

Eleven of the 12 studies (Neilson et al.[73] excepted) featured regression analysis to examine the association between levels of BNP or NT-proBNP and the outcome of interest. In two of the 11 studies, one BNP[69] and one NT-proBNP,[6] the reported regression results consisted only of p-values or chi-square test statistics. See Tables 11 and 12 for summary results for all 12 studies.

BNP was treated as a categorical variable in four studies,[9,71,72,74] with the categories based on the cut points discussed above. Higher levels of BNP were consistently found to be positively associated with all-cause mortality or the occurrence of cardiac events (e.g., HF).[9,71,74] The adjusted measures of association (OR or hazard ratio (HR)) ranged from 1.10 to 4.26 and did not appear to differ by outcome in two studies (point estimates < 2.00 in both studies).[9,74] In one mortality study,[71] though, the estimated OR for BNP (≥ 700 pg/mL versus < 700 pg/mL) was found to be much larger at 4.26.

In the final study where BNP was treated as categorical,[72] the outcome was survival to hospital discharge. For the study participants, some of whom had prior surgery, all of the adjusted, estimated ORs were less than 1.00. Since the ORs decreased as the level of BNP increased, higher levels of BNP were negatively associated with survival.

The results of the study[10] where BNP was treated as a continuous variable showed that higher values of BNP were positively associated with the occurrence of cardiovascular events (adjusted risk ratio (RR) = 1.02; 95 percent CI: 1.01 to 1.02).

NT-proBNP was also treated as a categorical variable in four studies.[4,15,24,70] Again, the categories were based on the cut points discussed above. Higher levels of NT-proBNP were consistently found to be positively associated with composite endpoints that included both cardiovascular mortality and other cardiac events such as non-fatal MI.[4,70] Positive associations were also found between levels of NT-proBNP and all-cause mortality.[15,24] The adjusted

measures of association (RR or HR) ranged from 1.85 to 5.40, with a concentration between 2.8 and 3.6.

In 10 of the studies, all of the adjusted measures of association (i.e., OR, HR, RR) were statistically significant at the 5 percent level. In the other two studies,[9,24] all of the measures except for three were also statistically significant at the 5 percent level.

Several variables were included in many of the regression models as covariates, including age, gender, blood pressure, cholesterol level, left ventricular mass or function, and smoking.

Quality Assessment of Studies

Selection and information bias are two common threats to the internal validity of observational studies. One method of minimizing selection bias is to evaluate all patients who present at the research site between a certain set of fixed dates. Patients who meet the inclusion criteria are then entered into the study. This method of enrollment – often called 'consecutive enrollment' – helps to prevent a conscious or unconscious bias from affecting the selection of patients into the study. The bias would occur if, for example, patients with multiple risk factors for CAD, or with higher risk factors for CAD, were the only persons selected for the study. In the 12 studies of persons with risk factors for CAD, the authors of only four studies[15,24,71,73] explicitly wrote that patients were enrolled consecutively. The other eight studies contained no mention of consecutive enrollment. The authors of future studies should be explicit about the order of patient enrollment so as to allow readers to assess study quality.

Information bias occurs when study subjects are misclassified on their exposure or disease status. Misclassification can occur due to random chance (e.g., inaccurate measures of BNP or NT-proBNP), or because the persons who take study measurements have knowledge of a subject's exposure and disease status. For example, knowing that subjects have very high levels of BNP or NT-proBNP could trigger additional clinical investigations that lead to what would have otherwise been unmade diagnoses or treatments. This could inflate the association between BNP or NT-proBNP and the outcome of interest. Blinding is one way to avoid the problem. In the 12 studies involving persons at risk for CAD, the authors of five publications[4,6,70,73,74] reported that blinding had occurred and the authors of seven studies did not mention anything about blinding. Again, authors should be explicit about what they do (blinding, no blinding) so as to facilitate the assessment of study quality.

The absence of information about consecutive enrollment or blinding makes the presence of bias impossible to rule out for a majority of the studies. The same absence of information prevents the extent of any bias from being ascertained.

Question 3aii: With diagnosed CAD

Design and Sample Characteristics of Studies

Thirty-eight studies examined the association between BNP or NT-proBNP and outcomes such as mortality or re-infarction in persons with CAD. Twenty-eight of the studies were prospective cohorts,[3,13,19-22,29,33,75-94] nine were RCTs,[8,14,27,28,95-99] and one was cross-sectional.[100] Sample sizes ranged from a low of 14[94] to a high of 7800.[8,97] The mean age of study participants was clustered around 55 and 65 years, with a range of approximately 40 to 70 years. The widest age range spanned 54 years and was observed in two studies (21 to 75 years,[27] and 26 to 80

years[80]). The percentage of males in 31 of the studies ranged from a low of 45 percent[3] to a high of 100 percent.[91] The percentage was not reported in five studies.[20,22,78,83,94] Lengths of follow up varied greatly between the studies. The mean, median, or maximum follow up was up to and including 6 months in 12 studies,[3,21,27,28,76,86,87,90,92,93,96,99] 7 to 12 months in eight studies,[8,33,77,78,83,91,95,97] 13 to 24 months in eight studies,[14,20,29,75,84,85,89,94] and more than 24 months in eight studies.[13,22,79-82,88,98] Follow up time was not reported in two studies.[19,100] The shortest follow up time was 72 hours[99] and the longest was 4.9 years.[88]

CAD Diagnosis

Study participants were recruited after admission to hospital for a CAD related event. CAD related events included MI (16 studies),[3,13,27,29,33,77,78,80,82,84,85,88,91,92,95,100] angina (10 studies),[8,20,76,77,82,85,92,95-97] ischemia (five studies),[22,81,90,96,100] chest pain (three studies),[21,77,86] stenosis (three studies),[19,79,85] LVD (one study),[98] ACSs (one study),[3] cardiac arrest (one study),[99] and hypertension (one study).[89] More than one CAD event was involved in several studies.

CAD was diagnosed with a plethora of clinical tests such as electrocardiography, ST elevation, development of left bundle blockade, rises in creatinine kinase levels, T-wave inversion, and blood pressure. In some studies,[14,28,83,87] persons were enrolled on the basis of whether test results exceeded a certain threshold value (e.g., ST elevation $\geq$ 1 mm). In other studies, persons were enrolled if they were undergoing percutaneous transluminal coronary angioplasty (PTCA)[75] or CABG.[91,93,94,99]

BNP and NT-proBNP Tests and Threshold Values

BNP was measured using the Triage method in nine studies,[3,19,28,29,77,78,83,95,96] the Shionoria-IRMA method in seven studies,[13,33,79,88,90,93,94] and the ADVIA Centaur method in one study.[27] NT-proBNP was measured using either the Elecsys system in 13 studies[8,14,21,22,75,76,85-87,92,97,99,100] or by a variety of other methods in seven studies.[20,80-82,84,89,98]

BNP or NT-proBNP cut points were not uniform. Twenty-four of the studies[3,13,19-21,27-29,75,77-79,81-83,87-90,93,95,96,98,100] reported a single cut point and six[8,76,86,91,92,97] reported multiple cut points. Another six studies reported a single cut point, but the analyses were stratified by disease,[33,84,85] gender,[22] BNP versus NT-proBNP,[80] or time period during follow up.[14] The cut points were based on the medians or quartiles of measured BNP or NT-proBNP in the study participants,[8,13,14,19,22,75,76,78,80-82,85-87,89,95,97,98,100] ROC curves,[3,21,27,29,33,79,84,88,91,92] previously published literature,[20,28,77,83,90,96] or regression analysis[93]Cut points were not reported in two studies.[94,99]

Definition of Outcomes

Primary outcomes were death in 32 studies,[3,8,13,14,19-22,27-29,75-77,80-90,92,94-98,100] non-fatal MI in 15 studies,[8,14,21,22,75,77,80,83,85,86,92,95-98] HF or cardiogenic shock in 10 studies,[28,33,78,80,83,87,89,90,92,100] re-infarction in four studies,[19,28,29,100] repeat hospitalizations for ACS in five studies,[28,80,91,95,96] angina in three studies,[29,79,94] ischemia in two studies,[33,87] miscellaneous cardiovascular complications (e.g., arrhythmia, cardiogenic shock) in two studies,[91,92] BNP or NT-proBNP levels in two studies,[93,99] and LVD in one study.[33] Twenty-five studies[8,14,19,21,22,28,29,33,75,77,80,83,85-87,89-92,94-98,100] included more than one outcome or had a composite outcome that was formed by aggregating two or more single outcomes. The outcomes were ascertained using clinical

definitions (e.g., LVEF < 35 percent) in 20 studies.[3,8,21,29,33,75,77-79,83,84,87,89-92,97-100] In the other 18 studies,[13,14,19,20,22,27,28,76,80-82,85,86,88,93-96] the authors simply named the outcomes without specifying how they were assessed. This lack of specification was often the case with mortality: authors did not describe their method (e.g., review of death certificates) of determining whether and why a participant died.

Nine studies had secondary outcomes, including death,[33,88,97] coronary HF or cardiogenic shock,[78] recurrent MI,[90] poor myocardial perfusion or failed ST segment resolution,[27] recurrent ischemic events and severe HF,[76] stroke,[98] and thrombosis in MI.[3]

Adjusted Results – Multiple Regression Analysis

Thirty-three of the studies used regression analysis to examine the association between levels of BNP or NT-proBNP and the outcome of interest. Multiple regression was used in 31 of the studies[3,8,13,14,19-22,27,28,33,75-78,80-90,93,96-98,100] and simple regression was used in two of the studies.[79,94] Logistic regression was the sole approach in 17 studies.[3,8,19-21,27,28,33,76-78,84,86,87,90,96,100] Logistic regression was also employed with Cox regression in two studies[75,97] and with linear regression in two studies.[14,89] Cox regression was utilized alone in ten studies.[13,22,79-83,85,88,98] Regression analysis was not used in five studies.[29,91,92,95,99] The studies were stratified according to type of B-type natriuretic peptide (BNP or NT-proBNP). Further stratification was done according to whether patients received prior cardiac related surgery (yes/no) and whether the outcome was mortality or non-fatal event (e.g., MI). For BNP, measures of association (OR, HR, etc.) ranged from 1.60 to 16.30 in studies of prior surgery patients and mortality[3,28,77,96] (Table 13). The measures of association were concentrated in the range of 1.60 to 2.96 and they were statistically significant at the 5 percent level in three of the four studies.[3,28,77] In two studies of prior surgery patients and non-fatal outcomes, point estimates of the measures of association were 3.9[28] and 41.12[79] (Table 14). Both estimates were statistically significant at the 5 percent level.

The predictive ability of BNP was found to be 2.53 (HR)[13] or 7.20 (OR)[27] in two mortality studies of patients with no prior cardiac related surgery. Three studies[33,78,83] were conducted to examine non-fatal outcomes in patients with no prior surgery and the measures of association ranged from 1.01 to 3.03 (Table 14). The measures of association in all five studies were statistically significant at the 5 percent level.

Turning to NT-proBNP, the measures of association spanned from 1.33 to 6.63 in six mortality studies of patients with prior cardiac related surgeries, with most measures concentrated in the range of 1.33 to 3.42.[8,21,75,76,80,82] All of the measures were statistically significant at the 5 percent level in five studies. In the sixth study,[76] only one of three ORs was significant at 5 percent. Studies[8,21,80] of non-fatal outcomes in patients with prior surgery yielded measures of association that ranged from 1.01 to 3.51. However, the measures were statistically significant at the 5 percent level in only one study (Table 15).[80]

In studies of NT-proBNP as a predictor of mortality in persons who did not have a prior cardiac related surgery, the measures of association ranged from 1.01 to 19.70, with a concentration in the range of 1.50 to 4.80. The measures were all statistically significant at the 5 percent level in four studies,[20,22,81,84] two of the three measures were significant in one study,[97] and none were significant in two studies.[87,98] In the case of non-fatal outcomes in persons who did not have a prior surgery, measures of association ranged from 0.64 to 5.90 and the concentration was between 1.30 and 5.50. The measures were all significant in two studies,[84,86]

three measures of 13 were significant in three studies,[85,87,97] and none were significant in two studies (Table 16).[22,98]

In one[89] of the two studies where linear regression was used as an analytic tool, NT-proBNP was found to be a predictor ($p = 0.03$) of left ventricular systolic volume after MI. However, the authors did not quantify the relationship by providing an estimated regression coefficient. In the other study, several variables were found to predict baseline levels of, and rates of change in, NT-proBNP.[14] These variables were age, gender, diabetes, previous MI, cTnT level greater than or equal to 0.01 μg/L, calculated creatinine clearance less than 73 ml/min, C-reactive protein greater than 10 mg/l, ST-segment depression, and use of diuretics or nitrates on admission to hospital (Table 17).

Table 17 shows the studies for which no regression results were reported (even though the authors claimed to have conducted regression analyses) as well as the studies for which no regression analyses were performed.

Several variables were included in many of the regression models as covariates, including age, gender, biological markers (e.g., heart rate, blood pressure, baseline creatine kinase, LVEF), and disease history (e.g., history of MI, hypertension, diabetes).

Quality Assessment of Studies

The authors of 11 studies[3,20,21,33,75,77,79,82,84,91,92] indicated that participants were consecutively enrolled in their research. The authors of the remaining 28 studies did not report whether or not enrolment was consecutive. For blinding, reporting was only slightly better as the authors of 14 studies[3,8,13,19,21,28,29,78,81,87,92,95,97,99] reported that outcomes were assessed in a blinded fashion, while the authors of the remaining 25 studies did not mention blinding in their published manuscripts. The lack of reporting in both areas meant that it was impossible to rule out the presence of selection or information bias in a majority of the studies.

Question 3aiii: With diagnosed HF

Thirty-eight publications evaluated BNP levels and 14 evaluated NT-proBNP and the association with cardiac events in patients with HF. The predictive value of BNP and NT-proBNP are presented separately with respect to the ability to predict future outcomes of interest. Six publications evaluated both BNP and NT-proBNP.[41,103,112,125,126,128] The findings from these studies are presented in the BNP section only.

Prognosis Studies Using BNP Levels

Design and Sample Characteristics of Studies. All the studies evaluating BNP levels were prospective cohort designs with the exception of three publications based on the ValHeFT[106,110] including a sub-study[41]which were randomized trials. The evaluation of the VaLHeFT cohort included both arms of the trial in the evaluations. In addition to the ValHeFT publications, an additional two publications reported on the same study cohort[125,128] with different follow up periods. Twelve studies[12,23,104,105,107,111,113,118-120,124,129] recruited patients that were admitted as hospital inpatients for acute episodes; three studies contained patients recruited from both emergency and inpatients,[102] and outpatient clinics and inpatients combined.[25,117] Twenty studies[30,36,41,101,103,106,108-110,112,115,116,121-123,125-128,130] indicated that patients were recruited from

primary care, general population, specialty clinics and outpatient settings (see Tables 18 and 19). Three studies recruited patients with HF from emergency departments.[32,48,114]

Sample sizes ranged from a low of 33[32] subjects to a high of 4300 subjects.[106,110] The mean sample size for all 36 studies was 327 (± 829) and the median was 102. The mean age of study participants was clustered around 65 years, with the widest range of 68 years[113] ranging from 17 to 85 years. The percentage of males in 32 of the studies ranged from a low of 44 percent[111] to a high of 100 percent.[48,119] The percentage was not reported in four studies.[101,106,110,122] One cohort[102] based on the REDHOT study had a high proportion of African Americans (63.4 percent).

Lengths of follow up varied greatly between the studies, with the shortest time being 30 days[119] and the longest being 92 months.[126] For studies with short term follow up, the period varied from 30 days[119] to 90 days[32,48,102] and six months.[107,109,111,114,124] For the remaining studies the mean or median follow up was 7 to 12 months,[118,130] 13 to 24 months,[12,23,30,101,103,105,115,116,125,129] 25 to 48 months,[25,36,41,104,113,117,120,121,123] and greater than 48 months.[126,127] Several other studies did not report median or mean follow up times but rather end points of 12 months,[112] 18 months,[108] 36 months,[110,128] and 60 months[122] or did not specify.[106]

HF Diagnosis and Severity. The diagnosis of HF was established in a number of ways, but predominately confirmed using echocardiography, carried out as part of the study, or obtained from previous medical records. The exceptions were three studies that used ventriculography[41,121,187] and eight that used clinical evaluation (signs and symptoms).[102,103,105,108,114,122,126,188] All but two studies[48,107] reported some rating of the NYHA classification for all the subjects or a subgroup.

The majority of studies included subjects across all levels of the NYHA classification I-IV. The exceptions were eight studies[23,32,108,109,119,120,123,124] that restricted subjects to levels III-IV and one that possibly restricted to level IV.[107] A single study[121] enrolled subjects with level I and II; three other studies[36,127,130] had predominately level I and II with less than 10 percent of subjects with level III, and none at level IV. Three studies[48,114,122] did not specify the NYHA classification of their subjects.

LVEF was not reported in seven studies[102,104,105,111,114,122,127]. Mean LVEF percentages were reported in 22 studies and varied between 50 percent,[115] 40 to 49 percent,[32,129] 30 to 39 percent,[12,23,36,107,113,118,119,123,123,126,130] and 20 to 29 percent.[25,108,109,112,117,120,125,128] Seven studies reported a threshold LVEF of less than 45 percent,[48,101,106,110,121] less than 40 percent,[124] and less than 30 percent.[30]

BNP and Cut Points. BNP was measured using the Triage method in 11 studies[48,107-109,111,112,114,119,125,128,189] and by Shionoria-IRMA method in the remaining 25 studies (see Tables 18 and 19). Four studies[112,125,126,128] also measured NT-proBNP using the Biomedica method. Results are described in the NT-proBNP section of this report.

The rationale for selecting the BNP cut points differed and as such, the values varied significantly (Table 18 and 19). Sixteen studies[12,30,32,36,101,106,110,117-121,123,124,126,130] selected the mean or median values as the cut point for categorizing high and low BNP groups . Eight studies[23,108,114,120,125,128,129,190] selected values based on ROC. Five studies categorized the sample BNP values into two levels,[127] three levels,[107,109] four levels,[119] and five levels.[122] Six studies[104,105,111-113,115] did not specify a threshold as they used the BNP values as a continuous variable in their statistical analyses. Three studies used other rationale for threshold selection including: previous literature reference,[48] 75th percentile value,[116] and an unspecified internal analysis.[102]

Definition of Outcomes. All studies with the exception of one,[48] had a primary outcome of mortality or a composite endpoint. These endpoints typically included death, other cardiac events, readmission or worsening HF. There were 21 studies[12,23,30,32,36,102,104,106,109,112,114,117,119-123,125-127,130] that evaluated either all-cause mortality, cardiac related mortality or both. There were 25 studies[23,25,101-103,105-108,110-120,123,124,126,128,129] that evaluated composite endpoints that included a mixture of fatal and non-fatal cardiac events. One study[116] evaluated the performance of BNP relative to the Heart Failure Survival Score. Most authors did not specify how the outcomes of death were verified or subsequent events (such as other events or re-admission to hospital) were evaluated.

Adjusted Results – Multiple Regression Analysis. Twenty-nine studies undertook Cox proportional hazards regression analyses and five studies undertook logistic regression analyses to evaluate the relationship between BNP levels and various outcomes (Table 18 and 19). For the studies using Cox regression analyses, three studies[32,111,115] presented only univariate analyses, 10 studies[101,105,110,112,113,122-124,126,127] presented only the results from multivariate analyses, and the remaining 16 studies[12,23,30,36,104,106-109,117,118,120,121,125,129,130] undertook both univariate and multivariate computations. Four studies undertook multivariate logistic regression[25,48,102,116] and one study[119] univariate logistic regression, to evaluate the strength of the association between levels of BNP and the outcomes of interest. A single study[114] reported unadjusted RRs and another study[121] undertook an unspecified type of linear regression.

BNP Studies with Mortality Outcomes. Table 18 details the 21 studies with the outcomes of all-cause mortality, cardiac mortality and sudden death. The results are expressed as both univariate and multivariate HR,[12,23,30,36,104,106,109,113,117,122,123,127] Chi square statistic and probabilities values,[12,32,102,120,125,126,130] beta values,[102,130] and unadjusted RR.[114] One study measured, but did not report, findings specific to mortality.[119] Some studies[102,123,125]reported the estimates of risk based on the log of the BNP levels, which makes interpretation of the magnitude somewhat limited. In general, there were 11 studies[12,23,30,36,106,109,113,123,125,127,130] that found baseline BNP levels to be significant predictors for mortality related outcomes after adjustment in multivariate models. For those studies that presented adjusted HR, the risk estimates varied from 2.48 (95 percent CI: 2.13 to 2.88)[106] to 7.2 (95 percent CI: 1.6 to 32.1),[30] with the majority point estimates clustering around 2.5 to 3.0. It should be noted that despite the differing cut points, (> 97 pg/mL,[106] > 172 pg/mL,[30] > 230 pg/mL,[114] > 260.4 pg/mL,[36] > 700 pg/mL,[32] 1000 pg/mL,[109] > 346 pg/mL,[127]), the multivariate models found baseline BNP to be a significant predictor of mortality outcomes. All these regression models used a variety of variables within their models, which makes comparisons across studies challenging.

Six of the studies evaluating mortality recruited decompensated HF patients,[12,23,102,112] emergency department patients,[32,114] or mixed patients.[114] Five of these studies reported 46 to 100 percent of patients in NYHA class III and IV suggesting relatively severe HF patients. Although all studies reported that BNP was a significant predictor of mortality, only one study[23]provided an estimate of the HR; the multivariate model included a variable of troponin T and baseline BNP. The log BNP had a HR = 3.11 (95 percent CI: 1.61 to 6.01, p = 0.0005).

One study reported unadjusted RR for HF death for baseline BNP greater than 230 pg/mL vs. less than 230 pg/mL: RR = 24.1 (95 percent CI: 6.3.5 to 491.1); for the outcome of cardiac death unadjusted baseline BNP greater than 230 pg/mL vs. less than 230 pg/mL: RR = 37.9 (95 percent CI: 5.7.5 to 755.8). The widely varying CI suggests instability with the estimate; therefore, results must be interpreted with caution.

There were six studies that found BNP levels to be not significant predictors of mortality based on univariate analyses alone,[32,126] or on multivariate analyses;[30,104,117,122] one study[123] found sudden unexpected death to be significant but not HF death. One of these studies[32] had a small sample size (n = 33) and 73 percent of patients were NYHA level IV. No clear trend from these studies can account for the non-significance.

BNP Studies with Composite Outcomes. Table 19 details the 27 studies with composite outcomes which included death in all but four publications.[111,113,118,128] The results are expressed as both univariate and multivariate HR,[23,25,106,110,115,117] chi square and probabilities values,[113,119,121,124,128,129,191] and unadjusted RR.[114] Some studies[23,102,118,119,123,128,129] reported the estimates of risk based on log BNP levels, which makes comparison with studies not using log values difficult.

In general, there were 9 studies[12,30,36,106,109,123,125,127,130] that found baseline BNP levels to be significant predictors for composite outcomes after adjustment in multivariate models. Two studies[105,111] with only univariate analyses showed baseline BNP levels to be not significant predictors and three studies (multivariate estimates[106,117] and univariate estimate[115]) showed only marginal significance.

For those studies that presented adjusted risk estimates for baseline BNP, the values varied from HR = 1.66 (95 percent CI: 1.36 to 2.04, p less than 0.0001)[110] to RR = 3.23 (95 percent CI: 1.32 to 7.94, p = 0.01)[25], with the majority point estimates clustering around 2.0. Three studies[23,108,123] included estimates of HR that combined levels of troponin I, troponin T and LVEF with baseline BNP. One study[114] reported unadjusted RR for HF events that varied from baseline BNP greater than 230 pg/mL vs. less than 230 pg/mL: RR = 15.5 (95 percent CI : 6.2 to 43.7) to BNP greater than 480 pg/mL vs. less than 230 pg/mL: RR = 8.2 (95 percent CI: 4.7 to 14.3).

Comparison of NT-proBNP and BNP. Six studies[41,103,112,125,126,192] evaluated both BNP and NT-proBNP levels within the same group of subjects. Van Beneden et al.[126] compared a small number of subjects who had mild to moderate HF (NYHA I-II) with severe HF patients (NYHA level IIII-IV). Their univariate analysis showed that NT-proBNP was a significant predictor of mortality. However, no association between BNP and mortality was observed using either assay method. Two studies evaluated both B-type natriuretic peptides in predominately NYHA level II patients (approximately 78 percent). One study[103] found log BNP levels significant in predicting worsening HF in both univariate and multivariate analyses while NT-proBNP was significant only in the univariate model. In contrast, a second study,[41] with mild to moderate HF subjects, found that BNP and NT-proBNP levels differed in their ability to predict 4-year mortality with respect to whether baseline levels, or measurement taken at last follow up, were considered. In this study, BNP was significant in the univariate analysis for baseline and significant for last follow up in the multivariate analysis; NT-proBNP was not significant at baseline in the univariate analysis but significant for the multivariate analysis that included last follow up NT-proBNP level. The findings of this study[41] would suggest that measures of either BNP or NT-proBNP may be independent predictors of mortality, but the sample size for this study was relatively small (n = 100).

Two other studies (based on three publications)[112,125,128] from the same research team evaluated BNP and NT-proBNP. With respect to predicting event free survival at 1 year in an ambulatory group of patients, one study[112] found both BNP and NT-proBNP were significant predictors at 1 year in univariate analysis. The subsequent multivariate analysis found four of the nine variables to be significant and included BNP, N-ANP, RAAS antagonists, and Living with

Heart Failure questionnaire. From the same research group, but in a different study cohort, Berger et al.,[125] using univariate analysis, found the log transformation of both B-type natriuretic peptides to be significant predictors of pump failure death; however, only the log of NT-proBNP was significant in multivariate analyses. A sub-analysis, which excluded patients with atrial fibrillation, showed that BNP was the best independent predictor of sudden death. Their findings suggest that the magnitude of the prognostic prediction is dependent on the specific mode of death and the specific form of the natriuretic peptide. A re-analysis of this same cohort of subjects was undertaken in a third study.[128] The sample was classified according to severity levels based on LVEF and NYHA classification; a multivariate analysis was undertaken to see which factors predicted combined death and urgent heart transplant (for each of the 3 years of follow up). For Group A (NYHA I-II, LVEF ≤ 20 percent) log BNP was significant in both year 2 and 3. For Group B (NYHA I-II, LVEF < 20 percent, or, NYHA III-IV, LVEF ≤ 20 percent) only the log BNP was a significant predictor for year 1, but only log NT-proBNP was significant for years 2 and 3. For Group C (NYHA III-IV, LVEF < 20 percent) both log BNP and log NT-proBNP were significant for year 1; only log NT-proBNP was a significant predictor for years 2 and 3. These results would suggest that the strength of prediction for the B-type natriuretic peptides is also dependent on the year of follow up and less so on the severity of the HF.

Overall, of the six studies evaluating both BNP and NT-proBNP, only two studies found both BNP and NT-proBNP to be independent predictors of mortality. In one study[128] year of follow up and group stratification, and in a second study[41] the timing of the B-type natriuretic peptide measurement, similarly altered the predictive ability. No clear pattern emerges to suggest superiority of one type of B-type natiruetic peptide relative to the other in these head to head studies.

Comparison of Studies That Evaluated Baseline and Predischarge Measures.

All studies with the exception of seven publications[36,41,107,111,118,119,124] evaluated only baseline BNP levels. One of these studies[36] evaluated outpatients and measured BNP levels at two time points with an interval of 8 to 12 months. Another study evaluated patients BNP and NT-proBNP levels at successive follow up intervals over a 4-year period.[41] Three[107,119,124] of these studies had severe HF patients (NYHA III-IV) and approximately LVEF less than 40 percent; a fourth study[111] had 88 percent of subjects at NYHA level III and IV (LVEF not reported). Logeart et al.,[107] which had the largest sample size of all these seven studies, found the univariate HR for each 100 pg/mL increase of BNP to be slightly larger for predischarge BNP levels (HR = 1.22, 95 percent CI: 1.15 to 1.30, p = 0.0001) than baseline BNP levels (HR = 1.06, 95 percent CI: 1.03 to 1.10, p = 0.0001) for the composite outcome (death and readmission). In addition, they demonstrated a gradient of increasing risk from the first quartile (0 to 130) to the last quartile (660 to 1725) with the latter having the largest HR risk estimate (HR = 13.77). Similarly, the adjusted HR in this study showed increasing risk for poor outcome with increasing predischarge ranges, with the highest threshold (> 700 pg/mL) having a HR = 15.2, (95 percent CI: 8.5 to 27). Hamada et al.[124] found predischarge BNP levels to be the only significant (p = 0.0086) predictor of re-hospitalization within 1 year in a multivariate analysis that included baseline admission BNP levels. Cheng et al.[119] undertook only univariate logistic regression and found admission BNP and discharge BNP to both be significant for the composite endpoint and 30 day readmission; however, the small sample in this study size did not permit a true multivariate analysis. Given the likely strong correlation between admission and discharge BNP levels, it would be important to use multivariate analyses to adjust for strong correlations between these two measures of BNP. Similarly, Bettencourt et al.[111] in a univariate analysis did

not find median levels of either admission BNP (> 541 pg/mL) or discharge BNP (> 321 pg/mL) to be significant predictors of their composite endpoint (death or readmission).

Cheng et al.[119] and a second study[118] specifically recruited for new onset or first episode of HF. However, Tamura et al.[118] measured BNP at discharge only and found the discharge log BNP to have the largest risk (HR = 2.656, p = 0.015) relative to the other variables significant in the model (NYHA class, LVEF, and left ventricular mass index) for predicting cardiac events.

A single study[36] evaluated patients in an outpatient clinic (sample was 93 percent NYHA level I-II) and measured BNP levels at initial visit and second time-point (8 to12 months later), as well as the change in BNP levels (per 100 pg/mL) and any BNP level increase (versus decrease) during follow up. However, they did not include discharge BNP as a unique variable in subsequent univariate or multivariate models. In this study, the change in BNP (HR = 1.34, 95 percent CI: 1.10 to 1.63) and change in NYHA class (HR = 6.68, 95 percent CI: 2.23 to 19.12) were the only significant variables in the multivariate model.

Kaplan Meier Survival Analyses. Twenty-seven studies[12,23,30,32,36,41,101,103-105,108-118,120-123,129,130] reported results from Kaplan Meier survival analyses using various cut points that were based primarily on median/mean or best values from ROC curves. All studies that undertook Kaplan Meier analysis, regardless of the outcome or cut point, found significant differences between the two groups.

Quality Assessment of Studies. For this research question, which evaluated prognosis, the eligible studies were based predominately on prospective cohort designs. As such, selection biases attributed to non-consecutive enrolment, and misclassification bias attributed to blinding, were chosen as the main criteria for methodological quality evaluation. Thirteen studies[30,104,105,107,108,112-114,118,120,121,129,130] selected patients in a consecutive manner. The remaining studies did not specify, and likely did not employ, this strategy to minimize bias as convenience samples were generally selected.

Attempts were made to evaluate the potential for misclassification bias through lack of blinding of clinicians who evaluated subjects or those who ascertained the endpoints. Blinding of the clinicians to the BNP level was undertaken in only four studies[23,36,102,115] and this minimized the potential for clinicians to systematically provide differential treatments or request additional tests. Blinding to NT-proBNP levels was not undertaken in any study; however, three studies[113,120,193] indicated that the outcome was judged by researchers external to the clinical setting and had some potential to minimize ascertainment bias.

Prognosis Studies Using NT-proBNP Levels

Study Design and Sample Characteristics of Studies. For those studies evaluating NT-proBNP, four were RCTs[41,136,138,140] and the remaining 14 were prospective cohort studies.[26,35,103,112,125,126,128,131-135,137,139] Six of these studies evaluated both NT-proBNP and BNP[41,103,112,125,126,128]. Two publications were based on the same COPERNICUS study[35,140] and an additional two publications reported on the same study cohort[125,128] with different follow up periods.

Only four studies[26,135,136,139] recruited patients that were admitted to hospital for acute episodes. The remaining 14 studies[35,41,103,112,125,126,128,131-134,137,138,140] indicated that patients were recruited from primary care or specialty clinics and outpatient settings (see Tables 20 and 21).

Sample sizes ranged from a low of 48[131] to a high of 2320 subjects.[133] The mean sample size for all 18 studies was 378 (± 596) and the median was 121. The mean age of study participants

clustered around 65 years but varied from 51 to 78 years; the widest age range spanned 64 years (40 to 104 years).[133]

Lengths of follow up varied greatly between the studies and the shortest time was 6 months[139] while the longest time was 92 months[126]. The mean or median follow up time varied from 7 to 12 months,[135,136] 13 to 24 months,[103,134] 25 to 48 months,[35,128,131,194] and greater than 48 months.[126] Several studies specified only endpoints of 6 months,[139] 12 months,[112,133,137] 17/18 months,[26,138] 24 months,[140] and 48 months[41] (Tables 19 and 20).

HF Diagnosis and Severity. The diagnosis of HF was established in a number of ways, and these included echocardiography (carried out as part of the study or obtained from previous medical records) in six studies,[35,112,125,132,133,140] ventriculography in four studies,[41,134,137,138] clinical evaluation (signs and symptoms or NYHA classification) in six studies,[103,126,131,135,136,139] and other methods in one study.[26] All studies used the NYHA classification, with the exception of one study[135] which used the Killip method, and three studies[35,133,140] which did not report any rating.

With respect to severity of HF, the majority of studies included subjects across all levels of the NYHA classification. The exception to this was one study[139] that restricted subjects to levels III-IV. A single study[112] enrolled subjects with predominately level II. Three studies[35,133,140] did not specify the NYHA classification of their subjects. A single study[135] used the Killup method of classification, and these patients varied from levels II to IV.

LVEF was not reported in four studies on admission.[26,135,136,139] Four studies[35,132,137,138] reported a threshold LVEF of less than 45 percent, five studies[112,125,126,128,134] less than 35 percent, and five studies[41,103,131,133,140] less than 25 percent.

NT-proBNP and Cut Points. NT-proBNP was measured in nine studies using the Elecsys method , six studies used the Biomedica method,[41,103,112,125,126,128] two used the Roche ELISA method, [135,137] and one study used the Christchurch method[138] (Tables 20 and 21). Six of these studies evaluated both NT-proBNP and BNP.[41,103,112,125,126,128]

From the two publications based on the COPERNICUS study, one of the reports[35] stated that a newly developed NT-proBNP Roche ELISA method was used and that samples would subsequently be retested using the Elecsys method. The re-analysis was published the same year but does not reference the previous report. Since this is the same cohort, we assume that the assay met our eligibility criteria but was not adequately reported.

Definition of Outcomes. Ten of these reports examined mortality as a discrete end point.[35,41,125,126,131,133,134,136,138,140] Nine studies[103,112,128,134-137,139,140] reported composite end point of death or worsening HF. The remaining studies evaluated the ability to predict recommendation of heart transplantation,[132] worsening HF alone,[138] and in one case no estimate of risk was provided.[26]

Adjusted results – Multiple Regression Analysis. One[26] study examined stratification with troponin level and presented no relative measure of risk such as a HR. However, it did make the limited statement that there were fewer events when NT-proBNP levels were below rather than above the median admission level (1357 pg/mL, $p < 0.01$).

Eleven studies undertook Cox proportional hazard regressions analyses and six studies undertook logistic regression analyses to evaluate the relationship between BNP levels and the relationship to the various outcomes. For the studies using Cox proportional hazard regression analyses, two studies[112,138] presented only multivariate estimates and the remaining studies undertook both univariate and multivariate computations. Six studies undertook multivariate

logistic regression[126,132,133,135-137] to evaluate the strength of the association between levels of BNP and the outcomes of interest. A single study[26] did not report estimates of risk.

NT-proBNP Studies With Mortality Outcomes. Eleven studies[35,41,112,125,126,131,133,134,136,138,140] evaluated mortality outcomes and these are detailed in Table 20. The results are expressed as both univariate and multivariate HR,[35,131,140] chi square statistic,[41,112,126,134] OR,[133,134,136]or not specified.[138] Some studies[41,126,131,133] reported the estimates of risk based on the log NT-proBNP levels. In general, all studies that undertook univariate or both univariate and multivariate analyses found NT-proBNP to be a significant predictor of mortality. One study[135] found multivariate estimate on a subsample with HF to be significant (OR = 5.30, 95 percent CI: 1.4 to 168.9, p = 0.026) but the CI was wide. For those studies that presented adjusted HR, the risk estimates varied from HR = 2.17 (NT-proBNP > 1767 pg/mL) (95 percent CI: 1.33 to 3.54, p < 0.02)[140] to HR = 9.35 (log NT-proBNP) (95 percent CI: 2.42 to 36.10, p = 0.001). These estimates encompass baseline, discharge and change of NT-proBNP levels.

NT-proBNP Studies With Composite Outcomes. Table 21 details the ten studies with the composite end points, which included death as a component of the outcome. The results are expressed as both univariate and multivariate HR,[139,140] chi square statistic,[103,112,128,134,137] OR,[134-136] or not specified.[195] One study[128] reported the estimates of risk based on the log NT-proBNP levels.

In general, there were seven studies[112,128,134-137,140] that found baseline, discharge or change levels of NT-proBNP levels to be significant predictors for composite outcomes after adjustment in multivariate models. Two studies[103,139] showed marginal or no statistical significance. All these regression models used a variety of variables within their models, which makes comparisons across studies challenging.

For those studies that presented adjusted risk estimates for NT-proBNP, the values varied from HR = 2.11 (95 percent CI: 1.54 to 2.90, p < 0.0001) for NT-proBNP greater than 1767 pg/mL,[140] to HR = 5.96 (95 percent CI: 3.23 to 11.01) for change in NT-proBNP vs. decrease greater than 30 percent or increase greater than 30 percent.

Quality Assessment of Studies. As with the BNP studies, potential for selection bias (attributed to non-consecutive enrolment) and misclassification bias (attributed to blinding) were chosen as the main criteria for methodological quality evaluation. Eight studies[26,112,132-135,137,139] selected patients in a consecutive manner. The remaining studies did not specify and likely did not employ this strategy to minimize bias, as convenience samples were generally selected. Blinding of the clinicians or the investigators to the NT-proBNP levels with respect to the outcomes was undertaken in only three studies[132,136,139] suggesting some potential for ascertainment bias for of the outcome.

Question 3b: What Are the Screening Performance Characteristics of BNP or NT-proBNP in General Asymptomatic Populations?

Definition of Screening

A screening test can be used in defined populations who need not believe that they are at risk of a disease or that they are already affected by it or by its complications. It may also be used in clinical practice in individuals who do not have established or overt disease, but who may have one or more risk factors for the disease. In this review, a screening test was defined as being used to detect preclinical cardiac dysfunction, systolic or diastolic, in general asymptomatic population.

Design and Sample Characteristics

There were eight studies[5,74,122,141-145] identified in populations apparently without established or overt disease (or heart failure). Two studies had no sensitivity or specificity data.[74,122] Six studies had relevant data,[5,141-145] two were cross-sectional[141,143] and four were prospective cohort studies.[5,142,144,145] The age of the population included in these six studies ranged between 40 and 84. All but one study[145] evaluated BNP.

Study Outcomes

Although, these studies using BNP and NT-proBNP for screening focused primarily on LVD, there were differences in the specific outcomes with respect to the type and level of severity. One study[5] evaluated preclinical ventricular dysfunction, both diastolic and systolic components, (EF at < 40 percent); similarly, another study[141] evaluated left ventricular systolic dysfunction alone (EF at < 40 percent). One study[143] evaluated asymptomatic systolic (EF < 55 percent) and diastolic dysfunction (diastolic dominant pulmonary vein flow with EF of $\geq$ 55 percent).

Other studies broadened the types of dysfunction. One study[142] evaluated cardiac dysfunction (defined as left ventricular systolic and diastolic, unknown LVD, and valvular dysfunction), while another study[144] used three outcomes that included left ventricular mass, EF of less than 50 percent and moderate to severe LVSD (EF < 40 percent). The sole study[145] evaluating NT-proBNP evaluated the outcomes of LVSD, mortality, chronic heart failure admissions, and other cardiac admissions.

Screening Properties

To ensure comparability of the test characteristics, the sensitivity, specificity, LR+ and LR-, and AUC are included (Table 22), either as listed in the original publications or calculated[141,142,145] from the available data. Comments on the performance of the index test are based on a LR+ greater than 10 or LR- less than 0.1 and AUC greater than 0.8 providing convincing evidence for accuracy. Moderate to strong evidence for accuracy is provided by a LR+ greater than 5 or LR- less than 0.2 and AUC 0.70 to 0.80. Poor evidence for accuracy comes from LR+ less than 5, LR- greater than 0.2 and AUC less than 0.70.[168]

The study by Redfield et al.[5] showed the AUC for detection of LVEF less than 50 percent or mild diastolic dysfunction were consistently less than 0.70, so the authors then confined the use of BNP to detecting an EF less than 40 percent or moderate to severe diastolic dysfunction. This study explored a variety of factors with respect to screening properties including systolic versus diastolic dysfunction within these categories: age over 65 years, gender, and high-risk groups. For the diastolic category alone, the subgroup of moderate to severe dysfunction had some or all diagnostic properties assessed. The prevalence rates varied significantly within these sub groupings, with the lowest values in the general population and women with systolic dysfunction, and the greatest rates for the population with diastolic dysfunction of moderate to severe levels (Table 22). The corresponding diagnostic estimates of accuracy reflected moderate strength at best for LR+ (7.4) for two of the thirty subgroups they evaluated; similarly, the LR- reflected poor accuracy. With the exception of systolic dysfunction in high-risk men, the AUC was generally in the moderate range. In general, within the systolic and diastolic groups there were no differences due to gender and age. Overall this would suggest poor detection characteristics for BNP as a screening test. The low prevalence of preclinical systolic dysfunction and the observed specificity would result in a large number of screened people requiring an echocardiogram and nearly all of them would be negative. Using a higher cut point, for example one based on the upper normal value, would result in fewer confirmatory echocardiograms but would miss 30 percent or more of people with preclinical systolic dysfunction.

These results are similar to those of Vasan et al.[144] which showed the test characteristics of BNP are limited at each of the three discriminatory levels; this study only reported AUC as a metric of accuracy. Overall, the AUC for BNP was less than 0.75 for elevated LSVD and left ventricular mass in both genders. This estimate exceeded 0.80 in high-risk women, but this was based on a very small sample size and the confidence interval was wide suggesting caution in interpretation. When maximizing the sums of sensitivity and specificity the cut point for women is BNP 27 pg/mL for LV mass greater than 90th percentile, it is 34 pg/mL for any LVSD and is also 34 pg/mL for moderate to severe LVSD (< 40 percent). For LV mass this gives a sensitivity of 26 percent, specificity 86 percent, LR+ 1.82, LR- 0.86. For any LVSD it gives a sensitivity of 26 percent, specificity 89 percent, LR+ 2.49, LR- 0.82, and for moderate to severe LVSD (< 40 percent) the sensitivity is 80 percent, specificity 90 percent, LR+ 7.67, LR- 0.22 (Table 22). The performance of the test improved in women but not in men when select high-risk subgroups were targeted. Discriminatory limits that were based on a high specificity (95 percent) give better positive predictive values and LR, yet identified less than one third of the participants who had elevated LV mass or LVSD. Both these studies[5,144] highlight the need for different BNP levels for women.

In the study by Hedberg et al.[141] a BNP greater than 28 pg/mL gave the highest specificity at a sensitivity greater than 95 percent in detecting LVSD, but the highest accuracy was found with a concentration greater than 73 pg/mL in a random sample of subjects 75 years of age. Both of these values produce negative predictive values of 98 to 99 percent but the routine predictive value for BNP greater than 28 pg/mL is 13 percent (95 percent CI: 9 to 19) and for BNP greater than 73 pg/mL it is 34 percent (95 percent CI: 24 to 47), and the latter cut point will miss more individuals with preclinical systolic dysfunction. The combination of ECG and BNP greater than 28 pg/mL and BNP less than 28 pg/mL found LVSD in less than 1 percent of the study population irrespective of the BNP concentrations, leading to the conclusion that the BNP had

screening value in addition to the ECG, but only in those with abnormal ECG's. Overall, the AUC for either cut point of greater than 731 or greater than 28 show the same AUC (0.88).

The screening test characteristics for BNP for systolic and/or diastolic dysfunction are also poor in one study[142] in which a BNP value of 20 pg/mL was pre-selected. The overall negative predictive value was 57 percent (95 percent CI: 48 to 65) and the accuracy of BNP did not change with higher cut points but these produced decreasing sensitivity and negative predictive value. The AUC were not estimated, but the LRs indicate poor evidence for accuracy. Another study[143] of patients with stable CAD and a pre-selected BNP cut point of 100 pg/mL had all of the participants undergo an extensive examination and an exercise stress treadmill test to ensure no overt symptoms of HF. The test characteristics for BNP were poor for systolic dysfunction with a 38 percent sensitivity, 80 percent specificity, LR+ 1.9 (95 percent CI: 1.2 to 2.9), LR- 0.8 (95 percent CI: 0.60 to 1.00) and AUC 0.59 (95 percent CI: 0.49 to 0.69). They were also poor for diastolic dysfunction with a 55 percent sensitivity, 85 percent specificity, LR+ 3.8 (95 percent CI: 2.4 to 5.9), LR- 0.8 (95 percent CI: 0.4 to 0.8 and AUC 0.79 (95 percent CI: 0.71 to 0.87).

Only one study[145] used NT-proBNP as the index test and accuracy was evaluated with respect to LVEF levels, European Society Cardiology (ESC) criteria for HF and further stratified by age over 70 years, and high risk medical history. The subgroup classified by ESC criteria, LVEF less than 40 percent, and age over 70 years, showed very strong evidence for accuracy (LR+ 10.71, LR- 0.10, AUC 94); values for a similar group (without the age restriction) showed moderately high values (Table 22). This suggests that for these groups there is some potential benefit for screening for LVSD. Using the Cox proportional hazard model, Log NT-proBNP (HR = 5.70), and male gender (HR = 3.10) were shown to be significant independent predictors of mortality in patients that were followed up for a median of 805 days. Log NT-proBNP (HR = 13.83), male gender (HR = 2.71) and dyspnea (HR = 1.45) were significant independent predictors of admission for heart failure. Finally, log NT-proBNP (HR = 3.69), abnormal ECG (HR = 2.56) and history of ischemic heart disease (HR = 1.9) were independent predictors of other cardiac admissions, eliminating LVEF from all prognostic models.

Quality Assessment of Studies

BNP was the index test in five[5,141-144] of the accepted studies and NT-proBNP in the sixth one.[145] In all six echocardiography was a reference test. The subjects were either randomly selected from the community,[5,141] were part of another prospective community cohort,[144,145] or cross-sectional study.[141,143] In the selected studies subjects may have had risk factors for HF, such as stable CAD, but none had overt or symptomatic HF. The patient samples were consecutively or randomly selected, the index and reference tests were clearly described, the index test was not available to those making the clinical diagnosis, the study populations were not classified by disease state, and appropriate descriptions were given as to the steps taken to ensure that the subjects did not have overt cardiac dysfunction.

Question 4: Can BNP or NT-proBNP Measurement Be Used To Monitor Response to Therapy?

Sample and Design Characteristics

There were 18 studies meeting the eligibility criteria to be included in this section.[31,37-47,110,146-150] In brief, the included studies enrolled chronic HF patients with at least three B-type natriuretic peptide measurements over time. The LVEF was reported as less than 25 percent,[41,150] ≤ 35 percent,[149] ≤ 40 percent,[39,42,43,43-47,110,147,148] less than 45 percent,[37,38] less than 50 percent;[31] it was not reported in two studies.[40,146] A total of nine of these papers reported the change in BNP or NT-proBNP and related the change to other outcomes including cardiac function, exercise capacity, symptoms or clinical events.[31,37,38,41,44,110,148-150] The other nine studies reported changes in BNP or NT-proBNP and also may have reported the changes in other variables; however, there was no determination in these studies of the relationship between change in the B-type natriuretic peptide and change in these other variables.[39,43,45-47,146,147,196,197] Five[39,43,45,46,110] of the 18 papers that reported findings, examined in different ways, data from a recently published large randomized clinical trial (Val-HeFT). Two other studies also used the same database[147,148], but one of these was a comparison of two different NT-proBNP methods.[147] Although all these studies described collection of at least three B-type natriuretic peptide measurements, there were only ten studies that provided values for each of the time points.[31,37-41,44,146,147,149]

Response to Therapy

In the studies where change in BNP or NT-proBNP was related to other clinical findings, it was found that the B-type natriuretic peptide was related to at least one other variable in seven of the nine studies (Table 23). A study by Murdoch et al. was the first to evaluate whether plasma BNP would be useful to tailor therapy in patients with chronic stable HF (BNP guided group).[149] They randomized 20 patients to receive optimization ACE inhibitor therapy based on serial plasma BNP measures or clinical assessment with up-titration of ACE inhibitor to the target levels used in clinical trials, over the 8 week course of the study. They found only the BNP driven approach was associated with greater reductions in plasma BNP concentration throughout the course of the study and that there was a significantly greater suppression when compared to the clinical assessment group after 4 weeks of therapy ($p = 0.03$), but not at 8 weeks ($p = 0.73$) (Figure 7D). Although there was a decrease in BNP observed, there were no significant changes observed in haemodynamics within either group; however, heart rate was significantly different between groups ($p = 0.02$).

Troughton et al. examined whether titration of treatment to reduce plasma NT-proBNP concentrations in systolic HF patients (NT-proBNP guided group) would be superior to clinically based treatment.[148] There were 69 NYHA class II-IV HF patients with LVEF less than 40 percent recruited into the study, with a median follow up of 9.5 months. Although the mean NT-proBNP concentrations decreased to 668 pg/mL below baseline in the NT-proBNP guided group, compared with 25 pg/mL in the clinical group, this difference was not significant ($p = 0.16$) (Figure 7D). The BNP guided group had fewer cardiovascular events (death, hospital admission, or HF decompensation) compared to the clinical group (19 versus 54; $p = 0.02$). Changes in left

ventricular function, quality-of-life score, 6 minute walk test, blood pressure, renal function, and adverse events were similar in both groups.

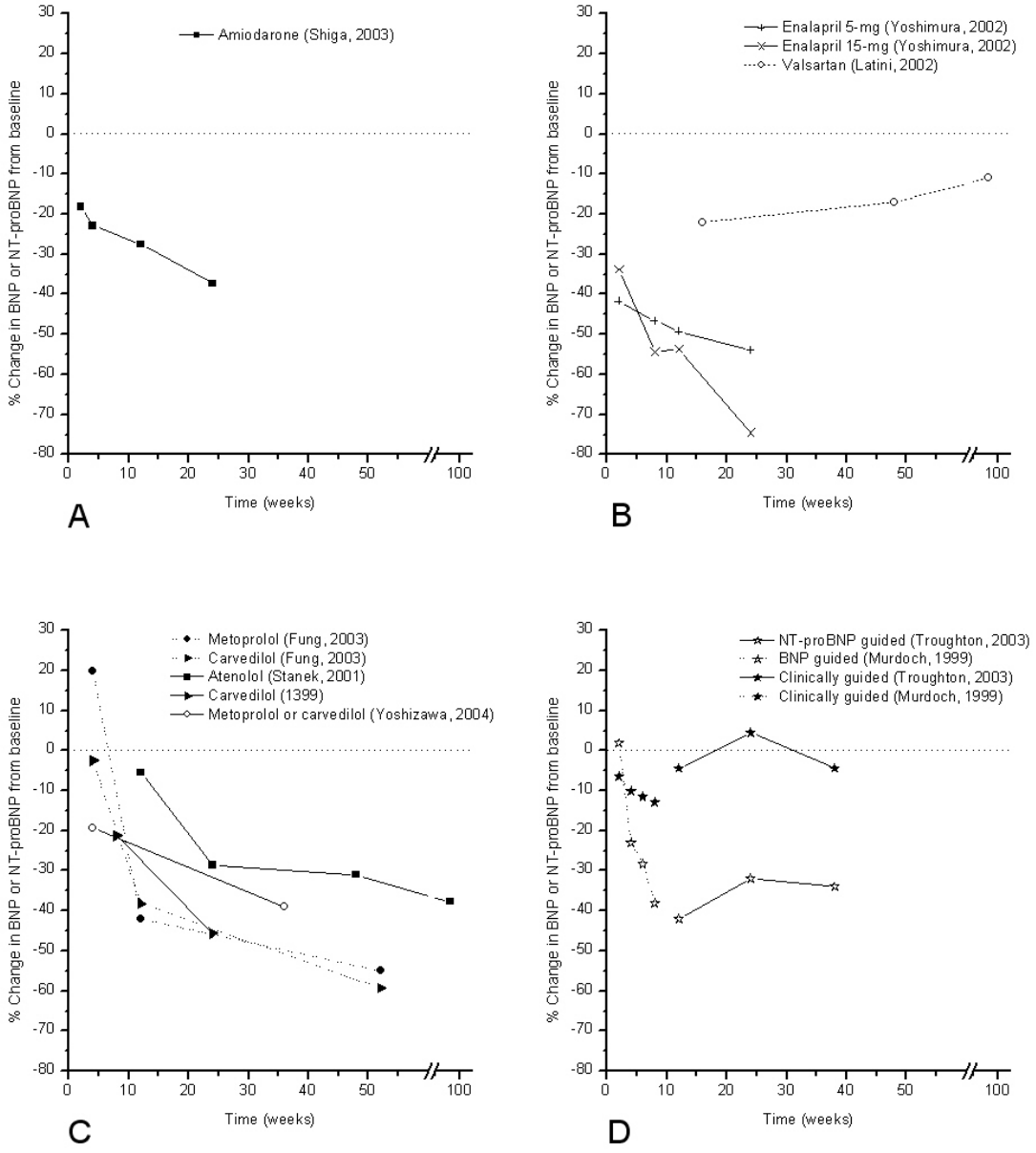
Three additional studies have demonstrated that changes in BNP or NT-proBNP concentrations relate to changes in mortality and morbidity.[37,41,110] Two of these three papers had study sizes of less than 100 patients.[37,41] The third study[110] was part of a large clinical trial and the BNP was measured at baseline in 4305 NYHA class II-IV HF patients (Val-HeFT). Follow up measurements were made at 4, 12, and 24 months after randomization. They found the baseline BNP predicted all-cause mortality and first morbid events. The study results demonstrated at study end that the group taking valsartan (the study drug) had a decline in BNP (decreased by 21 ± 5 pg/mL) compared to the placebo group (increased by 23 ±5 pg/mL). Patients with the greatest percent decrease in BNP from baseline to 4 months had the lowest, whereas patients with the greatest percent increase in BNP had the highest all-cause mortality and first morbid events.

In six of the papers, change in NT-proBNP or BNP was related to change in cardiac function, functional capacity or quality-of-life.[31,37,38,44,148,149] In three of these papers, despite changes in BNP or NT-proBNP, there was no relationship to changes in these other variables.[37,148,149] The two exceptions were blood pressure ($p = 0.015$)[148] and heart rate ($p = 0.02$).[149] One of these studies demonstrated changes in left ventricular end diastolic dimension and end systolic dimension, but no change in BNP concentrations.[44] This study also found a significant difference in BNP change in patients with HF of non-ischemic etiology in both early and late phases ($p < 0.05$), but not in those of ischemic etiology. In this study all the patients were receiving beta blocker therapy.

There were two studies[31,38] demonstrating that the changes in BNP or NT-proBNP were related to changes in cardiac function. Patients with ischemic heart disease treated with metoprolol showed significant differences at 12 weeks and 1 year from baseline for LVEF (32 percent and 38 percent, respectively, $p < 0.01$), symptom questionnaire score (3.9 and 3.6, $p < 0.01$) and 6 minute walk test (1310 and 1269 feet respectively, $p < 0.05$).[38] In the other study, patients with idiopathic dilated cardiomyopathy treated with carvedilol demonstrated significant differences in all parameters measured.[31] These parameters included NYHA ($r = 0.50$, $p < 0.0001$), systolic blood pressure ($r = 0.31$, $p = 0.014$), heart rate ($r = 0.43$, $p = 0.0007$), LVEDD ($r = 0.84$, $p < 0.0001$), LVESD ($r = 0.84$, $p < 0.0001$), LVEF ($r = -0.60$, $p < 0.0001$), and LV mass index ($r = 0.66$, $p < 0.0001$).

There were nine papers that examined the response of BNP or NT-proBNP to different types of HF therapy.[39,40,42,43,45-47,146,150] In four of these studies BNP or NT-proBNP changes were related to changes in HF therapy.[40,42,146,150] These studies demonstrated that the B-type natriuretic peptide concentration varied in response to the intensity of drug therapy[40,42,146,150] or the use of various types of left ventricular assist devices.[150] The other studies [39,45-47] demonstrated that HF patients receiving active therapy had a greater reduction in B-type natriuretic peptide concentration than those not taking the therapy. However, none of these studies examined whether BNP or NT-proBNP were related to change in drug dose.

Figure 7. Change in BNP or NT-proBNP concentration after treatments



Change in BNP or NT-proBNP concentration after treatment with A) an antiarrythmic (amiodarone), B) an angiotensin converting enzyme inhibitor (enalapril) and an angiotensin receptor blocker (valsartan), C) beta-blockers (atenolol, carvediolol, metoprolol), and D) heart failure therapy that is clinically or BNP guided. The dashed line in each figure indicates no change from baseline.

Figure 7 is a compilation of all studies with abstractable data showing percent change from baseline in BNP[31,37,39,40,44,149] or NT-proBNP[38,41,147] concentration with time and drug therapy. There were four studies, which treated patients with beta blockers,[31,38,41,44] and all showed a decrease in BNP or NT-proBNP with time. The metoprolol and carvedilol treated patients[31,38,44] were very similar in their changes to BNP or NT-proBNP levels over time in contrast to the atenolol treated patients.[41] The one study with the antiarrhythmic amiodarone showed a rate of change similar to the beta blocker group.[37] Valsartan treated patients had lower BNP values from baseline at 4 months after treatment but exhibited a slight increase over time.[39] The ACE inhibitor enalapril showed a greater rate of change and greatest overall change from baseline compared to all treatments.[40] The high dose treatment group showed a similar change in BNP as those in the low dose treatment group up to 12 weeks but there was a large departure at 24 weeks (75 percent versus 54 percent, respectively). Of these nine studies, only four included a placebo group.[31,37,39,41] In two of these studies, the placebo groups[37,41] showed no significant change from baseline at any time point.

In the valsartan therapy study,[39] all time points levels in the placebo group were higher than the treated group and increased with time. The carvedilol therapy study with a placebo group[31] provided data at baseline and end of study only. Both the placebo and carvedilol treated groups had significantly lower BNP levels at six months compared to baseline and were not significantly different from each other over time ($p = 0.18$).

There were two studies which assessed change in BNP[149] and NT-proBNP[147] in patients guided by the B-type natriuretic peptide level compared to patients following a clinically driven protocol (Table 23). Both studies demonstrated that the B-type natriuretic peptide guided therapy groups sustained faster and lower concentrations. The study that did not use any beta blocker therapy showed the smallest change overall, particularly in the clinically guided treatment group.[147] Overall, Figure 7 shows that drug treatment decreases B-type natriuretic peptide levels in a time-dependent mode indicating that BNP or NT-proBNP might be reasonably good markers for monitoring the effect of treatment of chronic HF patients.

Quality Assessment of Studies

Of the 18 studies, 12 were RCTs. The quality of these 12 studies were evaluated using the Jadad scale[167]. Two studies[147,148] scored 4, one study[41] scored 3. The remaining studies[39,40,43-47,110,149] scored less than 3, indicating poor quality.

Table 3. The effect and association of various biological determinants on BNP and NT-proBNP levels.*

Determinant	Increase		None		Decrease	
	BNP	NT-proBNP	BNP	NT-proBNP	BNP	NT-proBNP
Demographic Characteristics						
African-American			1			
Age	8	4	2			
Female	2	3	2	4		
Smoker, current				2		
Cardiac Disease						
Acute coronary syndrome		1				
Acute right heart failure (no CPE group)			1			
Angina, stable		1		1		
Aortic stenosis		3				
Arrhythmia		1				
Atrial fibrillation			1			
Cardiac decompensation		1				
Cardiogenic pulmonary edema (CPE)	1					
Diastolic dysfunction	3	1			2[a]	1[a]
Dilated cardiomyopathy			1			
Hypertension, with diastolic dysfunction	2					
Ischemic heart disease		1	1			
LAD culprit lesion	1					
LAD lesion, proximal vs mid	1					
Left ventricular mass	1					
Multi-vessel disease		1				
Myocardial infarction	1	2				
Myocardial infarction, history		2				
Previous CHF		1				
Revascularization		1				
Valvular disease		1				
Non–cardiac Disease						
Diabetes		1		3		
Diabetic nephropathy		1				
Diabetic retinopathy				1		
Dyspnea, non-cardiac	2	1				
Hyperlipidemia				1		1
Hypertension	2	3		1		
Hypertension, duration			1			
Lung disease					1[b]	1[c]
Peripheral vascular disease				1		
Stroke		1				
Stroke and TIA				1		

Table 3. The effect and association of various biological determinants on BNP and NT-proBNP levels.*

Determinant	Increase		None		Decrease	
	BNP	NT-proBNP	BNP	NT-proBNP	BNP	NT-proBNP
Biochemical and Hematological Markers						
ACE genotype DD		1				
Adrenomedullin				1		
Aldosterone			1			
ANP	3	1				
Big endothelin-1	2					
cGMP	1	1				
Cholesterol			1	1		
Creatinine kinase			1			
Creatinine kinase-MB	2	1	1			
C-reactive protein		3				
Creatinine	2	3	2			
Endothelin-1		1				
Epinephrine	1					
Glucose, random	1					
Glucose, fasting				1		
HbA1c			1	1		
Hemoglobin						1
Interleukin-6		1				
Lymphocytes			1		1	
Myoglobin		1				
Norepinephrine	5	1				
NT-proANP	5	2				
Osteoprotegerin		1				
Plasma renin activity					1	
Relaxin				1		
ST2, soluble receptor			1			
Total protein			1			
Troponin-I	3			1		
Troponin-T	2	9				
Functional and Physiologic Measures						
Activities of daily living score	1					
BMI			2			
Creatinine clearance			1			
Exercise						1[d]
Glomerular filtration rate					2	
Weight						1
Hemodynamic, echocardiographic and electrocardiographic measures						
Blood pressure			3			
Blood pressure, systolic		2	2			

Table 3. The effect and association of various biological determinants on BNP and NT-proBNP levels.*

Determinant	Increase		None		Decrease	
	BNP	NT-proBNP	BNP	NT-proBNP	BNP	NT-proBNP
Cardiac index			1			
E/A ratio			2			
Fibrosis			1			
Fractional shortening			2			
Heart rate	2	1	2			
Left ventricular diastolic dimension	1					
Left ventricular end-systolic diameter	1					
Left ventricular mass index	6					
Left ventricular relative wall thickness			1			
MIBG activity					1	
Mid-wall left ventricular fractional shortening			1			
PCWP	1					
Perfusion defect size	1					
Pulmonary arterial pressure	1					
Pulse pressure	1					
Restrictive filling pattern of deceleration time					1	
Right atrial pressure	1					
ST-segment depression		2				
Telesystolic volume			1			
Drug treatment						
Amiodarone					2	
Atenolol					1	
Beta-blockers			1		1	
Carvedilol			2	1		2
Enalapril					3	
Furosemide, dosage			1			
Lisinopril, dosage					1	
Metoprolol			1			
Perindopril				1		
Valsartan					4	
Treatment – Nondrug						
Left ventricular assist device					1	

Abbreviations: ACE=angiotensin converting enzyme; ANP=atrial natriuretic peptide; BMI=body mass index; E/A=early to late(atrial) echocardiographic phases of ventricular filling; cGMP=cyclic guanosine mononucleotide phosphate; CHF=congestive heart failure; CPE=cardiogenic pulmonary edema; HbA1c=hemoglobin A1c; LAD=left anterior descending coronary artery; MIBG=^{123}I-etaiodobenzylguanidine; PCWP=pulmocapillary wedge pressure; TIA=transient ischemic attack

* Study details for the determinants in alphabetical order including sample size, method, type, statistical method and values can be found in Evidence Table 1 in Appendix C.

** The numbers given for each determinant refer to the number of associations abstracted from the studies according to effect and type of B-type natriuretic peptide**.**

[a] = Compared to systolic dysfunction; [b] = Compared to CHF; [c] = CHF and CHF + lung disease; [d] = Increased physical activity

Table 4: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in emergency or urgent care settings

Report	Study Design	Study Population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Barcarse[48] 2004	Prospective Cohort	Convenience sample VA with SOB	98 65 y 100%	58	1 Cardiologist review	clinical	BNP(2)	110	96*	91*	10.67	0.04	0.979
								170	82	94	13.67	0.19	0.979
								300	70	99	70.00	0.30	0.979
Bayes-Genis[16] 2004	Prospective Cohort	SOB NYHA III or IV	89 71 y 54%	83	2 Cardiologists review	clinical	NT-ProBNP (9)	>254	98.6	46.7	1.85	0.03	0.957
								>423	95.7	73.3	3.58	0.06	0.957
								>592	94.3	73.3	3.53	0.08	0.957
								>761	91.4	73.3	3.42	0.12	0.957
								>973	91.4	93.3	13.64	0.09	0.957
								>1099	90	93.3	13.43	0.11	0.957
Dao[56] 2001	Cross-sectional	SOB	250 63 y 94%	39	2 Cardiologists review	clinical	BNP(2)	80	98	92	12.25	0.02	0.98
								100	94	94	15.67	0.06	0.98
								115	90	96	22.50	0.10	0.98
								120	90	96	22.50	0.10	0.98
								150	87	97	29.00	0.13	0.98
Jose[53] 2003	Cross-sectional	SOB of > 6 m	119 54 y 66%	61	NR	Framingham Echo	NT-ProBNP (8)	1691	97	89	8.82	0.03	0.94
Knudsen[50] 2004	Diagnostic	SOB Male	69 74 y 100%	58	2 Cardiologists review	clinical	BNP(2)	≥50	95	37.9	1.53	0.13	0.9
								≥100	90	55.2	2.01	0.18	0.9
								≥150	92.5	62.1	2.44	0.12	0.9
								≥200	90	72.4	3.26	0.14	0.9
		SOB Female	86 78 y 0%	41	2 Cardiologists review	clinical	BNP(2)	≥50	100	37.3	1.59	0.00	0.86
								≥100	94.3	54.9	2.09	0.10	0.86
								≥150	91.4	58.8	2.22	0.15	0.86
								≥200	88.6	62.7	2.38	0.18	0.86
		SOB Age ≥ 76 y	NR NR NR	NR	2 Cardiologists review	clinical	BNP(2)	NR	NR	NR	NR	NR	0.82
		SOB Age < 76 y	NR NR NR	NR	2 Cardiologists review	clinical	BNP(2)	NR	NR	NR	NR	NR	0.88

Table 4: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in emergency or urgent care settings (continued)

Report	Study Design	Study Population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Knudsen[51] 2004	Cross-sectional	SOB	880 64 y 55%	51	2 Cardiologists review	clinical	BNP(2)	≥100	90	75	3.66	0.14	NR
								≥200	80	87	6.08	0.23	NR
								≥300	71	90	7.18	0.32	NR
								≥400	64	92	8.10	0.39	NR
Lainchbury[7] 2003	Diagnostic	SOB	205 70 y 49%	34	2 Cardiologists review	clinical	NT-ProBNP (9)	1184	87	71	3.00	0.18	0.89
								2030	83	82	4.61	0.21	0.89
								2906	80	87	6.15	0.23	0.89
								3721	74	90	7.40	0.29	0.89
								4567	92	68	2.88	0.12	0.89
							BNP(2)	69	97	44	1.73	0.07	0.89
								104	97	49	1.90	0.06	0.89
								208	94	70	3.13	0.09	0.89
								277	83	78	3.77	0.22	0.89
								346	77	84	4.81	0.27	0.89
Logeart[17] 2002	Cross-sectional	SOB	163 67 y 67%	71	2 Cardiologists and 1 Pneumologist review	clinical	BNP(2)	80	97	27	1.33	0.11	0.93
								100	96	31	1.39	0.13	0.93
								150	93	45	1.69	0.16	0.93
								200	93	56	2.11	0.13	0.93
								250	91	68	2.84	0.13	0.93
								300	88	87	6.77	0.14	0.93
								400	79	93	11.29	0.23	0.93
Maisel[18] 2002	Cross-sectional	SOB	1586 64 y 56%	47	2 Cardiologists review	clinical	BNP(2)	≥50	97	62	2.55	0.05	0.91
								≥80	93	74	3.58	0.09	0.91
								≥100	90	76	3.75	0.13	0.91
								≥125	87	79	4.14	0.16	0.91
								≥150	85	83	5.00	0.18	0.91

Table 4: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in emergency or urgent care settings (continued)

Report	Study Design	Study Population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Maisel[49] 2004	Prospective Cohort	SOB	1586 64 y 56%	47	2 Cardiologists review	clinical	BNP(2)	≥100	90.4	72.9	3.34	0.13	NR
								≥200	81.4	85.1	NR	NR	NR
								≥300	72.5	88.6	NR	NR	NR
								≥400	62.7	91.1	NR	NR	NR
		SOB 18-69 y	NR NR NR	NR	2 Cardiologists review	clinical	BNP(2)	≥100	86	82	.69	0.17	0.915
								≥200	77	91	8.45	0.25	0.915
								≥300	69	94	11.10	0.33	0.915
								≥400	60	95	11.23	0.43	0.915
		SOB 70-105 y	NR NR NR	NR	2 Cardiologists review	clinical	BNP(2)	≥100	94	53	2.00	0.12	0.844
								≥200	85	72	3.03	0.21	0.844
								≥300	75	77	3.27	0.32	0.844
								≥400	65	83	3.85	0.42	0.844
		SOB Male	883 NR 100%	48	2 Cardiologists review	clinical	BNP(2)	≥100	92	76	3.84	0.10	0.918
								≥200	83	88	6.93	0.18	0.918
								≥300	73	90	7.49	0.30	0.918
								≥400	64	93	9.00	0.39	0.918
		SOB Female	703 NR 0%	46	2 Cardiologists review	clinical	BNP(2)	≥100	88	59	2.16	0.20	0.87
								≥200	78	82	4.27	0.27	0.87
								≥300	72	87	5.40	0.32	0.87
								≥400	61	89	5.55	0.44	0.87
		SOB White race	773 NR NR	50	2 Cardiologists review	clinical	BNP(2)	≥100	93	69	2.96	0.10	0.888
								≥200	82	82	4.63	0.21	0.888
								≥300	72	86	5.11	0.33	0.888
								≥400	60	90	5.86	0.44	0.888
		SOB Black race	715 NR NR	44	2 Cardiologists review	clinical	BNP(2)	≥100	87	76	3.61	0.17	0.903
								≥200	81	88	6.45	0.22	0.903
								≥300	74	91	8.24	0.28	0.903
								≥400	66	93	8.79	0.37	0.903

Table 4: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in emergency or urgent care settings (continued)

Report	Study Design	Study Population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
McCullough[54] 2002	Diagnostic	SOB	1538 64 y 56%	47	2 Cardiologists review	clinical	BNP(2)	≥100	90	73	3.33	0.14	0.9
Morrison[55] 2002	Cross-sectional	SOB	321 NR NR	42	2 Cardiologists review	clinical	BNP(2)	94	98	86	7.0	.023	0.99
								105	94	86	6.71	.069	0.99
								135	90	90	9.00	0.11	0.99
								195	85	94	14.16	.159	0.99
								240	79	96	19.75	.218	0.99
Ray[57] 2004	Cross-sectional	SOB > 65 y Respiration measures cutoffs	308 80 y 49%	45.7	2 of: Cardiologist Pulmonologist GM Internist Geriatrician ED Physician	clinical	BNP(2)	≥100	90	59	2.20	0.17	0.67
								≥150	85	71	2.93	0.21	0.67
								≥200	82	84	5.13	0.21	0.67
								≥250	78	90	7.80	0.24	0.67
								≥300	72	92	9.00	0.30	0.67
								≥350	67	92	8.38	0.36	0.67
								≥400	60	95	12.00	0.42	0.67
Villacorta[52] 2002	Cross-sectional	SOB	70 72 y 47%	51	1 Cardiologist review	clinical	BNP(2)	200	100	97	33.33	0.00	0.99

Abbreviations: ACS=acute coronary syndrome, AU ROC=area under the receiver operator characteristics curve, ED=emergency department, LR- =negative likelihood ratio, LR+ =positive likelihood ratio, NR=not reported, Sens% =sensitivity(%), SOB=shortness of breath, Spec% =specificity, uLL=unadjusted log likelihood, VA=Veterans Administration., y=years.

- estimated from ROC curve

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide

** Mean age if given in report

Table 5: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of or with HF in outpatient or specialty clinic settings

Report	Study design	Study population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index Test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Bettencourt[11] 2000	Cross-sectional	Suspected HF	100 69 y 54%	100	Clinical by 2 Internists and 1 Cardiologist	HF	BNP(1)	NR	NR	NR	NR	NR	0.92
						Systolic HF	BNP(1)	NR	NR	NR	NR	NR	0.78
						Diastolic HF	BNP(1)	NR	NR	NR	NR	NR	0.89
Hammerer[60] 2001	Cross-sectional	Stable chronic HF	57 45-80 y NR	100	LVEF	impaired (< 48% by 3D echo and <55% by RNV)	BNP(1)	142	NR	NR	NR	NR	0.75
							NT-proBNP(8)	4127	NR	NR	NR	NR	0.67
						resting LVEF <40%	BNP(1)	142	0.73	0.77	3.17	0.35	0.83
							NT-proBNP(8)	4127	0.70	0.73	2.59	0.41	0.79
Lee[59] 2002	Prospective cohort	HF	41 23-85 y 70%	100	Change in NYHA Class	none (correlation)	BNP(1)	NR	NR	NR	NR	NR	NR
Maeda[61] 1998	Cross-sectional	LVD (LVEF <50%)	72 61 y 74%	100	LVEDP	NR	BNP(1)	NR	NR	NR	NR	NR	NR
Seino[58] 2003	Cross-sectional	Chronic HF and Controls	105 64 y 80%	100	LVEF	< 40%	BNP(1)	NR	NR	NR	NR	NR	0.77
						< 50%	BNP(1)	135	72.3	73.2	2.7	0.38	0.794
						< 40%	NT-proBNP(9)	NR	NR	NR	NR	NR	0.754
						< 50%	NT-proBNP(9)	695	85.4	73.2	3.19	0.2	0.82
Yamada[62] 1997	Cross-sectional	various cardiovascular diseases	122 71 y 66%	NR	LVEDD	> 56mm	BNP(1)	NR	NR	NR	NR	NR	NR
					LVESD	≥ 40mm	BNP(1)	NR	NR	NR	NR	NR	NR
					LVEF	< 50%	BNP(1)	NR	NR	NR	NR	NR	NR
					IVS	< 11mm	BNP(1)	NR	NR	NR	NR	NR	NR

Abbreviations: AU ROC=area under the receiver operating characteristics curve, HF=heart failure, IVS=Interventricular septum,LR+=positive likelihood ratio, LR-=negative likelihood ratio, LVD=left ventricular dysfunction, LVEDD= left ventricular ejection diastolic dysfunction, LVEDP=left ventricular end-diastolic pressure, LVEF=left ventricular ejection fraction, LVESD= left ventricular ejection systolic dysfunction, NR=not reported, NYHA=New York Heart Association, SE=standard error, sens=sensitivity, spec=specificity, RNV=radionuclide ventriculography. y= years.

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

** Mean age if given in report

Table 6: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in primary care settings

Report	Study Design	Study Population	n Age**% Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Alehagen[67] 2002	Cross-sectional	65-82 years Symptoms of HF	415 72 y 52%	48	Clinical and Echo	LVEF ≤ 40%	BNP(1)	NR	NR	NR	NR	NR	NR
Bettencourt[34] 1999	Cross-sectional	Community HT and normal controls	47 65 y 47%	33	Doppler Echo	LV diastolic dysfunction	BNP(1)	NR	NR	NR	NR	NR	0.874
Gustafsson[68] 2003	Cross-sectional	Dyspnea referred for echo	367 69 y 46%	10	Doppler Echo	LVEF ≤ 40 %	NT-proBNP (9)	125	97	46	1.79	0.06	0.93
Hobbs[63] 2004	Diagnostic	General population	307 >45 y NR	1	LVSD by Doppler Echo	LVEF < 40%	BNP(1)	>115	80	88	6.71	0.23	0.88
		HF diagnosis	103 >45 y NR	20					71	52	1.5	0.54	0.7
		On diuretics	87 >45 y NR	8					86	65	2.44	0.022	0.8
		High risk of HF	133 >45 y NR	8					50	67	1.51	0.75	0.7
		General population	307 >45 y NR	1			NT-proBNP (9)	>338	80	73	2.95	0.27	0.76
		HF diagnosis	103 >45 y NR	20					100	18	1.22	0	0.7
		On diuretics	87 >45 y NR	8					86	40	1.43	0.036	0.81
		High risk of HF	133 >45 y NR	8					100	46	1.86	0	0.73

Table 6: Diagnostic properties of studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of HF in primary care settings (continued)

Report	Study Design	Study Population	n Age** % Male	Prevalence %	Reference test	Reference standard	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AU ROC
Landray[66] 2000	Cross-sectional	Suspected HF	126 74 y 54%	32	X-Ray or Echo LVSD	LVEF NR	BNP(1)	>10	92	18	1.12	0.097	NR
								>17.9	88	34	1.32	0.35	NR
								>76	66	87	5.07	0.39	NR
Nielsen[65] 2004	Cross-sectional	Dyspnea Male	176 > 50 y 100%	27	HF	ESC HF definition LSVD by Echo	NT-proBNP (9)	93	96	67	2.9	0.06	0.93
		Dyspnea Female	169 > 50 y 0%	20				143	94	69	3.0	0.09	0.90
		Dyspnea Male	176 > 50 y 100%	27				76	100	60	2.5	0.00	0.93
		Dyspnea Female	169 > 50 y 0%	20				67	100	27	1.37	0.00	0.90
		Dyspnea Male	176 > 50 y 100%	27				152	89	79	4.2	0.14	0.93
		Dyspnea Female	169 > 50 y 0%	20				219	91	84	5.7	0.11	0.90
Wright[64] 2003	RCT	Dyspnea and/or edema	305 72 y 35%	25	HF	ESC definition of HF	NT-proBNP (6)	211	90	63	2.43	0.16	0.85

Abbreviations: AU ROC=area under the receiver operator characteristics curve, Clin=clinical, Dx= diagnosis, ESC=European Society of Cardiology working group, HF=heart failure, HT=hypertension, LVEF=left ventricular ejection fraction, LVSD=left ventricular systolic dysfunction, LR+=positive likelihood ratio, LR-=negative likelihood ratio, LV=left ventricular, NR=not reported, RCT=randomized controlled trial, Sens%=sensitivity (%), Spec%=specificity(%), y=years.

- Estimated from the ROC curve

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

** Mean age, if given in report

Table 7: Diagnostic odds ratios for studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of or with HF across all settings

Report	Setting	Test^	Cut point (pg/mL)	Sensitivity			Specificity			Diagnostic Odds Ratio			
					Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI	n
Seino[58] 2004	Clinic	BNP(1)	135	0.723	0.613	0.800	0.731	0.614	0.822	7	5.58	14	172
		NT-proBNP(9)	695	0.857	0.777	0.911	0.731	0.614	0.822	16	8	35	172
Barcarse[48] 2004	ED	BNP(2)	110	0.958	0.830	0.980	0.940	0.830	0.970	360	58	2257	98
			170	0.842	0.726	0.914	0.928	0.809	0.975	69	18	274	98
			300	0.701	0.573	0.809	0.976	0.876	0.995	96	12	759	98
Dao[56] 2001	ED	BNP(2)	80	0.979	0.927	0.994	0.921	0.869	0.954	558	122	2250	250
			100	0.912	0.839	0.954	0.941	0.892	0.968	167	63	441	250
			115	0.896	0.820	0.943	0.960	0.917	0.981	213	75	607	250
			120	0.869	0.820	0.943	0.960	0.917	0.981	213	75	607	250
			150	0.875	0.794	0.927	0.970	0.930	0.987	231	76	705	250
Logeart[17] 2002	ED	BNP(2)	80	0.969	0.920	0.988	0.270	0.165	0.410	12	3	41	163
			100	0.960	0.908	0.983	0.282	0.173	0.425	10	3	30	163
			150	0.930	0.868	0.964	0.458	0.325	0.597	11	5	28	163
			200	0.930	0.868	0.964	0.562	0.422	0.693	17	7	43	163
			250	0.913	0.847	0.952	0.687	0.546	0.800	23	9	56	163
			300	0.878	0.806	0.926	0.875	0.753	951.000	50	18	140	163
Maisel[18] 2002	ED	BNP(2)	50	0.970	0.955	0.980	0.620	0.586	0.652	54	34	84	1586
			80	0.930	0.909	0.946	0.739	0.709	0.768	38	27	52	1586
			100	0.901	0.876	0.920	0.760	0.730	0.787	27	22	38	1586
			125	0.869	0.843	0.891	0.890	0.761	0.816	25	19	33	1586
			150	0.849	0.822	0.873	0.830	0.803	0.854	28	21	36	1586

Table 7: Diagnostic odds ratios for studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of or with HF across all settings (continued)

Report	Setting	Test^	Cut point (pg/mL)	Sensitivity			Specificity			Diagnostic Odds Ratio			
					Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI	n
Morrison[55] 2002	ED	BNP(2)	94	0.977	0.936	0.992	0.855	0.798	0.898	258	77	872	321
			105	0.940	0.866	0.969	0.855	0.798	0.898	93	41	213	321
			135	0.903	0.841	0.942	0.898	0.846	0.934	82	39	173	321
			195	0.850	0.780	0.901	0.941	0.897	0.966	91	42	197	321
			540	0.791	0.714	0.851	0.962	0.924	0.981	97	41	231	321
Ray[57] 2004	ED	BNP(2)	100	0.900	0.840	0.939	0.592	0.517	0.664	13	7	25	308
			150	0.851	0.783	0.900	0.712	0.639	0.775	14	8	25	308
			200	0.822	0.751	0.876	0.838	0.775	0.886	24	13	44	308
			250	0.780	0.704	0.840	0.898	0.843	0.935	31	16	59	308
			300	0.732	0.644	0.790	0.922	0.871	0.953	31	15	61	308
			350	0.673	0.592	0.745	0.922	0.871	0.953	24	13	48	308
Villacorta[52] 2002	ED	BNP(2)	200	0.99	0.88	1.00	0.96	0.83	0.99	1635	64	4135	70
Lainchbury[7] 2003	ED	BNP(2)	69	.971	.901	.992	.437	.356	.521	26	6	112	205
			104	.971	.901	.992	.511	.427	.594	36	8	151	205
			208	.942	.862	.977	.703	.621	.774	39	13	115	205
			277	.828	.723	.899	.777	.700	.839	17	8	36	205
			346	.771	.660	.854	.837	.765	.889	17	8	36	205
		NT-proBNP(9)	1184	.871	.773	.930	.711	.629	.780	17	76	37	205
			2030	.828	.723	.899	.822	.749	.877	22	10	48	205
			2875	.800	.691	.877	.866	.799	.914	26	12	56	205
			3721	.742	.629	.830	.903	.842	.942	27	12	59	205
Bayes-Genis[16] 2004	ED	NT-proBNP(9)	254	0.986	0.925	0.997	0.467	0.248	0.698	62	7	572	87
			423	0.958	0.884	0.985	0.600	0.357	0.801	35	7	163	87
			592	0.944	0.865	0.978	0.800	0.855	0.929	68	13	343	87
			972	0.902	0.812	0.952	0.933	0.701	0.988	130	15	1142	87
			1099	0.917	0.830	0.916	0.933	0.702	0.988	154	17	1382	87

Table 7: Diagnostic odds ratios for studies that evaluated BNP and NT-proBNP in patients with symptoms suggestive of or with HF across all settings (continued)

Report	Setting	Test^	Cut point (pg/mL)	Sensitivity			Specificity			Diagnostic Odds Ratio			
					Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI		Lower 95% CI	Upper 95% CI	n
Jose [53] 2003	ED	NT-proBNP(8)	1691	0.972	0.905	0.992	0.891	0.769	0.952	291	54	1569	119
Landray[66] 2000	Primary Care	BNP(1)	10	0.925	0.801	0.974	0.186	0.118	0.281	3	1	10	126
			17.9	0.875	0.738	0.945	0.348	0.256	0.454	4	1	11	126
			76	0.675	0.520	0.799	0.872	0.785	0.927	14	6	36	126
Hobbs[63] 2004	Primary Care	BNP(1)	115	0.500	0.237	0.763	0.667	0.579	0.744	2	1	7	133
		NT-proBNP(9)	338	0.952	0.667	0.995	0.463	0.378	0.551	17	1	302	133
Gustafsson[68] 2003	Primary Care	NT-proBNP(9)	125	0.969	0.846	0.994	0.458	0.405	0.511	27	4	201	367
Wright[64] 2003	Primary Care	NT-proBNP(6)	211	0.831	0.732	0.898	0.771	0.713	0.821	17	9	33	305

Abbreviations: HF=heart failure, ED=emergency department, CI=confidence interval

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 8: Studies that performed multivariate analyses to compare the independent contribution of BNP and NT-proBNP with other diagnostic tests.

Report	Outcome criteria	Description of model	Variable	Response type	Value	95% CI
Dao[56] 2001	HF - Framingham Criteria	multivariate analysis	Heart size	Chi Square	31.9	
			Murmurs	Chi Square	19.2	
			Pulmonary venous hypertension	Chi Square	11.9	
			Pedal edema	Chi Square	10.0	
			Orthopnea	Chi Square	6.4	
			BNP	Chi Square	95.2	
Jose[53] 2003	HF- Framingham & echo	logistic regression	Rales	OR	1.8	1.2-2.7
			Increased JVP	OR	2.9	1.7-4.9
			Cardiomegaly	OR	3.1	1.7-5.7
			Ankle edema	OR	6.5	2.8-15.2
			Orthopnea	OR	8.8	2.9-26.8
			S-3 gallup	OR	11.3	2.9-44.9
			NT-proBNP	OR	8.9	3.9-20.5
Knudsen[51] 2004	HF @ 30 days - Framingham & NHANES	final multivariate model	Rales	OR	1.6	1.0-2.6
			Lower extremity edema	OR	2.3	1.5-3.6
			Cardiomegaly	OR	2.3	1.4-3.7
			Cephalization	OR	6.4	3.3-12.5
			Interstitial edema	OR	7.0	2.9-17.0
			BNP $\geq$ 100	OR	12.3	7.4-20.4
Logeart[17] 2002	HF - Framingham criteria	logistic regression	Increased JVP	OR	3.5	1.3-9.5
			Orthopnea	OR	4.0	1.3-12.8
			X-ray edema	OR	9.0	3.0-26.5
			BNP 80 to 300	OR	5.4	0.6-45.8
			BNP > 300	OR	221.0	24.6-1983.1

Table 8: Studies that performed multivariate analyses to compare the independent contribution of BNP and NT-proBNP with other diagnostic tests. (continued)

Report	Outcome criteria	Description of model	Variable	Response type	Value	95% CI
Maisel[18] 2002	HF - NHANES & Framingham	multiple logistic regression	Increased JVP	OR	1.9	1.0-3.3
			Rales	OR	2.2	1.4-3.6
			Edema	OR	2.9	1.8-4.6
			Cephalization of vessels	OR	10.7	5.3-21.5
			BNP $\geq$ 100	OR	29.6	17.7-49.4
Maisel[49] 2004	HF- expert review of medical record	simultaneous logistic regression	Clinical Judgment >50% sure	Exp Beta	9.73	NR
			Log BNP	Exp Beta	12.02	NR
McCullough[54] 2002	HF - Framingham & NHANES	logistic regression	Clinical Judgment	Diagnostic accuracy	74%	NR
			BNP > 100	Diagnostic accuracy	81.20%	NR
			Both	Diagnostic accuracy	81.50%	NR
Morrison[55] 2002	HF - Framingham, hospital course, echo, nuclear medicine EF, cardiac catheter	multivariate analysis	Rales	chi square	4.3	NR
			Pulmonary venous hypertension	chi square	6.4	NR
			Increased JVP	chi square	12.9	NR
			Chest X-ray enlarged heart	chi square	33.0	NR
			BNP	chi square	119.6	NR
Ray[57] 2004	cardiopulmonary edema - expert Dx using Framingham	forward logistic regression	Rales	OR	3.1	1.6-6.0
			Lower extremity edema	OR	4.6	2.0-10.6
			BNP > 250	OR	24.4	12.0-49.6

Abbreviations: CI=confidence interval, Dx=diagnosis, EF=ejection fraction, HF=heart failure, JVP=jugular venous distension, NR=Not reported, OR=odds ratio.

Table 9: Characteristics of the systematic reviews of diagnostic tests for HF that were eligible for this review

Report	Description	Number of papers reviewed	Results reported	Included in review	Measures estimated for review
Ahmed[180] 2003	Review of heart failure evaluation and management guidelines: relevance to elderly. Recommendations of expert panel.			No	
Cardarelli[174] 2003	Systematic Review. Randomized double blinded & well designed cohort studies. Included reference standard. Tests evaluated in complete spectrum of patients	4	No pooling, Results from papers presented. AUC, sens, spec, LR+, PPV, NPV	Yes	Estimated DOR
Clerico[151] 2004	Systematic review. Studies to evaluate Dx accuracy & prognostic relevance of NPs. Critical comparison of "gold standard"	9	No pooling, Results from papers presented. AUC, sens, spec, PPV, NPV	Yes	Estimated DOR
Craig[183] 2005	Systematic review. Diagnosis of HF in primary care & emergency - BNP, NT-proBNP, ECG	BNP 23 NT-proBNP 8 ECG 12	Pooled sens, spec, DOR (95% CI)	Yes	
Doust[184] 2002	Systematic review. Diagnosis of HF – signs, symptoms, investigations	Diagnosis & exam – 7 Increased JVP – 8 CXR for pulmonary HR – 3 CXR for cardiomegaly – 5 Abnormal ECG – 10 NT-proBNP - 2	No pooling, sens, spec. LR	Yes	Estimated DOR
Doust[173] 2004	Systematic review. Papers that evaluated NP against reference standard and results reported so that 2x2 table could be constructed.	20	Pooled DOR (95% CI), SROC, AUC	Yes	
Doust[163] 2005	Systematic review. BNP & cardiac outcome prediction in patients with HF			No	
Jortani[176] 2004	Review of biomarkers of HF and strategies for developing new biomarkers.	Not stated		No	
Khunti[177] 2004	Systematic review of 12 lead ECG in DX of HF. Studies of patients referred from primary care	4	No pooling - sens, spec, SROC	Yes	Estimated DOR
McGowan[179] 2003	Systematic Review. Accuracy of echcocardiography vs radionuclide or contrast vetriculography	25	correlation coefficients	Yes	

Table 9: Characteristics of the systematic reviews of diagnostic tests for HF that were eligible for this review. (continued)

Report	Description	Number of papers reviewed	Results reported	Included in review	Measures estimated for review
Thomas[178] 2004	Review of diastolic heart failure - prevalence, criteria, morbidity, mortality			No	
van der Sloot[175] 2003	Review of important papers published in 2002	1		No - this paper included in review already	
Khunti[181] 2000	Systematic review. Dx of heart failure in primary care - signs, symptoms, investigations.	Not stated	narrative	Yes	
Wang[182] 2005	Systematic review. Dx of heart failure in dyspneic patients in ED - signs, symptoms, CXR, ECG, BNP	22	Pooled sens, spec, LR (95%CI).	Yes	Estimated DOR

Abbreviations: AUC=area under the curve, CI=confidence interval, CXR=chest x-ray, DOR=diagnostic odds ratio, Dx= diagnosis, ECG=electrocardiogram, ED=emergency department, HF=heart failure, LR+=positive likelihood ratio, NP=,NPV=negative predictive value, PPV=positive predictive value, sens=sensitivity, spec=specificity, SROC=summary receiver operating characteristic.

Table 10: Diagnostic performance estimates of BNP and NT-proBNP compared to other diagnostic tests based on previous systematic reviews

Report	Included Studies	Results Reported	Clinical Exam	Nocturnal Dyspnea	S-3 Gallop	Increased JVP	CXR +ve for PVC	CM on CXR	Abnormal ECG	BNP	NT-proBNP	Echo
Cardarell[174] 2003	4 studies, OP and Urgent Care, BNP vs ref standard to DX HF	Max estimate from studies evaluated								BNP @ 80 pg/mL sens 0.98, spec 0.92, LR+ 12.3, AUC 0.98, **Est. DOR 569**		
Clerico[151] 2004	9 studies diagnostic accuracy vs "gold standard"	Max estimate from studies evaluated								BNP @ 28.9 pg/mL sens 0.94, spec 0.77, AUC 0.91(0.90 - 0.93) **Est. DOR 53**	NT-proBNP @ 304 pg/mL sens 1.0, spec 0.70 AUC 0.92 (0.82-1.0) **Est. DOR 230**	
Craig[183] 2005	BNP 23 studies, NT-proBNP 8 studies, ECG 12 studies Dx of HF in Primary Care and Emergency	pooled estimates (95% CI)							for LVSD - cardiologist read, sens 0.90 (0.88-0.92), spec 0.58 (0.56-0.60), **DOR 12.41 (7.09-21.71),** machine read sens 0.83 (0.74-0.91), spec 0.21 (0.17-0.25), **DOR 1.41 (0.46-4.34)**	For LVSD - sens 0.88 (0.84-0.91), spec 0.62 (0.60-0.63), **DOR 10.74 (6.51-17.72)**	for LVSD - sens 0.84 (0.80-0.88), spec 0.65 (0.64-0.67), **DOR 14.96 (10.69-20.94)**	
Doust[184] 2002	All Settings	Max estimate from studies evaluated	sens 0.68, spec 0.76, LR+ 2.6, LR- 0.4 **Est. DOR 7**			sens 0.17, spec, 0.98, LR+ 8.3, LR-0.8 **Est. DOR 10**	sens 0.64, spec 0.60, LR+ 1.6, LR-0.6 **Est. DOR 3**	sens 0.90, spec 0.15 **Est. DOR 2**	sens 0.98, spec 0.82, LR+3.2, LR- 0.2 **Est. DOR 223**	sens 1.00, spec 0.99, LR+ 6.0, LR - 0.13 **Est. DOR 498**		
Doust[173] 2004	25 studies BNP vs LVEF or Clinical Criteria, General Practice and Hospital	pooled estimates (95% CI)								BNP @ 15 pg/mL vs LVEF <40 DOR 11.6 (8.4 - 16.1) AUC 0.83, vs Clinical Criteria DOR 30.9(27.0-35.4)		

Table 10: Diagnostic performance estimates of BNP and NT-proBNP compared to other diagnostic tests based on previous systematic reviews (continued)

Report	Included Studies	Results Reported	Clinical Exam	Nocturnal Dyspnea	S-3 Gallop	Increased JVP	CXR +ve for PVC	CM on CXR	Abnormal ECG	BNP	NT-proBNP	Echo
Khunti[181] 2000	Primary Care	narrative	70% accurate in Dx of dyspnea				sens 0.37	sens 0.51	high sens, poor spec, used for confirmation of DX only			
Khunti[177] 2004	4 studies 12 Lead ECG vs Echo								sens 0.94, spec 0.65, AUC 0.84 (0.33-1.00) **Est. DOR 30**			
McGowan[179] 2003	25 studies accuracy of echo vs radionuclide or contrast ventriculo	correlation co-efficients, max and min from studies evaluated										Simpson's rule 0.98, 0.46, Wall motion index 0.89, 0.55, Visual 0.94, 0.71
Wang[182] 2004	22 studies Dx of HF in patients with dyspnea in ED	pooled estmates (95% CI)	sens 0.61, spec 0.86, LR+ 4.4 (1.8-10.0), LR- 0.45 (0.28-0.73) **Est DOR 10**	sens 0.4, spec 0.84, LR+ 2.6 (1.5-4.5), LR- 0.70 (0.54-0.91) **Est. DOR 4**	sens 0.13, spec 0.99, LR+ 11 (4.9-25.00, LR- 0.88 (0.83-0.94) **Est. DOR 15**	sens 0.39, spec 0.92, LR + 5.1 (3.2-7.9), LR- 0.66(0.57-0.77) **Est. DOR 8**	sens 0.54, spec 0.96, LR+ 12.0 (6.8-21.0), LR- 0.48 (0.28-0.83) **Est. DOR 28**	sens 0.74, spec 0.78, LR+ 3.3 (2.4-4.7), LR- 0.33 (0.23-0.48) **Est. DOR 10**	sens 0.50, spec 0.78, LR+ 2.2 (1.6-3.1), LR- 0.64 (0.47-0.88) **Est. DOR 3**	BNP @100 sens 0.93, spec 0.66, LR+ 2.7 (2.0-3.9), LR- 0.11 (0.07-0.16) **Est. DOR 23**		

Abbreviations: AUC=area under the curve, CI=confidence interval, CM=cardiomyopathy, CXR=chest x-ray, CM=, Dx=diagnosis, ECG=electrocardiogram, ED=emergency department, Est.DOR=estimated diagnostic odds ratio, HF=heart failure, JVP=jugular venous pressure, LR-=negative likelihood ratio, LR+=positive likelihood ratio, LVEF=left ventricular ejection fraction, LVSD=left ventricular systolic dysfunction, OP=outpatient, PVC=, sens=sensitivity, spec=specificity.

Table 11. Summary of studies in patients with risk of CAD: BNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Bhalla[69] 2004 USA	n: 482 Age: 52 y	Clinical suspicion of cardiac dysfunction	BNP(2)	120	All-cause mortality	uLR = 5.66
Kellett[71] 2004 Ireland	n: 646 Age: 73.7 y	Admitted for acute medical emergencies	BNP(2)	700	In-hospital mortality	aOR = 22.0
Nagao[72] 2004 Japan	n: 401 Age range: 61.5 – 65.4 y	Cardiac arrest	BNP(1)	100	Survival to hospital discharge	aOR range = 0.004 – 0.13
Suzuki[10] 2002 Japan	n: 229 Age: 66 y	Hypertensive	BNP(1)	68	Cardiovascular events (including death)	uRR = 1.015 aRR = 1.011
Ueda[9] 2003 Japan	n: 111 Age: 85.5 y	Electrocardiographic abnormalities, stroke, or IHD	BNP(1)	100	1) Cardiac event 2) Death	1) uHR = 2.1 2) uHR = 1.6
Wang[74] 2004 USA	n: 3,346 Age: 59 y	Not reported in article	BNP(1)	20.0 (men) 23.3 (women)	Death	aHR = 1.27

Abbreviations: aHR=adjusted hazards ratio, aOR=adjusted odds ratio, aRR=adjusted risk ratio, CAD=Coronary artery disease, IHD=ischemic heart disease uHR=unadjusted hazards ratio, uLR=unadjusted likelihood ratio, uRR=unadjusted risk ratio, y=years

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 12: Summary of studies in patients with risk of CAD: NT-proBNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Gaede[70] 2005 Denmark	n: 160 Age: 55.1 y	Diabetes	NT-proBNP(9)	33.5	Mortality	aHR = 3.6
Jernberg[24] 2002 Sweden	n: 775 Age range: 55 – 77 y	Chest pain	NT-proBNP(9)	≤ 112, 113-400, 401-1653, ≥ 1654	Death	uRRs = 1.85 – 5.40
Nielsen[73] 2004 Denmark	n: 2,224 Age range: 40 – 75 y	LVEF > 0.55	NT-proBNP(9)	368.00 – 2,114.25	Major adverse cardiac events	No regression analysis
Olsen[4] 2004 USA, Denmark, Nor.	n: 183 Age range: 66 – 70 y	LV hypertrophy	NT-proBNP(9)	184	Composite endpoint including death	uHR = 2.8
Tarnow[15] 2005 Denmark	n: 386 Age range: 41.0 – 42.5 y	Diabetic nephropathy	NT-proBNP(9)	125	All-cause mortality	aHR = 2.68
Weber[6] 2004 Germany	n: 209 Age: 60 y	Degenerative aortic stenosis	NT-proBNP(9)	550	Severity of aortic stenosis	Sensitivity = 71% Specificity = 68%

Abbreviations: aHR=adjusted hazards ratio, CAD=coronary artery disease, LV=left ventricular, LVEF=left ventricular ejection fraction, Nor= Norway, uHR=unadjusted hazards ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 13. Summary of studies in patients with CAD with surgery: BNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Grabowski[3] 2004 Poland	n: 126 Age: 58.8 y	Myocardial infarction, acute coronary syndrome	BNP(2)	100 pg/mL	All-cause mortality	uOR = 10.3 aOR = 16.3
Jiang[77] 2004 China, Saudi Arabia	n: 949 Age: 52.5 y	Chest pain, angina, acute myocardial infarction	BNP(2)	80 pg/mL	Mortality	uOR = 2.94
Morrow[28] 2003 USA	n: 1,676 Age range: 60 – 69 y	Miscellaneous electrocardiographic and laboratory data	BNP(2)	80 pg/mL	Mortality	uOR = 3.7 aOR = 3.3
Takase[79] 2004 Japan	n: 77 Age: 67 y	Angina	BNP1)	68 pg/mL	Recurrence of anginal attacks	uHR = 41.1
Wiviott[96] 2004 USA	n: 1,865 Age range: 60.2 – 64.5 y	Angina, eligibility for PCI, ischemia	BNP(2)	80 pg/mL	Combined outcome: death, myocardial infarction	uOR = 1.6

Abbreviations: aOR=adjusted odds ratio, CAD=coronary artery disease, PCI = percutaneous coronary intervention, uHR=unadjusted hazards ratio, uOR=unadjusted odds ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 14. Summary of studies in patients with CAD, no surgery: BNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Bettencourt[33] 2000 Portugal	n: 101 Age: 58.3 y	Acute myocardial infarction	BNP(1)	93.8 – 380.5 pg/mL	Left ventricular dysfunction	aOR = 1.01
Mega[27] 2004 USA	n: 438 Age range: 21-75 y	ST segment elevation myocardial infarction	BNP(3)	80 pg/mL	Mortality	aOR = 7.2
Omland[13] 1996 Scandanavia	n: 131 Age: 67.8 y	Unspecified	BNP(1)	115.22 pg/mL	Mortality	uOR = 2.53 aOR = 1.99
Sabatine[83] 2002 USA	n: 450 Age: not reported in the article	Non-ST elevation acute coronary syndromes	BNP(2)	80 pg/mL	Composite: death, MI, CHF	aHR = 2.1 (10 months) aHR = 1.6 (6 months)
Wylie[78] 2004 USA	n: 1,124 Age: NR	Ischemic discomfort, documented coronary artery disease	BNP(2)	80 pg/mL	Development of CHF or cardiogenic shock	aOR (30 days) = 1.85 aOR (10 months) = 3.03

Abbreviations: aHR=adjusted hazards ratio, aOR=adjusted odds ratio, CAD=coronary artery disease, CHF = congestive heart failure, MI = myocardial infarction, NR = not reported, uOR=unadjusted odds ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 15: Summary of studies in patients with CAD not surgery: NT-proBNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Bazzino[21] 2004 Argentina	n: 1,483 Mean age: 66+/- 12 y	Resting chest pain	NT-proBNP(9)	586 pg/mL	Mortality	aOR = 3.42
de Winter[75] 2004 Netherlands	n: 1,172 Age range: 60 – 68 y	PTCA	NT-proBNP(9)	456 pg/mL	Death	uOR = 13.47
Galvani[76] 2004 Italy	n: 1,726 Age range: 59 – 65 y	Angina	NT-proBNP(9)	≤ 107 pg/mL, 108-353 pg/mL, 354-1357 pg/mL, ≥ 1358 pg/mL	Mortality at 30 days	aOR range: 1.33 – 3.91
James[8] 2003 Sweden	n: 6,809 Mean age: 65 +/- 11 y	Angina	NT-proBNP(9)	≤ 237 pg/mL, 238-668 pg/mL, 669-1869 pg/mL, ≥ 1870 pg/mL	Mortality	Mortality (1 year): aOR range = 1.4 to 3.2
Omland[82] 2002 Sweden	n: 609 Age range: 62 – 69 y	Clinical diagnosis not specified	NT-proBNP(7)	4,609 pg/mL	All-cause mortality	uRR = 3.9 aRR = 2.1
Richards[80] 2003 New Zealand	n: 666 Age: 62.4 y	Myocardial infarction	NT-proBNP(6)	1,370 pg/mL	Mortality	aRR = 6.63

Abbreviations: aOR=adjusted odds ratio, aRR=adjusted risk ratio, CAD=coronary artery disease, PTCA = percutaneous transluminal coronary angioplasty, uOR=unadjusted odds ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 16: Summary of studies in patients with CAD no surgery: NT-proBNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Heeschen[86] 2004 Germany, NZ	n: 1,791 Mean age: 59.9–64.1 y	Chest pain	NT-proBNP(9)	246 pg/mL	Mortality or myocardial infarction	aOR = 2.68
James[97] 2004 Europe, USA	n: 1,381 Age: 65 y	Angina, ST-depression	NT-proBNP(9)	<237, 237-669, 670-1869, >1869 pg/mL	Mortality	aORs: 3rd, 4th quartiles were SS (graphic depiction)
Jarai[20] 2005 Austria	n: 120 Age: 63 y	Angina, myocardial ischemia	NT-proBNP(8)	2,791 pg/mL	Cardiovascular mortality	aOR = 4.8
Jernberg[22] 2003 Sweden	n: 2,019 Age range: 40-84 y	Myocardial ischemia	NT-proBNP(9)	535 pg/mL (men) 672 pg/mL (women)	Mortality	aRR = 3.76
Latini[87] 2004 Italy	n: 724 Age: 31.9 y	Persistent ST-segment elevation	NT-proBNP(9)	0-818 pg/mL 819-2012 pg/mL > 2012 pg/mL	All-cause mortality	aORs = 1.0, 2.3, 3.0
Palmer[81] 2003 New Zealand	n: 978 Age: 62.1 y	Cardiac ischemia	NT-proBNP(6)	186 pg/mL	Mortality	aHR = 1.01
Richards[84] 1998 New Zealand	n: 156 Age: 64 y	Acute myocardial infarction	NT-proBNP(6)	254 pg/mL 1,032 pg/mL	All-cause mortality	aORs = 5.9 (254 pg/mL); 19.7 (1032 pg/mL)
Schnabel[85] 2005 Germany	n: 904 Age range: 60.7– 62 y	Acute coronary syndrome	NT-proBNP(9)	<160.8, 160.8-538.1, 538.2-1356.0, >1356.0 pg/mL	Cardiovascular events	aORs = 0.64– 1.2
Ueland[98] 2004 U.K.	n: 249 Age range: 63– 72 y	Left ventricular dysfunction, heart failure	NT-proBNP(7)	10,537 pg/mL	All-cause mortality	uRR = 2.1

Abbreviations: aHR=adjusted hazards ratio, aOR=adjusted odds ratio, aRR=adjusted risk ratio, CAD=coronary artery disease, SS = statistically significant, NZ = New Zealand, uOR=unadjusted odds ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 17: Summary of studies in patients with CAD no regression analyses

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Dokainish[19] 2005 USA	n: 895 Mean age: 57.3–60.6 y	Coronary artery disease	BNP(2)	80	Death or Re-infarction	Not Reported
Hutfless[91] 2004 USA	n: 98 Age: 63 y	Coronary artery disease (multiple clinical diagnoses)	BNP(2)	120 280 385	Intra- and post-operative cardiac events	Not Reported
Julier[99] 2003 Switzerland	n: 72 Age: 63.5 y	Cardiac arrest	NT-proBNP(9)	None	postoperative cardiovascular and renal adverse events	Not Reported
Kerbaul[92] 2004 France	n: 60 Age range: 67–68 y	Myocardial infarction, angina, peripheral arteriosclerosis	NT-proBNP(9)	397, 430, 491	Cardiovascular complications	Not Reported
Lindahl[14] 2005 Sweden	n: 961 Age: 67 y	Chest pain, ischemia	NT-proBNP(9)	529	Mortality	Not Reported
Panteghini[29] 2003 Italy	n: 92 Age: 52.5 y	Acute myocardial infarction	BNP (2)	83	All cause mortality	Not Reported
Richards[89] 2002 New Zealand	n: 747 Age: 63.6 y	Antecedent hypertension	NT-proBNP(6)	1,015	Mortality	Not Reported
Sadanandan[95] 2004 USA	n: 276 Age: 61–67 y	Unstable angina, myocardial infarction	BNP(2)	80	Mortality	Not Reported
Shimpo[90] 2004 USA	n: 810 Age: 58 y	Ischemic discomfort	BNP(1)	80	Mortality	Not Reported
Song[93] 2004 Japan	n: 40 Age range: 66.7–71.6 y	New York Heart Association	BNP(1)	450	1) Pleural effusion 2) Atrial fibrillation	BNP of > 450 pg/mL predicted the outcomes

Table 17: Summary of studies in patients with CAD no regression analyses. (continued)

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Suzuki[88] 2004 Japan	n: 145 Age: 64.7–66.7 y	Acute myocardial infarction	BNP(1)	180	Cardiac related mortality	Univariate X^2 = 20.06; multivariate X^2 = 7.003
Watanabe[94] 2003 Japan	n: 14 Age: NR	Elective CABG with cardiopulmonary bypass	BNP(1)	None	1) Death 2) Angina	Not reported
Zeller[100] 2004 France	n: 101 Age: 69 y	Myocardial infarction	NT-proBNP(9)	1150	Death, recurrent myocardial infarction, heart failure	NT-proBNP level was dependent variable

Abbreviations: CABG=coronary artery bypass graft, CAD=coronary artery disease, NR = not reported, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 18. Summary of studies in patients with HF and mortality outcomes: BNP

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Akioka[32] 2000 Japan	n:33 Age: 71 y	Chronic HF with decompensation. NYHA III-IV Mean LVEF 41%	BNP(1)	> 700 pg/mL	1) Cardiac mortality, baseline BNP 2) Cardiac mortality, deceleration time <120 and Baseline BNP > 700 pg/mL	1) uChi Sq. = 2.17, p = 0.141 2) uChi Sq. = 5.87, p = 0.015
Alehagen[127] 2004 Sweden	n:458 Age: 73 y	Clinical evaluation NYHA I-III LVEF < 40%	BNP(1)	173 - 346 pg/mL > 346 pg/mL	Cardiovascular mortality: 1) BNP 173-346 pg/mL 2) BNP >346 pg/mL All cause mortality: 3) BNP 173-346 pg/mL 4) BNP >346 pg/mL	1) HR = 1.58 2) HR = 3.38 3) HR = 0.99 4) HR = 1.90
Berger[125] 2005 Austria	n:452 Age: 54 y	Clinical evaluation NYHA I -IV LVEF < 35%	BNP(2)	> 130 pg/mL	Pump failure death 1) BNP 2) Log BNP 3) Log BNP	1) aChi Sq. = 7·4 2) uChi Sq. = 33·4 3) aChi Sq. = 10·7
Bettencourt[130] 2000 Portugal	n:139 Age: 69 y	Clinical examination NYHA I-III Mean LVEF = 33.5%	BNP(1)	> 274 pg/mL	All cause mortality	uBeta = 0.001 aBeta = 0.0001
Bettencourt[36] 2004 Portugal	n:84 Age: 69 y	Clinical examination NYHA I –III Mean LVEF 31.2%	BNP(1)	1) > 260.4 pg/mL 2) Increase vs decrease BNP 3) Per increase of 100 pg/mL	Mortality	1) uHR = 2.96 2) uHR = 2.64 3) uHR = 1.28 aHR = 1.34
Cheng[119] 2001 USA	n:72 Age: 68 y	Framingham criteria NYHA III-IV LVEF < 50%	BNP(2)	430 pg/mL 840 pg/mL 1090 pg/ml 1220 pg/mL	Death in hospital or death within 30 days after initial discharge	Mortality outcomes not reported
Harrison[114] 2002 USA	n:325 (41% with HF) Age: 65 y	At ED with dyspnea Previous Echocardiogram NYHA NR LVEF NR	BNP(2)	>230 pg/mL vs. </=230 pg/mL	1) HF death 2) Cardiac death	1) uRR = 24 2) uRR = 37
Imamura[117] 2001 Japan	n:171 Age: 63 y	Clinical evaluation NYHA II-IV Mean LVEF 27%	BNP(1)	<160 pg/mL	Cardiac mortality	u HR = 1 aHR = NS

Table 18. Summary of studies in patients with HF and mortality outcomes: BNP (continued)

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Ishii[129] 2002 Japan	n:98 Age: 69 y	Worsening HF Admission to CCU Echocardiography NYHA (mean) 3.5 Mean LVEF 42%	BNP(1)	> 440 pg/mL	Cardiac death	uChi Sq.= 6.66 aChi Sq. = 4.45
Ishii[23] 2003 Japan	n:100 Age: 68 y	Hospitalized for worsening HF NYHA III-IV Mean LVEF 36% in 12% of patients	BNP(1)	> 160 pg/mL	Cardiac death	uHR = 5.66 aHR = 3.11
Kyuma[30] 2004 Japan	n:158 Age: 64 y	HF Symptoms NHYA I-IV LVEF NR	BNP(1)	>172 pg/mL	1) Cardiac death due to pump failure 2) Cardiac mortality	1) uHR = 1.001 aHR = 1.001 2) uHR = 7.2
Latini[106] 2004 Italy	n: 4300 Age: NR	Stable but symptomatic HF NYHA I-IV LVEF < 40%	BNP(1)	1) > 97 pg/mL 2) Change >/= 10 pg/mL	Mortality	1) uHR = 2.47 aHR = 2.48 2) aHR = 1.012
Maeda[120] 2000 Japan	n:102 Age: 63 y	Hospitalized for HF NYHA III-IV Mean LVEF 23%	BNP(1)	> 170 pg/mL > 240 pg/mL	Cardiac death for BNP: 1) baseline 2) 3 m post treatment 3) baseline 4) 3 m post treatment	1) uChi Sq. = 5.79 2) uChi Sq. = 40.7 3) aChi Sq.= 2.61 4) aChi Sq. = 29.1
Maisel[102] 2004 USA	n:464 Age: Mean 64 y	Clinical evaluation NYHA (I-IV) LVEF NR BNP > 100pg/mL	BNP(2)	> 200 pg/mL	Mortality	aExp(Beta) = 4.531
Tsutamoto[12] 1997 Japan	n:85 Age: 60 y	Hospitalized with chronic HF NYHA II-IV LVEF < 45%	BNP(1)	> 73 pg/mL	Cardiac mortality	uChi Sq. = 60.83 aChi Sq. = 19.68 aHR = 1.003
Tsutamoto[121] 1999 Japan	n:290 Age: 59 y	Clinical evaluation NYHA I-II LVEF < 45%	BNP(1)	> 56 pg/mL	Cardiac mortality	aHR = 1.004 uChi Sq. = 100.5 aChi Sq. = 59.21

Table 18. Summary of studies in patients with HF and mortality outcomes: BNP (continued)

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Van Beneden[126] 2004 Belgium	n:117 Age: 67 y in severe HF	Clinical evaluation NYHA I-IV Mean LVEF Mild /moderate = 29.4% Severe = 20.8%	BNP(1)	Severe HF and BNP > 8,457 pg/mL	Mortality in severe HF	IRMA uLL Chi Sq. = 0.71
van der Meer[104] 2004 Netherlands	n:74 Age range: 26-90 y	European Society for Cardiology criteria NYHA II - IV LVEF NR	BNP(1)	Mean BNP 109.9 pg/mL	All cause mortality	uHR =1.006 aHR = Not significant
Vrtovec[109] 2003 New Zealand	n:241 Age: 67 y	Clinical evaluation NYHA III-IV Mean LVEF = 26% BNP >400 pg/mL	BNP(2)	i) 400-700 pg/mL ii) 701-1000 pg/mL iii) >1000 pg/mL iv) >1000 pg/mL	1) All cause mortality 2) Cardiac death 3) Pump failure death 4) Sudden cardiac death	Unadjusted: 1) i) p = 0.0003, ii) p = 0.0003, iii) p = 0.0001, iv) aHR = 1.99 2) i) p = 0.0004, ii) p = 0.0004, iii) p = 0.0003, iv) aHR = 1.76 3) i) p = 0.0003, ii) p = 0.0003, iii) p = 0.0001, iv) aHR = 3.78 4) All cut points were not significant
Wallén[122] 1997 Sweden	n:541 Age: 85 y	Clinical evaluation and heart volume NYHA NR LVEF NR	BNP(1)	39.8 -3816.4 pg/mL	All cause mortality: 1) total population 2) CV disorder 3) no CV disorder	1) aHR = 1.259 2) aHR = 1.240 3) aHR = 1.382
Watanabe[123] 2005 Japan	n:417 Age: 64 y	Framingham criteria NYHA III-IV LVEF < 50%	BNP(1)	> 132 pg/mL BNP and EF < 38%	Sudden death	aHR = 3.46

Abbreviations: aChi sq.=adjusted chi square, aHR=adjusted hazards ratio, CCU=cardiac care unit, CV = cardiovascular, ED=emergency department, EF=ejection fraction, HF=heart failure, IRMA=immunoradiometric assay, LVEF=left ventricular ejection fraction, , , NR=not reported, NYHA=New York Heart Association, uChi sq.=unadjusted chi square, uHR=unadjusted hazards ratio, uHR=unadjusted hazards ratio, uLL = unadjusted log likelihood, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 19. Summary of studies in patients with HF and mixed outcomes: BNP

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Anand[110] 2003 USA	n:4300 Age: NR	Stable, symptomatic HF NHYA I-IV LVEF =/< 40%	BNP(1)	1) > 97 pg/mL 2): % change 3rd vs 1st quartile 3) % change 4th vs 1st quartile	All cause mortality and first morbid event	1) uHR = 2.2 2) aHR = 1.66 3) aHR = 2.20
Barcarse[48] 2004 USA	n:98 Age: 64 y	Cardiologist review of medical record (58% HF) Echocardiogram LVEF <= 45%	BNP(2)	> 100 pg/mL	Cardiac death, readmission and ED visit within 90 days	NR
Berger[128] 2003 Austria	n:452 Age: 54 y	Clinical evaluation NYHA I -IV LVEF NR	BNP(2)	> 130 pg/mL	Death or urgent heart transplantation 1) Mild HF 2 yr 2) Mild HF 3 yr 3) Moderate HF 3 y 4) All Subjects	1) aChi Sq. = 5 2) aChi Sq. = 8 3) aChi Sq. = 8 4) NS
Bertinchant[25] 2005 France	n:63 Age: 54 y	Acute and chronic Clinical evaluation only NYHA I-IV LVEF < 45%	BNP(1)	> 254 pg/mL	Worsening HF and cardiac death	uChi Sq. = 7.332 aRR = 3.23
Bettencourt[111] 2002 Portugal	n:50 Age: 71 y	Hospitalized with decompensated heart failure Clinical evaluation only NYHA II-IV LVEF NR	BNP(2)	1) > 541 pg/mL 2) Increased BNP during hospital stay 3) DIscharge BNP > 321 pg/mL	Cardiovascular death or hospital re-admission	1) uHR = 1.0 2) uHR = 3.3 3) uHR = 2.3
Cheng[119] 2001 USA	n:72 Age: 68 y	New-onset HF by Framingham criteria or previously documented HF NYHA III-IV LVEF < 50%	BNP(2)	i) Mean admission ii) Mean discharge iii) % change in BNP	1) Hospital readmission for HF within 30 days 2) Death or readmission	1 i) BNP p = 0.03 i) Log BNP p = 0.01 1 ii) BNP = p = 0.05 ii) Log BNP p = 0.02 1 iii) p = 0.9 2 i) BNP p = 0.003 i) Log BNP p = 0.001 2 ii) BNP p < 0.0001 ii) Log BNP p < 0.0001 2 iii) p = 0.008
de Groote[101] 2004 France	n:407 Age: 57 y	HF patients referred to cardiology department NYHA III in 26% patients LVEF <= 45%	BNP(1)	> 109 pg/mL	Cardiac event-free survival	aHR = 3.45

Table 19. Summary of studies in patients with HF and mixed outcomes: BNP (continued)

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Dias[115] 2001 USA	n:46 Age: 70 y	European Society of Cardiology criteria NYHA NR EF > 40%	BNP(1)	NR	Death or hospitalization from cardiac cause 1) Atrial fibrillation group 2) Sinus rhythm group	1) uOR = 1.02 2) uOR = 1.002
Hamada[124] 2005 Japan	n:52 Age: 64 y	Chronic HF hospitalized for decompensation Clinical evaluation NYHA III-IV LVEF <40	BNP(1)	> 230 pg/mL i) Baseline BNP ii) Baseline BNP/(deceleration time)^2 iii) Discharge BNP iv) Discharge BNP/(deceleration time)^2	Re-hospitalization for acute decompensation of HF or cardiac death	i) aChi Sq.= 1.016 ii) aChi Sq.= 0.282 iii) aChi Sq.= 6.899 iv) aChi Sq.= 2.96
Harrison[114] 2002 USA	n:325 Age: 65 y	To ED with dyspnea (41% HF) Previous echocardiogram results NYHA NR LVEF NR	BNP(2)	i) > 230 pg/mL ii) > 480 pg/mL	1) HF event or HF death 2) Cardiac event or death for HF, ischemia, infarction	1) i) uRR = 15.5 ii) uRR = 8.2 2) i) uRR = 5.5
Horwich[108] 2003 USA	n:238 Age: 52 y	Referred for cardiac transplantation Clinical evaluation only NYHA class III-IV LVEF 0.25	BNP(2)	1) BNP < 485 pg/mL and Tropinin I < 0.04 ng/mL 2) BNP < 485 pg/mL and Tropinin I > 0.04 ng/mL 3) BNP > 485 pg/mL and Tropinin I < 0.04 ng/mL 4) BNP > 485 pg/mL and Tropinin I > 0.04 ng/mL	All cause mortality or urgent cardiac transplantation	1) aRR = 1.0 2) aRR= 2.1 3) aRR= 4.7 4) aRR = 12.3
Hulsmann[112] 2002 Austria	n:96 Age: 57 y	Clinic patients with HF based on LVEF function NYHA I-IV Mean LVEF 26%	BNP(2)	NR Mean BNP 2051.7 pg/mL in patients with death or worsening HF	Death or worsening heart failure	aChi Sq. = 8
Imamura[117] 2001 Japan	n:171 Age: 63 y	Clinical evaluation NYHA II-IV LVEF 27%	BNP(1)	> 160 pg/mL	Hospitalization and death for worsening HF	uRR = 1.006 aRR = 1.005
Ishii[129] 2002	n:98 Age: 69 y	In CCU for worsening HF Echocardiography	BNP(1)	>440 pg/mL	Cardiac or Readmission for worsening chronic HF	uChi Sq = 8.79 aChi Sq = 6.73

Table 19. Summary of studies in patients with HF and mixed outcomes: BNP (continued)

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Japan		NYHA mean 3.5 Mean LVEF = 42%			or MI	
Ishii[23] 2003 Japan	n:100 Age: 68 y	Hospitalized for worsening HF Clinical evaluation NYHA III-IV LVEF 36% in 12% of patients	BNP(1)	1) 10 fold increase 2) >160 pg/mL with increase in cTnT 3)) >160 pg/mL	Cardiac events including death	1) uHR = 4.26 2) aHR = 2.07 3) aHR = 2.35
Koglin[116] 2001 Germany	n:78 Age: 51 y	Chronic HF NHYA I-IV LVEF 36%	BNP(1)	i) > 107.5 pg/mL ii) per 100 pg/mL change	1) Changes in limitations of physical activity 2) Clinical event	1 i) uChi Sq. = 24.9 2 ii) uHR = 1.492
Latini[106] 2004 Italy	n:4300 Age: NR	Stable but symptomatic HF NYHA I-IV LVEF < 40%	BNP(1)	1) > 97 pg/mL 2) Change = 10 pg/mL	Mortality and morbidity	1) uHR = 2.06 2) aHR = 1.012
Logeart[107] 2004 France	n:223 Age: 70 y	Framingham criteria NYHA class IV LVEF 34.7	BNP(2)	Predischarge: 1) 100 pg/mL increase 2) > 700 pg/mL 3) Mean at 1 month 4) Mean at 6 months 5) >350 pg/mL 6) 50-700 pg/mL 7) >700 pg/mL 8) Mean at 6 months	Combined death or first re-admission for HF	1) uHR = 1.06 2) uHR = 13.77 3) aHR = 1.14 4) aHR = 1.17 5) aHR = 12.6 6) aHR = 5.1 7) aHR = 15.2 8) aHR = 1.25
Maeda[120] 2000 Japan	n:102 Age: 64 y	Hospitalized with HF Echocardiography NYHA III-IV LVEF 23%	BNP(1)	i) Pretreatment ii) 3 months post treatment iii) > 170 pg/mL	1) Mortality 2) Mortality or cardiac morbidity	1 i) uChi Sq. = 5.79 i) aChi Sq. = 2.61 ii) uChi Sq. = 40.7 ii) aChi Sq. = 29.1 iii) p = 0.0025 2 ii) aRR = 1.001 iii) p = <0.0001

Table 19. Summary of studies in patients with HF and mixed outcomes: BNP (continued)

Report	N Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Maisel[102] 2004 USA	n:464 Age: 64 y	Clinical evaluation only NYHA I-IV LVEF NR BNP > 100pg/mL	BNP(2)	> 200 pg/mL	Cardiac mortality or events	aExp(Beta) for logBNP = 2.030
Sakatani[105] 2004 Japan	n:80 Age: 72 y	Clinical evaluation only Hospitalized HF patients NYHA I-IV LVEF NR	BNP(1)	Mean 402 pg/mL	Cardiac death or rehospitalization	aOR = 1.029
Tsutsui[113] 2002 Japan	n:84 Age: 63 y	HF with DCM or ischemic cardiomyopathy Echocardiogram NYHA II-IV LVEF < 45%	BNP(1)	NR Mean 334 pg/mL	Cardiac death or hospitalization for worsening HF, MI or fatal arrhythmia	uChi-Sq. = 36.77 aChi-Sq. = 13.65
Tamura[118] 2001 Japan	n:48 Age: 78 y	First episode of HF Clinical evaluation NYHA I-IV Mean LVEF 38.1% to 49.2%	BNP(1)	Predischarge > 132 pg/mL	Cardiac event	aHR = 2.656
Tsutamoto[121] 1999 Japan	n:290 Age: 59 y	Early-stage HF NYHA I-II LVEF < 45%	BNP(1)	> 56 pg/mL	CV hospitalization or CV mortality	uChi Sq. = 90.5 aChi Sq. = 23.83
Van Beneden[126] 2004 Belgium	In severe HF group: n:47 Age: 67 y	Clinical evaluation only NYHA III-IV in severe HF group LVEF severe HF = 20.8%	BNP(1)	NR	Mortality	uLL = 0.71
Watanabe[123] 2005 Japan	n:417 Age: 64 y	Framingham criteria Clinical evaluation and echocardiography NYHA III-IV LVEF < 50%	BNP(1)	Log BNP >=2.12 and low ejection fraction (<=38%)	HF mortality or HF hospitalization	aHR = 2.10

Abbreviations: aChi sq.=adjusted Chi square, aex(beta)=adjusted ex(beta), aHR=adjusted hazards ratio, aOR=adjusted odds ratio, aRR=adjusted risk ratio, CCU=coronary care unit HF=heart failure, DCM=dilated cardiomyopathy, ED=emergency department, EF=ejection fraction, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NR=not reported, NS=not significant, NYHA=New York Heart Association, uChi sq.=unadjusted Chi square, uHR=unadjusted hazards ratio, uLL=unadjusted log likelihood, uOR=unadjusted odds ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report
^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 20. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Berger[125] 2005 Austria	n:452 Age: 54 y	Clinical evaluation NYHA I -IV LVEF < 35%	NT-proBNP(8)	Log N-BNP	Pump failure death	uChi Sq. = 28·4
Gardner[134] 2003 Scotland	n:142 Age: 50 y	Advanced HF Clinical evaluation NYHA II-IV LVEF < 35%	NT-proBNP(9)	>1490 pg/mL	1) All cause mortality (2) All cause mortality or urgent transplantation	1) uOR = 5.0 aChi Sq. = 6.03 2) uOR = 6.8 aChi Sq. = 6.03
Hartmann[35] 2004 Germany	n:1048 Age: 62 y	Chronic severe HF NYHA NR Mean LVEF 20.4%	NT-proBNP(9)	1) 84.6 pg/mL increase 2) median 2727 pg/mL	All cause mortality	1) uRR = 1.005 2) uRR = 3.13
Hartmann[140] 2004 Germany	n:1011 Age: 62 y	Chronic severe HF Clinical evaluation NYHA NR Mean LVEF 20.4%	NT-proBNP(9)	> 1767 pg/ml	1) All cause mortality 2) All cause mortality or hospitalization for HF 3) All-cause mortality or protocol specified CV hospitalization	1) uRR = 2.7 aRR = 2.17 2) uRR = 2.4 aRR = 2.11 3) uRR = 2.09
Kirk[133] 2004 Denmark	n:2230 (161 with HF) Age: 78 y (with HF)	European Society of Cardiology criteria NYHA NR Mean LVEF 45.3%	NT-proBNP(9)	ln(NT-proBNP)	All cause mortality	aOR = 1.66
Richards[138] 2001 New Zealand	n:297 Age: NR	Chronic stable HF Clinical evaluation NYHA II-IV LVEF < 45%	NT-proBNP(6)	continuous variable	1) All cause mortality or worsening HF 2) Admission with acute coronary syndrome	1) Cox PH Significant 2) Cox PH NS
Rossig[131] 2004 Germany	n:48 Age: 57 y	Clinical evaluation NYHA II-IV LVEF 25%	NT-proBNP(9)	Baseline Log NT-proBNP per log (pro-BNP) 1) Baseline LogNT-proBNP 2) with NYHA class 3) with serum creatinine: 4) with blood pressure 5) with blood pressure and apoptosis	All-cause mortality	1) uHR = 7.76 2) aHR = 5.66 3) aHR =6.61 4) aHR = 9.18 5) aHR = 9.35
Rothenburger[132] 2004 Germany	n:550 Age: 54 y	Clinical evaluation NYHA II-IV Mean LVEF 32%	NT-proBNP(9)	> 1000 pg/mL	Prediction ability for selection of cardiac transplant	uOR = 10.6

Table 20. Summary of studies in patients with HF and mortality outcomes: NT-proBNP. (continued)

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Stanek[41] 2001 Austria	n:91 Age: 51 y	Clinical evaluation NYHA II-IV LVEF < 25%	NT-proBNP(8)	Log NT-proBNP	Cardiac mortality	aChi Sq. = 8.9
Taniguchi[26] 2004 Japan	n:71 Age: 68 y	Acute decompensated HF Clinical evaluation NYHA I-IV LVEF NR	NT-proBNP(9)	cardiac decompensation 1.050 pg/ml cardiac events 2,000 pg/ml	Sudden death, HF death, rehospitalization for HF, adverse cardiac events	NR
VAN BENEDEN[126] 2004 Belgium	n:117 Age: 64 y	Clinical evaluation NYHA I-IV Mean LVEF in severe HF 20.8%	NT-proBNP(8)	continuous variable	All cause mortality or urgent heart transplant	LL uChi Sq. = 5.68

Abbreviations: aChi sq.=adjusted Chi square, aHR=adjusted hazards ratio, aOR=adjusted odds ratio, aRR=adjusted risk ratio, CV=cardiovascular, ECG=electrocardiogram, HF=heart failure, LL=log likelihood, LVEF=left ventricular ejection fraction, NR=not reported, NS=not significant, NYHA=New York Heart Association, PH=proportional hazards, uChi sq.=unadjusted Chi square, uHR=unadjusted hazards ratio, uOR=unadjusted odds ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 21. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Berger[128] 2003 Austria	n:452 Age: 54 y	Clinical evaluation NYHA I -IV LVEF NR	NT-proBNP(8)	continous variable Baseline Log NT-proBNP	Death or urgent heart transplant 1) Mild HF 2) Moderate HF at 2 y 3) Moderate HF at 3 y 4) All subjects at 1 y 5) All subjects at 2 y 6) All subjects at 3 y	1) aChi Sq. NS for any year 2) aChi Sq. = 19 3) aChi Sq. = 22 4) aChi Sq. = 4 5) aChi Sq. = 10 6) aChi Sq. = 11
Bettencourt[139] 2004 Portugal	n:156 Age: 73 y	Decompensated HF European Society of Cardiology criteria or Framingham criteria NYHA III-IV LVEF NR	NT-proBNP(9)	i) Baseline per 1000 pg/mL increase ii) Discharge per 1000 pg/mL increase iii Decrease > 30% iv) Decrease > 30% or increase > 30%	1) Death or hospital re-admission 2) Death	**1 i) uHR = 1.012** 1 ii) uHR = 1.018 1 iii) uHR = 2.19 aHR = 2.03 1 iv) uHR = 6.64 aHR = 5.96 2 iii) aHR = 2.59 iv)aHR = 3.67
Fisher[136] 2003 UK	n:87 Age: 75 y	Hospitalized for HF Clinical evaluation NYHA II-IV LVEF not reported	NT-proBNP(9)	Predischarge NTproBNP > 2994 pg/mL	1) Death or readmission with HF 2) Death	1) aOR = 4.15 2) aOR = 2.22
Gardner[134] 2003 Scotland	n:142 Age: 50.4 y	Advanced HF NYHA II-IV LVEF < 35%	NT-proBNP(9)	>1490 pg/mL	1) All cause mortality 2) All cause mortality or urgent transplantation	1) uOR = 5.0 aChi Sq. = 6.03 2) uOR = 6.8 aChi Sq. = 6.03

Table 21. Summary of studies in patients with HF and mixed outcomes: NT-proBNP (continued)

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Gwechenberger[103] 2004 Austria	n:100 Age: 51 y	Stable HF Clinical examination NYHA II-IV LVEF <=25%	NT-proBNP(8)	NR LogNT-proBNP	Worsening HF	uChi Sq. = 3.857 aChi Sq. NS
Hartmann[140] 2004 Germany	n:1011 Age: 62.7 y	Chronic severe HF Clinical evaluation NYHA NR Mean LVEF 20.4%	NT-proBNP(9)	> 1767 pg/mL	1) All cause mortality 2) Death or hospitalized for HF 3) Death or hospitalized for CV as specified in protocol	1) uRR = 2.7 aRR = 2.17 2) uRR = 2.4 aRR = 2.11 3) uRR = 2.09
Hartmann[35] 2004 Germany	n:1048 Age: 62 y	Chronic severe HF NYHA NR Clinical evaluation Mean LVEF 20.4%	NT-proBNP(9)	NR specified as above and below median	(1) all cause mortality (2) all cause mortality or hospitalization for HF (3) all cause mortality or CV hospitalisation (4) all cause mortality or hospitalisation for any reason	1) RR = 3.13 2) RR = 3.11 3) RR = 2.60 4) RR = 1.96
Hulsmann[112] 2002 Austria	n:96 Age: 57 y	Documented HF NYHA I-III Mean LVEF 26	NT-proBNP(8)	continuous variable	Death or worsening HF	aChi Sq. = 58
O'Brien[135] 2003 UK	n:96 Age: 74 y	In CCU Clinical evaluation. Killip class II-IV LVEF NR	NT-proBNP(7)	continuous variable 1) Baseline NT-proBNP 2) Predischarge NT-proBNP	Combined endpoint of death, HF readmission, and worsening HF	1) aOR = 1.84 2) aOR = 15.30
Van Beneden[126] 2004 Belgium	For severe HF group: n:47 Age: 67 y	Clinical evaluation NYHA III-IV in severe HF group LVEF severe HF = 20.8%	NT-proBNP(8)	For severe HF: N-BNP 12,863 pg/mL	Mortality	uLL = 0.71

Table 21. Summary of studies in patients with HF and mixed outcomes: NT-proBNP (continued)

Report	n Age**	Diagnosis	Method^	Cut point (pg/mL)	Outcome	Result
Zugck[137] 2002 Germany	n:408 Age: 55 y	Chronic HF Clinical evaluation NYHA I-IV LVEF < 45%	NT-proBNP(7)	continuous variable	Cardiac death or hospital admission for worsening HF	uChi Sq. = 49.2 aChi Sq. = 8.1

Abbreviations: aChi sq.=adjusted Chi square, aHR=adjusted hazards ratio, aRR=adjusted risk ratio, aOR=adjusted odds ratio, CCU=cardiac care unit, CV=cardiovascular, HF=heart failure, LVEF=left ventricular ejection fraction, NR=not reported, NS=not significant, NYHA=New York Heart Association, uChi sq.=unadjusted Chi square, uHR=unadjusted hazards ratio, uLL=unadjusted log likelihood, uOR=unadjusted odds ratio, uRR=unadjusted risk ratio, y=years.

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 22. Summary of studies evaluating BNP and NT-proBNP in the general population.

Report	n Age** % Male	Study population	Reference Standard	Prevalence %	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AUC
Atisha[142] 2004 USA	202 65 y 96%	VA hospital admission with heart disease symptoms	Unknown LVD	29	BNP(2)	20	79	44	1.41	0.48	NR
			Only systolic dysfunction	13	BNP(2)	20	80	36	1.25	0.56	NR
			Only diastolic dysfunction	38	BNP(2)	20	75	38	1.21	0.66	NR
			Systolic and diastolic dysfunction	5	BNP(2)	20	100	35	1.54	0.00	NR
Bibbins-Domingo[143] 2003 USA	293 69 y 92%	Stable coronary disease with no HF	Sys. Dys., EF< 55%	16	BNP(2)	>100	38	80	1.9	0.8	0.59
			Sys. Dys.,EF< 55% for age < 65 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.53
			Sys. Dys.,EF< 55% for age 65 to 75 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.60
			Sys. Dys.,EF< 55% for age >75 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.75
			Diastolic dominant pulmonary vein flow with EF ≥55%	13	BNP(2)	>100	55	85	3.8	0.5	0.79
			Diastolic dominant pulmonary vein flow with EF ≥55% for age < 65 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.63
			Diastolic dominant pulmonary vein flow with EF ≥55% for age 65-75 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.85
			Diastolic dominant pulmonary vein flow with EF ≥55% for age >75 y	NR	BNP(2)	NR	NR	NR	NR	NR	0.83
			Sys. Dys., EF< 45%	NR	BNP(2)	>100	65	80	3.2	0.4	NR
			Sys. Dys., EF< 55%	16	BNP(2)	>30	60	47	1.2	0.8	NR
			Diastolic dominant pulmonary vein flow with EF ≥55%	13	BNP(2)	>30	90	53	1.9	0.2	NR
			Sys. Dys., EF< 45%	NR	BNP(2)	>30	76	48	1.5	0.5	NR

Table 22. Summary of studies evaluating BNP and NT-proBNP in the general population (continued).

Report	n Age** % Male	Study population	Reference Standard	Prevalence %	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AUC
Groenning[145] 2004 Denmark	672 50 -90 y 43%	Recruited from General Practitioners	LVEF ≤ 50 %	11.5	NT-proBNP(7)	351	70	63	1.89	0.48	0.70
			LVEF ≤ 45 %	8.6	NT-proBNP(7)	366	74	64	2.06	0.41	0.73
			LVEF ≤ 40 %	5.6	NT-proBNP(7)	414	76	67	2.3	0.36	0.79
			LVEF ≤ 35 %	3.1	NT-proBNP(7)	850	76	85	5.07	0.28	0.83
			ESC criteria for HF and LVEF ≤ 50 %	7.3	NT-proBNP(7)	616	65	80	3.25	0.44	0.77
			ESC criteria for HF and LVEF ≤ 40 %	1.9	NT-proBNP(7)	902	92	86	6.57	0.09	0.94
			ESC criteria for HF and LVEF ≤ 50 % , Age > 70 y	12.2	NT-proBNP(7)	902	64	74	2.46	0.49	0.74
			ESC criteria for HF and LVEF ≤ 40 %, Age > 70 y	3.7	NT-proBNP(7)	1937	91	91	10.11	0.10	0.94
			ESC criteria for HF and LVEF ≤ 50 %, High risk medical history	13.8	NT-proBNP(7)	615	68	72	2.43	0.44	0.73
			ESC criteria for HF and LVEF ≤ 40 %, High risk medical history	3.7	NT-proBNP(7)	902	89	80	4.45	0.14	0.90
Hedberg[141] 2004 Sweden	407 75 y 49.6%	Random sample of 75 year olds	LVEF < 40%	6.9	BNP(1)	>73l	79	89	7.2	0.28	0.88
			LVEF < 40%	6.9	BNP(1)	>28	93	55	2.1	0.13	0.88
			LVEF < 40% in pop with major ECG abnormalities	NR	BNP(1)	NR	96	38	1.55	0.11	NR
Redfield[5]	2042	Random	EF ≤ 40%		BNP(2)	25.9	62	63	NR	NR	0.79

Table 22. Summary of studies evaluating BNP and NT-proBNP in the general population (continued).

Report	n Age** % Male	Study population	Reference Standard	Prevalence %	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AUC
2004 USA	62 y 48%	sample of residents older than 44 y	Sys. Dys. in population	1.1	BNP(2)	54.5	90	76	3.8	0.1	NR
			Sys. Dys., EF ≤ 40% in >65 y	2.0	BNP(2)	75.3	80	72	2.9	0.3	NR
			Sys. Dys., EF ≤ 40% in men	1.9	BNP(2)	54.5	88	83	5.2	0.1	NR
			Sys. Dys., EF ≤ 40% in women	0.3	BNP(2)	98.5	67	87	5.2	0.4	NR
			Sys. Dys., EF ≤ 40% in high-risk men	5.3	BNP(2)	66.3	85	73	3.1	0.2	0.82
			Sys. Dys., EF ≤ 40% in high-risk women	0.6	BNP(2)	128.8	50	82	2.8	0.6	0.74
			Sys. Dys., EF ≤ 40% in population	1.1	BNP(2)	NR*	65	87	5.0	0.4	NR
			Sys. Dys., EF ≤ 40% in >65 y	2.0	BNP(2)	NR*	67	80	3.4	0.4	NR
			Sys. Dys. in men	1.9	BNP(2)	NR*	71	85	4.7	0.3	NR
			Sys. Dys., EF ≤ 40% in women	0.3	BNP(2)	NR*	33	89	3.0	0.8	NR
			Sys. Dys., EF ≤ 40% in high-risk men	5.3	BNP(2)	NR*	80	65	2.3	0.3	NR
			Sys. Dys., EF ≤ 40% in high-risk women	0.6	BNP(2)	NR*	0	77	0	1.3	NR
			Dia. Dys. in population	6.9	BNP(2)	36.4	75	69	2.4	0.4	NR
			Dia. Dys. in > 65 y	12.3	BNP(2)	58.0	67	69	2.2	0.5	NR
			Dia. Dys. in men	6.7	BNP(2)	20.6	81	64	2.2	0.3	NR
			Dia. Dys. in women	7.1	BNP(2)	53.1	71	74	2.7	0.4	NR
			Dia. Dys. in high-risk men	15.9	BNP(2)	113.6	52	93	7.4	0.5	NR
			Dia. Dys. in high-risk women	17.5	BNP(2)	124.3	41	87	3.2	0.7	NR
			Mod to sev Dia. Dys. in population	6.9	BNP(2)	36.4	75	69	2.4	0.4	NR
			Mod to sev Dia. Dys., EF ≤ 40% in >65 y	12.3	BNP(2)	58.0	67	69	2.2	0.5	NR
			Mod to sev Dia. Dys., EF ≤ 40% in men	6.7	BNP(2)	20.6	81	64	2.2	0.3	0.74
			Mod to sev Dia. Dys., EF ≤ 40% in women	7.1	BNP(2)	53.1	71	74	2.7	0.4	0.73
			Mod to sev Dia. Dys., EF ≤ 40% in high-risk men	15.9	BNP(2)	113.6	52	93	7.4	0.5	NR
			Mod to sev Dia Dys, EF ≤ 40% in high-risk women	17.5	BNP(2)	124.3	41	87	3.2	0.7	NR
			Mod to sev Dia. Dys., EF ≤ 40% population	6.9	BNP(2)	NR*	41	91	4.6	0.6	NR

Table 22. Summary of studies evaluating BNP and NT-proBNP in the general population (continued).

Report	n Age** % Male	Study population	Reference Standard	Prevalence %	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AUC
			Mod to sev Dia. Dys., EF ≤ 40% in >65 y	12.3	BNP(2)	NR*	47	85	3.1	0.6	NR
			Mod to sev Dia. Dys. in men	6.7	BNP(2)	NR*	44	89	4.0	0.6	NR
			Mod to sev Dia. Dys., EF ≤ 40% in women	7.1	BNP(2)	NR*	39	92	4.9	0.7	NR
			Mod to sev Dia. Dys., EF ≤ 40% in high-risk men	15.9	BNP(2)	NR*	58	70	1.9	0.6	NR
			Mod to sev Dia Dys, EF ≤ 40% in high-risk women	17.5	BNP(2)	NR*	56	84	3.5	0.5	NR
Vasan[144] 2002 USA	3177 (from 3532) 58 (±10) y 42%	Participants in prospective cohort study with no HF	All subjects male, Elevated LV mass	76	BNP(1)	NR	NR	NR	NR	NR	0.72
			All subjects male, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.72
			All subjects male, Moderate to severe LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.79
			All subjects female, Elevated LV mass	84	BNP(1)	NR	NR	NR	NR	NR	0.57
			All subjects female, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.56
			All subjects female, Moderate to severe LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.85
			Age >= 60 y male, Elevated LV mass	69	BNP(1)	NR	NR	NR	NR	NR	0.66
			Age >= 60 y male, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.71
			Age >= 60 y male, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.75
			Age >= 60 y female, Elevated LV mass	80	BNP(1)	NR	NR	NR	NR	NR	0.51
			Age >= 60 y female, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.67
			Age >= 60 y female, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.79
			Hypertensive subjects male, Elevated LV mass	73	BNP(1)	NR	NR	NR	NR	NR	0.70
			Hypertensive subjects male, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.75
			Hypertensive subjects male, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.78
			Hypertensive subjects female, Elevated LV mass	80	BNP(1)	NR	NR	NR	NR	NR	0.54
			Hypertensive subjects female, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.70
			Hypertensive subjects female, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.92
			Prevalent CVD male, Elevated LV mass	70	BNP(1)	NR	NR	NR	NR	NR	0.71

Table 22. Summary of studies evaluating BNP and NT-proBNP in the general population (continued).

Report	n Age** % Male	Study population	Reference Standard	Prevalence %	Index test^	Index cut point (pg/mL)	Sens %	Spec %	LR+	LR-	AUC
			Prevalent CVD male, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.70
			Prevalent CVD male, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.74
			Prevalent CVD female, elevated LV mass	78	BNP(1)	NR	NR	NR	NR	NR	0.58
			Prevalent CVD female, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.75
			Prevalent CVD female, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.77
			>=2 high risk features male, Elevated LV mass	70	BNP(1)	NR	NR	NR	NR	NR	0.65
			>=2 high risk features male, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.71
			>=2 high risk features male, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.72
			>=2 high risk features female, Elevated LV mass	79	BNP(1)	NR	NR	NR	NR	NR	0.51
			>=2 high risk features female, Any LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.72
			>=2 high risk features female, Mod to sev LVSD	NR	BNP(1)	NR	NR	NR	NR	NR	0.86

Abbreviations: AUC=area under the curve, , CVD=cardiovascular disease, Dia Dys=diastolic dysfunction, EF=ejection fraction, ESC=European Society of Cardiology, HF=heart failure, LV=left ventricular, LVD=left ventricular dysfunction, LVSD=left ventricular systolic dysfunction, LVEF=left ventricular ejection fraction, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, Mod=moderate, NR=not reported, sens=sensitivity, Sev=severe, spec=specificity, Sys Dys=systolic dysfunction, VA=Veterans Administration, y=years

* Based on age and sex specific upper normal values

** Mean age if given in report

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

Table 23. Evidence table for studies using BNP or NT-proBNP to monitor treatment.

Report	Population	n	Treatment	Dosing	Time (weeks)	Concentration change	Variable compared to change in BNP or NT-proBNP concentration
Anand[110] 2003	Stable symptomatic heart failure patients who were undergoing prescribed heart failure therapy, LVEF <40%, and LVIDd/BSA >= 2.9 cm/m^2	4305	Prescribed heart failure therapy		24	At 4 months patients with the greatest decrease (< 51 pg/mL) or greatest increase (>= 19 pg/mL) has the highest mortality risk. Similar findings were observed at 12 months.	BNP increased in the placebo group (23 +/-5 pg/mL) and decreased in the valsartan group (21 +/-5).
Fung[38] 2003	5 with ischemic cardiomyopathy and 10 with hypertensive heart disease; treated with furosemide	24	Metoprolol	4-week titration period at weekly intervals from 6.25 to 50 mg twice daily.	52	998 to 406 pg/mL	At 12 weeks and 1 year there was a significant difference compared to baseline ($p < 0.01$) for LVEF (32.0 +/- 2.8 % and 38.0 +/- 3.8 %, respectively) and symptom questionnaire score (3.9 +/- 0.9 and 3.6 +/- 1.0, respectively). For the 6-minute walk test at 12 weeks and 1 year the change was 1310 +/- 63 and 1269 +/- 66, $p < 0.05$. Also LVEF at 12 weeks and 1 year was negatively correlated to NT-proBNP ($r = -0.52$, $p = 0.001$ and $r = -0.63$, $p < 0.001$).
Fung[38] 2003	11 with ischemic cardiomyopathy and 16 with hypertensive heart disease; all but one treated with furosemide	49	Metoprolol or Carvedilol	as above	52	913 to 381 pg/mL ($p = 0.003$)	LVEF - Baseline ($r = -0.29$, $p = 0.047$), 12 weeks ($r = -0.52$, $p = 0.001$), 52 weeks ($r = -0.63$, $p < 0.001$)
Fung[38] 2003	6 with ischemic cardiomyopathy and 6 with hypertensive heart disease; all but one treated with furosemide	25	Carvedilol	4-week titration period at weekly intervals from 3.125 to 25 mg twice daily.	52	846 to 381 pg/mL	LVEF at 12 weeks and 1 year was negatively correlated to NT-proBNP ($r = -0.52$, $p = 0.001$ and $r = -0.63$, $p < 0.001$)

Table 23. Evidence table for studies using BNP or NT-proBNP to monitor treatment. (continued)

Report	Population	n	Treatment	Dosing	Time (weeks)	Concentration change	Variable compared to change in BNP or NT-proBNP concentration
Kawai[31] 2001	Patients with idiopathic dilated cardiomyopathy but no underlying systemic hypertension, manifest vulvular disease, congentital malformation of the heart and vessels, and intrinsic pulmonary or renal disease	21	Carvedilol	titrated to full dosage	24	A significant difference from baseline at 6 months (69 +/-92 pg/mL vs 127 +/- 113 pg/mL, p <0.0166), but not at 2 months (100 +/- 111 pg/mL). P value over time = 0.014 and 0.18 vs control.	Pooled data relationships (r and p, respectively): NYHA (0.50, < 0.0001), systolic blood pressure (0.31, 0.014), heart rate (0.43, 0.0007), LVEDD (0.84, <0.0001), LVESD (0.84. < 0.0001), LVEF (-0.6, <0.0001), and LV mass index (0.66, <0.0001). Correlations were also calculated at baseline, 2 months and 6 months.
Murdoch[149] 1999	Well-compensated chronic heart failure patients receiving stable treatment included ACEi for at least 3 months prior to the study	20	ACEi (captopril = 4, enalapril = 9, lisinopril = 3, trandolapril = 2, perinodopril = 1, quinapril = 1) Losartan in some cases.	*BNP group* - higher ACEi dosage if BNP not below 50 pg/mL at clinic visit. Losartan at 25 to 50 mg if BNP remained elevated despite maximum ACEi dosage. *Clinical group* - increased dosing as per suggested by clinical trial data. Clinician at discretion to add Losartan.	8		*BNP vs clinical group*: Mean RAP (p = 0.17), mean PAP (p = 0.95), mean PAWP (p = 0.63), cardiac output (p = 0.37), stroke volume (p = 0.50), systemic vascular resistance (p = 0.55), pulmonary vascular resistance (p = 0.88), heart rate (p = 0.02), mean blood pressure (p = 0.47).
Shiga[37] 2003	Compensated heart failure - NYHA class II to IV; treatead with diuretics, ACEi or AT1-blocker	46	Amiodarone	Loading dose: 400 mg daily for 14 days or 800 mg daily for 7 days. Maintenance dosage: 100 to 200 mg daily (mean dose +/-SE 168 +/- 6 mg daily at month 6).	24	303 +/- 48 to 180 +/- 30 pg/mL (p<0.001)	Mean heart rate (p = 0.097), ventricular premature complexes (p = 0.315), fractional shortening (p = 0.243), creatinine (p = 0.149), thyroid stimulating hormone (p = 0.189) Follow-up after 48 months found the survival for patients to be 100% for BNP < 100 pg/mL and 83% for BNP > 100 pg/mL.

Table 23. Evidence table for studies using BNP or NT-proBNP to monitor treatment. (continued)

Report	Population	n	Treatment	Dosing	Time (weeks)	Concentration change	Variable compared to change in BNP or NT-proBNP concentration
Stanek[41] 2001	Heart failure patients with LVEF <25% and treated with digitalis and enalapril	91	Atenolol	50 to 100 mg/day, mean dosage 89 mg/day or placebo	24	At 6, 12 and 24 months the change from baseline was p < 0.01 for all.	Mortality was higher in 30 patients with baseline BNP levels >= 50 pmol/L compared to 61 patients below this cut off (log rank p < 0.0004).
Troughton[148] 2000	Impaired left-ventricular systolic dysfunction (LVEF <40%), NYHA II - IV and treated with ACE inhibitors, loop diuretic with or without digoxin	69	Enalapril, furosemide, digoxin, spironolactone, metolazone, isorbide mononitrate, felodipine	*BNP group* - titration with medications to achieve an NT-proBNP concentration < 1691 pg/L. *Clinical group* - titration with medications according to an objective score (heart failure score <2).	38	BNP group mean change 668 pg/L below baseline by 6 months compared to only 25 pg/L in the clinical group.	*BNP vs clinical group:* LVEF - 3 months (increase, p = 0.23), blood pressure (decrease, p = 0.015), creatinine clearance (decrease, p = 0.32), clinical status score (decrease, p = 0.25), 6 min walk test, quality-of-life score. At the end of the study there were 39 vs 54 events in the BNP group compared to the clinical group (p = 0.02) or 0.7 vs 0.2 per patient-year (0.01). Events included cardiovascular death, hospital admission, and outpatient heart failure.
Yoshizawa[44] 2004	NYHA class II to IV, LVEF <40%. Excluded patients with baseline heart rate <50 bpm, systolic BP <90 mm Hg, contradictions to beta-blockers such as obstructive pulmonary disease and renal dysfunction. Therapy included digitalis glycosides (59%), diuretics (77%), and ACE inhibitors or angiotensin receptor antagonists (95%).	78	Metoprolol	Metoprolol (n = - 5 mg/day titrated to target dose of 80 mg/day over 12 weeks. Carvedilol (n = 58) - 2.5 mg/day titrated to target dose of 20 mg/day over 12 weeks.	4 (early phase) 16 to 48 (late phase)	No change from baseline (290 +/- 384 pg/mL) at the early phase (234 +/-284 pg/mL) or late phase (177 +/-256 pg/mL) for either beta-blocker. However, patients in the 0 to 25th percentile in the early phase had increased levels (n = 22, 51 +/-37 vs 37 +/-17 pg/mL, p < 0.05) whereas patients in the 75th to 100th percentile had decreased levels (n = 21, 562 +/-385 vs 815 +/-454 pg/mL, p < 0.05).	BNP in nonischemic heart failure showed a significant difference in both the early and late phases (p < 0.05), but there was no difference in the ischemic etiology group.

Abbreviations: BP=blood pressure, LVEDD=left ventricular ejection LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic dimension, NYHA=New York Heart Association, PAP=pulmonary artery pressure, PAWP=pulmonary artery wedge pressure, RAP=right atrial pressure, SE=standard error.

Chapter 4: Discussion

Question 1: What Are the Determinants of Both BNP and NT-proBNP?

Factors associated with changes in B-type natriuretic levels were extracted from all studies used to answer Questions 2, 3 and 4 of this review. The identification of determinants is important, as they are potential confounders to accurate diagnosis of heart failure (HF), prediction of cardiac events, and the ability to monitor therapy in patients with HF. The identification of determinants is also useful for the purpose of defining reference intervals and for interpreting unanticipated, patient specific, BNP or NT-proBNP values. Furthermore, they can be used to gain an increased understanding of the physiology and pathophysiology of BNP and NT-proBNP as well as to identify aspects which have been well investigated and to identify gaps where further research is needed. It is also important, for effective design and interpretation of future research, to know what the determinants for BNP and NT-proBNP are.

The determinants found in this systematic review were clinical or biological parameters such as age, gender, diseases, and treatments. There were no data available on factors that affect the analytical test method for BNP or NT-proBNP. Much of this data is not published in journals, but is instead largely in the grey literature, most commonly in the literature supplied by the diagnostic company when applying for FDA approval to market their test method. One recent review, however, does present an overview of analytical determinants.[198]

The impact of age and gender on B-type natriuretic peptide levels has been reported extensively in the literature and this systematic review has clearly shown that increasing age is positively associated with increased B-type natriuretic peptide levels. In the populations evaluated in this systematic review, the female gender did not consistently show higher levels of B-type natriuretic peptides compared to the male gender. In healthy populations B-type natriuretic concentrations are significantly higher in females compared to males, but it appears that these differences are attenuated with disease processes, at least in the studies included for this systematic review.

The relationships of the B-type natriuretic peptides with various diseases and measures are listed in Table 3. For the most part, all cardiac diseases showed an increase in B-type natriuretic peptides. Stable angina and ischemic heart disease showed a positive effect only when other cardiovascular risk factors were also present. Furthermore, B-type natriuretic peptides were positively associated with many biochemical markers of inflammation such as C-reactive protein (CRP), interleukin-6, ST2 soluble receptor and osteoprotegerin, supporting their role as potential risk markers for cardiovascular disease (CVD). The most frequently reported non-cardiac determinants were non-cardiac dyspnea, hypertension and diabetes. The B-type natriuretic peptides were elevated in both non-cardiac dyspnea and hypertension. For diabetes, three of four studies reported no association. However, other diabetes related determinants including creatinine levels, decrease in glomerular filtration rate, and nephropathy, were positively associated with B-type natriuretic peptides. From this it is rational to extrapolate that B-type natriuretic peptides could be a marker of diabetes complications.

There were few studies[5,8-10,14,34,199] in this systematic review that looked at the independent association of B-type natriuretic peptide with any determinant using multivariate models. Of these studies, only two included HF severity using left ventricular ejection fraction (LVEF) as a continuous variable in the model.[5,11] There were three determinants (age, gender and creatinine level) which appeared more than twice among the studies that performed multivariate analysis. All studies included age as a variable and all except one study found age to be independently associated with B-type natriuretic peptides. The reason this one study[34] did not find this association is probably due to its very small sample size (n = 36). There was also no association with creatinine levels seen in this study. However, the level of creatinine was positively and independently associated with BNP[9] and NT-proBNP[8] in two other studies. Female gender was associated with increased BNP[5] and NT-proBNP[8,14] in three studies, and no increase in one study that contained a high proportion of females (79 percent).[9]

Even though determinants, such as age, gender and creatinine levels, may be found to be independently associated with B-type natriuretic peptide levels, it is not clear how clinically important it would be to adjust for them. The identification of determinants found in this systematic review does not imply either their causal association with, or their importance in regards to, altered BNP or NT-proBNP concentration. Rather, they offer a basis towards a better understanding of variance in BNP and NT-proBNP levels.

These determinants reflect what is reported in studies central to our clinical research questions but may have different effects in other studies. The magnitude or consistency of the determinant's association with the B-type natriuretic peptides will dictate how it is used. In addition, their use may vary depending on the situation in which they are used, from epidemiological studies and large clinical cohorts to specific clinical settings and individual patient care. Consideration of these variables is made in the context of the individual's disease state and treatment. A statistically significant effect may not translate to a clinically significant effect. Also, the populations where an effect has been shown may range from a small homogenous population to a large heterogeneous population and that effect may not be applicable to an individual. Specifically, in relation to this systematic review, these determinants may be used to explain variation among studies.

Question 2a: What Are the Clinical Performance Characteristics of Both BNP and NT-proBNP Measurement in Patients with Symptoms Suggestive of HF or with Known HF in the Four Clinical Settings of Emergency Department, Specialized Clinic or Outpatient, Primary Care, and Long Term Care?

One objective of this systematic review was to focus on studies that enrolled patients with clinical symptoms of HF as the presenting complaint regardless of comorbidity in order to generate a clinically applicable summary with maximum generalizability. With the exception of HF referred to specialized clinics, this review excluded all studies in which a diagnosis of any disease or medical condition (e.g., heart transplant) was an inclusion criterion for enrolment. To this end, and compared to previous systematic reviews, we screened a greater number of primary

studies and evaluated the diagnostic performance of BNP and NT-proBNP as a function of clinical setting.

The diagnosis of HF is challenging. It is typically based on the clinical history, physical examination, electrocardiogram (ECG), chest x-ray, and assessment of left ventricular function.[54] Diagnosis by consensus decisions of cardiologists based on interpretation of these clinical data will reveal that many patients with symptoms of HF do not have the disease.[200] This can be explained in part by the fact that some of these patients may have comorbidities that could account for their symptoms.[173] Conversely, not all patients with left ventricular dysfunction (LVD) have symptomatic HF.[201-203] The concern is that cardiac function can be interpreted as normal in the presence of a normal systolic function if an assessment of diastolic function is not also included. Diagnostic imaging methods best suited for evaluation of diastolic function (doppler echocardiography, M-mode echocardiography, multiple gated acquisition scan, cardiac catheterization) were not used in the majority of studies evaluated in this review. Diagnostic tests other than those specified above were used as reference standards and this is problematic. Therefore, the misinterpretation of normal systolic function as indicating the absence of HF could result in misclassification by the reference test. Given that the levels of B-type natriuretic peptide markers are reported to rise in the presence of myocardial wall stress resulting from systolic and/or diastolic dysfunction, this misclassification can result in a false negative interpretation of the corresponding B-type natriuretic peptide measurement.

The high pooled diagnostic odds ratios (DORs) and high sensitivities reported in this review indicate that these B-type natriuretic peptide markers have diagnostic value. However, there is no consensus on the optimum cut point for clinical application. Doust et al.[173] found, as we did in this review, that there is variation in the estimates of diagnostic accuracy between studies, and that this does not seem to be accounted for by differences in the clinical setting or the type of test used. This is explained, in part, by misclassification bias, which can underestimate the diagnostic accuracy of the B-type natriuretic peptides and subsequently yield a falsely elevated cut point.

Raymond et al.[204] also reported problems in determining a cut point for the diagnosis of HF. They concluded that in the determination and application of a cut point, an adjustment should be made at least for the independent effects of age and gender. Hence, the changes in BNP and NT-proBNP are not specific to HF; a conclusion that has also been supported by the results of Question 1 in this review. This means that elevated peptide markers do not confirm HF as a cause of the patient's symptoms. These markers, however, do appear to be sensitive to HF.

In summary, patients who present with symptoms of HF who are found to have a normal BNP or NT-proBNP are highly unlikely to have HF as a cause of their symptoms. These patients require further investigation of their condition to determine the reason for increased B-type natriuretic peptide levels.

Question 2ai: Emergency Department

With regards to emergency department (ED) settings, the findings are consistent with suggesting that BNP and NT-proBNP tests may be useful in ruling out cardiac dysfunction. In general, all studies enrolled patients with shortness of breath, which is typical of ED settings. Although, a variety of different cut points were evaluated, in all studies the sensitivity was reported as greater than 90 percent, however specificity varied widely from 27 to 91 percent. A similar pattern of high sensitivity and widely ranging specificity was observed for NT-proBNP.

Although a cut point cannot unequivocally rule in HF, according to Doust,[173] BNP values less than 51.75 pg/ can be used to exclude the disease in patients in whom it is suspected. This is lower than most of the cut points reported in this systematic review. There have been fewer studies evaluating the diagnostic performance of NT-proBNP than BNP. Januzzi et al.[205] report an age-independent cut point of NT-proBNP to rule out acute HF of 300 pg/mL (95 percent CI: 241 to 369) demonstrating a sensitivity of 99 percent, specificity of 60 percent, and a negative predictive value of 98 percent. However, their pooled analysis was not based on a systematic review, but rather on three selected clinical trials without any specific a priori inclusion criteria. Our review revealed that a study by Jose employing a cut point of 200 pg/mL had the highest sensitivity (97.2 percent) and DOR (291).[53]

In the studies reviewed, there was minimal insight into the diagnostic utility of B-type natriuretic peptides in complex cases where there is uncertainty in diagnosis. It is these cases that present a greater diagnostic challenge where it would be particularly valuable to have a test that could increase the certainty for HF. Based on the findings of our systematic review, the most likely use of B-type natriuretic peptides in the ED setting would be to identify which patients require further investigation to determine the cause of their symptoms. Patients with normal peptide levels will most likely have a condition other than HF as a cause of their symptoms, while those with elevated levels will likely need confirmatory testing for the disease.[173] One study[17]considered cases with inconclusive BNP values (80 to 300 pg/mL) and found BNP to be a poor predictor of the final diagnosis using multivariate regression analysis (OR 1.85, 95 percent CI: 0.4 to 7.8, p = 0.4). Overall, the quality of the studies in the ED setting was high. Except for the problem with misclassification bias, the literature was very consistent and the external validity was good. Future research should ideally include multicentre studies enrolling patients with symptoms of HF and employing definitive diagnostic imaging as the objective determinant of the presence or absence of the disease. Given large enough study populations, subgroup analyses will identify confounding variables and their impact on B-type natriuretic peptide levels.

Question 2aii: Specialized Clinic or Outpatient Setting

With regards to specialized clinics and outpatient settings, BNP and NT-proBNP levels correlate with cardiac function as well as symptoms. However, there are some important limitations to all of these studies. They have generally had relatively small sample sizes and have exclusively been single centre studies. The wide range of cut points for both BNP and NT-proBNP was also apparent in this setting as it was in other settings. It should be recognized that a rather select group of patients has been evaluated in these studies. These are patients referred for symptoms suggestive of HF or are patients with stable chronic HF. As sensitivity, specificity and the AUC for the ROC curves are dependent on the patient population studied, it is difficult to generalize these results to the broader population and to those within specialized clinics. A single study[60] that compared BNP with NT-proBNP in stable HF patients found no difference in the performance characteristics of these two markers.

Based on the limited number of studies in clinical or outpatient settings, the B-type natriuretic peptides are not useful to rule in HF. The low specificity of the test precludes it from being used in this way. In some situations within specialized clinics the high sensitivity of these peptides may be useful in ruling out HF as a cause of the symptoms. In both cases, however, supplementary investigations may be required to guide clinical management of the patient.

Measurement of the natriuretic peptides does not reduce the need for these additional investigations. Overall, these studies had high internal validity as they scored well on the QUADAS items. The results of these studies are very encouraging, but further studies are required to better define the role of BNP and NT-proBNP in diagnosing HF in a specialized clinic or outpatient setting.

Question 2aiii: Primary Care

With regards to the primary care setting, the findings of this review do not differ from those in the ED and clinic settings. One of the dilemmas facing physicians is how to appropriately manage patients who present with suspected HF. BNP and NT-proBNP tests are less expensive and are probably easier to obtain in primary care situations than echocardiography and thus offer the possibility of use as a first line diagnostic test. Echocardiography will be needed in the confirmation of the diagnosis and for staging and prognosis. BNP or NT-proBNP measurement might aid the physician in distinguishing between those patients who can be safely discharged and those who should be sent to specialist clinics or physicians for further work up and confirmation.

Of the few studies included in the meta-analysis, only one study[63] stood out as being different from the others. In this study, a random sampling of patients over 45 years old was selected (using computerized practice registers) from 16 random primary care practices in England. The sample was stratified by age and socioeconomic status. Four cohorts were identified: general population, patients labelled as having HF (may not be confirmed), patients prescribed diuretics, and those at high risk for HF (history of previous myocardial infarction (MI), angina, hypertension, or diabetes). The high-risk cohort group from this study was compared to the other cohorts which were selected based on a family practitioner's suspicion that the patient may have HF. The data from the high risk cohort shows a lower prevalence of HF and poorer diagnostic performance of the B-type natriuretic peptides (Figures 3, 4). Furthermore, the large difference in the DOR between BNP and NT-proBNP measurements in this study suggests either the cut point(s) chosen were not comparable or that the NT-proBNP test has a higher diagnostic accuracy.

Table 24 presents the results of a hypothetical analysis designed to answer who can be safely discharged and who should be referred on. Following the example set in the paper by Redfield et al.,[5] we calculated the following: (1) the portion of the population that would test positive if BNP or NT-proBNP were used as a first line diagnostic test, (2) the portion of those positive tests that would subsequently be confirmed as negative, (3) the portion that would test negative and not be further followed, and (4) the portion of subjects with a positive outcome that would be missed.

Two studies using BNP,[5,66] three using NT-proBNP,[64,68,145] and one using both,[63] could be analyzed in this way (Table 24). Using this two-step approach would mean that 13 to 63 percent of the population would be referred for an ECG. In all cases (except one,[64] which used a high NT-proBNP cut point of 245 pg/mL), 60 to 90 percent of these positive tests would be subsequently confirmed negative by echocardiography. Ten to 40 percent of those with a positive B-type natriuretic peptide test result would be confirmed positive by echocardiography. The portion of the general primary care population with a false negative result that would be missed using this approach is less than 4 percent. Negative likelihood ratios (LR-) (Table 6) ranged from 0 (highly useful) to 0.27 (marginally useful). These two pieces of information suggest that B-

type natriuretic peptides measurement is useful for ruling out HF. Because of the poor specificity of the test, a positive result does not necessarily rule in HF.

One randomized controlled trial (RCT)[64] examined the effect of NT-proBNP measurement on the diagnosis of HF in a primary care situation. Patients in the study group had their NT-proBNP results sent to their general practitioner along with an interpretive comment, whereas those in the control group had their NT-proBNP results withheld. The ability of physicians to accurately diagnose HF was compared between the two groups. The diagnostic accuracy was significantly increased when the NT-proBNP was available to the physician, with the greatest improvement being in the ability to rule out HF. They conclude that NT-proBNP measurement adds value over and above the current diagnostic strategies available to primary care physicians.

One paper,[206] published after the close of the literature search for this systematic review, describes the results of a multicentre trial to assess the diagnostic accuracy of BNP, NT-proBNP and ECG in 306 primary care patients referred for investigation of suspected HF. They report a high sensitivity for NT-proBNP (0.98 at 125 pg/mL) and a somewhat lower sensitivity for BNP (0.87 at 65 pg/mL). Negative likelihood ratios were 0.05 and 0.23 respectively. These authors' conclusions are similar to those in our systematic review, which is that B-type natriuretic peptides are useful to rule out HF as a cause of the symptoms, but not useful as a rule in tool. In primary care situations, B-type natriuretic peptide measurements may aid in the diagnosis of HF. Results below the diagnostic cut point can reliably rule out the diagnosis. Results above the cut point identify patients who require additional investigations to determine the cause of their symptoms.

Question 2aiv: Long Term Care Settings

This review did not find any relevant papers to address this question. Patients in long term care settings are likely to be older and have more comorbidities than the general population. This places them at higher risk for the development of HF. This is an area that requires further investigation to assess the utility of BNP or NT-proBNP as a diagnostic marker of HF.

Question 2a: All Settings Combined

The diagnostic ability of BNP and NT-proBNP was examined by setting in Question 2ai through 2aiii. Further investigations were performed to assess the diagnostic performance of BNP or NT-proBNP, irrespective of the clinical setting.

In each of the clinical settings, measurement of the B-type natriuretic peptides was shown to be of value in the diagnosis of HF. Patients who are found to have a BNP or NT-proBNP below the diagnostic cut point are unlikely to have HF as a cause of their symptoms.

In the ED setting there were enough papers to justify combining them to determine pooled estimates of the diagnostic characteristics. This was not the case for either the specialized clinic or primary care settings and therefore we combined all studies together. Since there is no guideline for pooling studies that present results with single and multiple cut points the choice was made to select the lowest one in studies with multiple cut points. The lowest cut point corresponds to the highest sensitivity and is therefore the best test characteristic to rule out HF. We also examined the special case of BNP using the cut point of 100 (±5) pg/mL. This was the

single most common cut point amongst the studies in this review. It is also the cut point suggested by manufacturers of the common commercial assays.

The meta-analysis indicated the diagnostic parameters remain similar even when results from all settings are combined. The pooled sensitivity was high (94 percent for BNP and 92 percent for NT-proBNP) and the pooled specificity was low (66 percent for BNP and 65 percent for NT-proBNP). In the absence of clearly demonstrated superiority of either BNP or NT-proBNP, the choice of analyte will likely depend on factors such as local expertise and availability of analytical instruments.

The largest difference among studies in all settings was seen with specificity. There are number of factors that could explain the heterogeneity including test type (BNP or NT-proBNP), test method, setting, study population, study design, study sample size, and reference test (from LVEF measurement alone to clinical classification with all available patients results). Multivariate analysis did not show a difference with respect to study design, sample size or reference test. There were too few studies in the subgroups of test type or test method to perform a sub-group analysis.

The determinants for BNP and NT-proBNP were not often considered in the diagnostic papers. The effect of determinants such as age, obesity, other diseases (e.g., hypertension, diabetes, renal failure) or drugs (e.g., beta blockers, diuretics, angiotensin converting enzyme (ACE) inhibitor) on B-type natriuretic levels is important to consider and is the only reason we could find that could explain the wide variation in specificity among the studies.

Further analyses to examine the issue of heterogeneity was possible using six studies that used the BNP Biosite test with a cut point of 100 pg/mL (±5 pg/mL). The average study sample size was 472 (range 163 to 1586). Five of the six studies were cross-sectional in design and one was a diagnostic study design. All studies used a clinical diagnosis of HF for the reference test. However, even with this high level of homogeneity among the studies there was still a wide range in specificities (28 to 94 percent) (Figure 5). The sensitivities were much higher and tighter ranging from 90 to 97 percent. The only explanation to account for these diagnostic parameters appears to lie in the heterogeneity of the study populations.

The average age range was 63 to 80 years and the percentage of males ranged from 49 to 94 percent. All six studies included patients with dyspnea, two studies had no exclusion criteria,[7,57] and the other four had various exclusion criteria. Three studies[18,55,56] excluded patients with cardiac tamponade, MI and trauma. Additional exclusion criteria for these studies were renal failure,[18] unstable angina,[18,55] and acute coronary syndrome (ACS).[56] The sixth study[17] excluded patients with acute MI, trauma, recent surgery and treatments started 2 hours before arrival to the ED (mechanical ventilation, diuretics, nitrates, or inotropic agents). Since many of these included and excluded parameters are factors that affect the BNP concentration, it is not surprising that there is a wide variation in the specificity of the test.

The specificity of the BNP is higher (76, 86 and 94 percent) [18,55,56] in those studies that excluded patients that were very likely to have elevated BNP levels compared to those that did not (28, 51 and 59 percent).[7,17,57] The false positive (FP) rate in the three studies with the highest specificity ranged from 3.6 to 12.7 percent compared to a much higher FP rate (20.2 to 32.2 percent) in the three studies with the lowest specificity. If further exclusion criteria are employed in studies assessing HF in the ED such as chronic obstructive pulmonary disease (COPD) there could be a further reduction in the FP rate.

The number of misclassified patients who would be ruled out with a B-type natriuretic peptide test but who would actually have HF is low. The overall mean false negative (FN) rate

for ED studies including BNP and NT-proBNP tests was 1.9 percent (range = 0.7 to 4.6 percent, n = 11) using a variety of cut points (10 to 200 pg/mL for BNP and 125 to 1691 pg/mL for NT-proBNP). The FN rate is similar even if limited to studies using the Triage BNP method using 100 (± 5) pg/mL as the cut point (mean = 2.9 percent, range = 1.0 to 4.6 percent, n = 6). Based on this data, the FN rate would only be expected to go lower if the patient selection was more specific.

Question 2b: Does Measurement of BNP or NT-proBNP add Independent Diagnostic Information to the Traditional Diagnostic Measures of HF in Patients with Suggestive HF?

We examined the subset of primary papers that performed multivariate logistic regression analysis to determine whether or not BNP or NT-proBNP measurement provided independent information in the diagnosis of HF. Odds ratios for the B-type natriuretic peptides ranged from 9 to 220 and were usually as high as, or higher than, other diagnostic variables. The conclusion from this analysis is that measurement of the B-type natriuretic peptides does indeed provide information independent from the traditional diagnostic measures.

Secondly, we examined existing systematic reviews of the diagnosis of HF. These reviews considered many diagnostic tests for HF, both alone and in combination. The DORs, actual and estimated, ranged from 10 to 569 for BNP and 14 to 230 for NT-proBNP.

These two lines of evidence both point to the conclusion that the measurement of the B-type natriuretic peptides is as good as, or better than, the traditional diagnostic measures for ruling out cardiac dysfunction. For these purposes, BNP and NT-proBNP appear to be of equivalent value. The information provided by the BNP or NT-proBNP tests is independent of that provided by the other measures.

A recent systematic review compared the ECG to BNP and found no difference in diagnostic accuracy for LVSD.[207] The echocardiogram is a better diagnostic test for HF; however, there were no systematic reviews identified which either evaluated the echocardiogram for HF or that compared BNP to the echocardiogram. If there is difficulty obtaining an echocardiogram or, if reducing costs is an issue, the B-type natriuretic test is a sensitive test to rule out HF. The caveat is that there will be FP cases that will need further workup.

Question 3a: Do BNP or NT-proBNP Levels Predict Cardiac Events in Populations at Risk of CAD, with Diagnosed CAD and HF?

Across the three different cardiac groups evaluated for Question 3a, both BNP and NT-proBNP have predictive value with respect to the outcomes of mortality or composite cardiac endpoints. The discussion is summarized according to each of these cardiac groups. In general, there were fewer studies evaluating NT-proBNP than BNP and even less comparing both these.

Question 3ai: At Risk of CAD

There were 12 studies that examined whether BNP or NT-proBNP had prognostic value for mortality or the occurrence of cardiac events in persons with risk factors for coronary artery disease (CAD). The 12 studies differed from one another in terms of the age and gender of the participants, the methods of diagnosing risk factors for CAD, the length of follow up, and the outcomes.

Despite these differences, the results of the multiple regression analyses consistently showed that the level of BNP or NT-proBNP was positively associated with the outcome, which was usually mortality. The adjusted measures of association in cases where BNP or NT-proBNP was treated as categorical were in the relatively tight range of 1.10 to 5.40. Although point estimates of the measures of association appeared to be larger for NT-proBNP than for BNP, the heterogeneity of the studies allowed for only tenuous comparisons between the two forms of peptide. There was no firm evidence to suggest that NT-proBNP was a better prognostic marker of mortality or cardiac events than BNP. Due to study heterogeneity, a meta-analysis was not conducted to summarize the data.

In conclusion, the overall consistency of the studies' results suggests that BNP and NT-proBNP do have prognostic value for persons who present with risk factors for CAD. This agrees with the conclusion of Doust et al.[163] Future research should compare the relative merits of BNP and NT-proBNP, as well as focus on how this prognostic information can be applied for patient care.

Question 3aii: With Diagnosed CAD

Overall, the 38 studies evaluating CAD patients varied from one another with respect to the age and gender of participants, sample size, length of follow up, and outcomes. Despite the heterogeneity, consistent positive associations were found between the level of BNP or NT-proBNP and the outcome of interest (mortality or otherwise). This suggests that BNP and NT-proBNP do have some predictive value with respect to these outcomes. However, given the diversity of the studies – a fact that precluded the use of a meta-analysis to summarize the data and the potential for selection or information bias, a single, global predictive effect for either peptide cannot be estimated from the available data.

If BNP and NT-proBNP are taken separately, then the approximate general effects appear to be in the range of an odds or hazard ratio of 2.00 to 3.00 for BNP and 1.50 to 3.00 for NT-proBNP (excluding studies with extreme results[3,79,84]). However, in the case of both peptides, the small number of studies does not allow for a determination of whether outcomes are predicted differently in persons with or without prior cardiac related surgery. Nor can a judgment be made about whether one of the peptides is a better predictor of mortality or non-fatal outcomes. In fact, there is no evidence at this time to suggest that BNP or NT-proBNP are different from one another in predicting outcomes such as mortality or re-infarction in persons with CAD.

Question 3aiii: With Diagnosed HF

The majority of the 38 studies evaluated in this review found baseline BNP levels to be an independent predictor of mortality outcomes across various cut points. When calculated, the adjusted HR varied from a 2.5 to a 7.2 fold increase relative to those subjects with lower BNP levels. Similarly, baseline BNP values were independent predictors of composite outcomes with HR estimates varing from 1.7 to 3.2. Some studies compared baseline and predischarge BNP levels and the findings would suggest differences in the ability to predict subsequent mortality; more research is required to establish the relative contribution between these two measurements of BNP. Several studies evaluated the combined use of baseline BNP levels with other markers of cardiac dysfunction (e.g., troponin I and T, percent VO2 max, or EF) as predictors of mortality and composite outcomes. The studies evaluating these markers were primarily single studies. Although the findings may suggest that the combined markers increase the ability to predict future outcomes, more research is needed to establish the relative benefit of these combined parameters. Similar to BNP levels, the majority of the 18 studies showed that NT-proBNP was a significant independent predictor of death or composite endpoints. The estimates of adjusted risk estimates varied from 2.17 to 9.35 for mortality outcomes, and 2.11 to 5.96 for cardiac composite outcomes. Similar to BNP, NT-proBNP was shown to be a significant predictor of outcomes at various cut points. Overall, the quality of studies was limited suggesting the potential for selection and particularly, misclassification bias in the majority of studies.

There was some interest in evaluating the evidence with respect to potential differences in the predictive ability of BNP and NT-proBNP for future cardiac events in HF patients. These two B-type natriuretic peptides are different molecules with different half-lives and blood concentrations and so there are some plausible physiological reasons to consider potential differences in performance as a clinical test. As such, there is currently some controversy about whether poor kidney function is a confounder for the interpretation of NT-proBNP levels. In addition, since the concentration of NT-proBNP is higher than BNP it has the potential to have greater (or finer) sensitivity. With respect to prognosis, few studies overall evaluated NT-proBNP and even fewer evaluated both types within the same study (n = 6). Within these six studies at least one of these B-type natriuretic peptides was a significant predictor of the outcome. Only two studies found both BNP and NT-proBNP to be independent predictors of mortality and the ability to predict varied with the year of follow up and the timing of the measurement. In general, the sample sizes within these studies were small and this may have been a factor in the multivariate analyses. No clear pattern emerges to suggest superiority of one type of B-type natriuretic peptide relative to the other in these head to head studies. Further research aimed at exploring potential differences in the prognostic abilities of these tests is required.

Methodological Caveats with Interpretation of BNP and NT-proBNP as Predictors of Future Cardiac Events

Much of the variation in the strength of BNP and NT-proBNP as a predictor of mortality and composite endpoints can be attributed to several key factors including: (1) differing HF populations with respect to severity, (2) the study settings, (3) differing BNP cut points, and (4)

differing parameters included in multivariate regression models. Many studies had small sample sizes and the outcomes were relatively rare in some severity groups; small sample sizes reduce the validity of undertaking multivariate analyses. There were also a number of important potential confounders identified in Question 1 of this review that was not controlled for in many studies. In particular, most studies did not control for treatment interventions as a confounder. For example, ACE inhibitors, which are commonly used in the management of HF patients, are suspected to affect HF prognosis. The mechanism of influence of some of these commonly used drugs on B-type natriuretic peptide levels is poorly understood in the literature. In general, the types of drug therapies and their doses were not controlled for or well described in many studies. Similarly, the majority of studies employed prospective cohort research designs and as such subjects were not randomized; this decreases confidence that differences between groups within these studies did not exist with respect to treatment interventions. Moreover, standard treatment varied between studies, which may serve as an important source of heterogeneity. Although drugs are an important intervention within this population, other treatments had the potential to influence prognosis estimates. For example, several studies performed catheterization procedures after admission and evaluation of B-type natriuretic peptide levels and as such, the estimates of prognosis would be influenced by these if not controlled for in the analysis. Thus, future research should attempt to control for and evaluate the influence of various treatments for HF on B-type natriuretic peptide levels.

Other diseases that HF subjects had were also not consistently controlled for in many studies. An overriding aim of most studies was to determine the independent contribution of B-type natriuretic peptide levels relative to other hemodynamic markers. Diseases such as diabetes or renal dysfunction, which affect both the B-type natriuretic peptide levels and prognosis estimates, were not always included in regression models.

Many studies did not specify the time the B-type natriuretic peptide measurements were taken, although the majority did so at some point in the admission process. Whether sampling of B-type natriuretic peptide levels occurred before or after acute interventions (in emergency for example) was not always specified. For baseline measures of B-type natriuretic peptide, it is not known if time dependent changes in B-type natriuretic peptide levels can improve or worsen prognosis estimates. In the case of longer-term studies, B-type natriuretic peptide levels may change due to worsening HF and influence the strength of the prediction estimate. The ValHeft studies[106,208] would suggest that the changes in BNP levels are related to prognosis as well. Whether baseline measures are sufficient in longer-term studies may be a concern for future research in this area. Conversely, it may be difficult to determine the best timing or interval for BNP measurement during the clinical course of HF. Consensus on best timing is required, particularly for those that maintain that serial measurements improve the ability of BNP or NT-proBNP to serve as a predictor of outcomes.[36]

Diagnosis of HF is another important source of heterogeneity within the studies evaluated in this systematic review. Specifically, classification of HF severity (disconnect between clinical presentation and hemodynamic function of the heart) is problematic; in part this is due to the differing classification systems and reference tests used to establish diagnosis. Accepted classification systems currently used to assist in determining the severity and functional status of patients serve to broadly classify HF groups and are limited in their precision. Alternative classifications have been recently proposed [209] for acute HF syndrome, dividing patients into three clinical groups: worsening chronic HF associated with reduced or preserved LVEF, (70 percent of all admissions); de novo HF, (25 percent of all admissions); and advanced HF (i.e.,

refractory to HF) with severe LV systolic dysfunction, associated with a continually worsening low output state (5 percent of admissions). These authors acknowledge that it may be difficult to classify patients at time of hospital presentation, but may be more useful in classifying patients in hospital or post discharge. Similar to problems with admission for HF, variations in discharge criteria for HF patients following an acute episode[107] are also an important source of heterogeneity for the prognosis estimates. Thus, not only is the diagnosis of HF potentially inconsistent and inaccurate, but also, the clinical impressions of "sufficient circulatory stabilization" may be inconsistent between studies in addition to being inaccurate.[107] Greater uniformity in criteria for discharge would also assist in understanding the role of BNP levels in predicting future outcomes.

Variation between studies in the types of HF patients or HF subgroups that were excluded was also evident and a rationale was frequently not provided. This variation in exclusion criteria may have had the potential to influence prognosis. For example, one study[124] excluded patients with a degree of mitral regurgitation, as this might influence a hemodynamic parameter (transmitral flow). The aim of that study was to evaluate how well transmitral flow as well as BNP levels predicted mortality; this exclusion likely influenced prognosis and limited comparison of results with other studies. Differentiation between subgroups of HF patients (for example those with and without preserved systolic function) were not always evaluated within studies; demonstrating that there were no differences between subgroups rather than assuming this would have been preferred. The problem in defining some subgroups is further compounded by the lack of consensus on features to classify patients (for example, the exact percent EF to classify those with or without preserved left ventricular systolic function is not currently established).

Unbiased verification of the outcomes was limited in the studies in this review, as most assessors were not blinded. Some studies did attempt to have adjudicators of outcome that were external to those managing the patients (who were blind to BNP or NT-proBNP levels). However, there are some additional challenges in determining some of the outcomes, such as sudden death or sudden cardiac events and whether these are "witnessed" or not; consensus on what constitutes sudden is not yet established. For subjects who were admitted to acute care hospitals some medications would be stopped, new ones introduced, and doses of existing maintenance drugs altered as a strategy to manage the acute episode. It has been suggested that often patients with the worse conditions receive less therapy because they can tolerate only lower doses (for example ACE inhibitor).[112] Thus, hospitalized patients, particularly those with increasing severity of HF, may have worse outcomes because of the use or contraindications of medications (beta blockers versus ACE inhibitor for example) rather than their BNP levels.

Study setting was also another important source of heterogeneity amongst studies influencing the magnitude of predictive estimates of risk. Most patients were either recruited at admission to acute care hospital, to ED or outpatient clinics. Those admitted to acute care centers were typically in a decompensated state and required rapid and intense interventions to stabilize conditions. For those enrolled in studies from outpatient and emergency settings, subjects that were subsequently hospitalized (versus those that were not) were not always stratified in the analyses; as such differential bias was a concern. It was not always clear if those studies that admitted patients with high acuity also had increased severity of HF relative to those patients that were not hospitalized or were recruited in outpatient settings or ED. Disentangling the relationships between study setting, patient acuity (decompensated versus stable), and severity of HF should be an important consideration in future research evaluating prognosis. Exploration of

these factors will account for the heterogeneity of the estimated risk levels and the varying thresholds that were observed in this systematic review.

Many studies in this systematic review were aimed at establishing the relative strength and independent contribution of BNP or NT-proBNP levels in predicting the outcomes of interest. Moreover, the literature reflected interest in establishing the relative merit of B-type natriuretic peptides in combination with other parameters such as troponin T and I, percent VO2max, percent lymphocytes and in particular hemodynamic factors. Since HF is complex and HF mortality is not only caused by mechanical dysfunction of the heart but also by arrhythmic disturbances,[116] it is likely that consideration of a wide variety of factors (rather than a single hemodynamic parameter) may improve their diagnostic and prognostic ability.

Question 3b: What Are the Screening Performance Characteristics of BNP or NT-proBNP in General Asymptomatic Populations?

In general, a test is considered important to utilize as a screening tool if the burden of suffering is high, the test itself is accurate and if early detection of the disease with the test is an effective intervention such that mortality/morbidity is reduced for those that were screened.

In the studies that used BNP as the index test, adequate screening characteristics were not observed, and this is true even for the detection of moderate to severe LVSD. It is even less accurate for detection of milder degrees of systolic dysfunction, which is more common in the general population. BNP is also quite poor for the detection of diastolic dysfunction. One requirement for screening is that there is evidence that early detection and intervention reduces morbidity and mortality. This evidence cannot be provided for BNP since it fails to detect those with milder degrees of systolic dysfunction who are known to be at increased risk. A single study using NT-proBNP as the index test with Danish patients recruited from general practices showed some promise for select subgroups of patients. There is also a need for more screening studies using NT-proBNP before any conclusions can be reached.

Question 4: Can BNP or NT-proBNP Measurement Be Used To Monitor Response to Therapy?

The findings from these studies suggest that BNP or NT-proBNP may be useful to monitor therapy in HF patients. A number of these studies demonstrated a relationship between the change in BNP or NT-proBNP and either mortality, morbidity or other clinical parameters such as left ventricular function. However, the findings have not been uniform as some of the studies do not show a relationship and therefore would not support the suggestion that BNP or NT-proBNP could be used to monitor a response to treatment. There are a number of limitations to the studies undertaken to date. Aside from one large study of over 4000 patients that was part of a clinical trial, the studies have been small with patient enrolment in most cases being less than 100 individuals. In some cases the studies have been single blinded and some were retrospective observational studies. Only two of the studies have altered therapies in response to the change in BNP or NT-proBNP and then assessed the outcome in a group treated by natriuretic peptides guided therapy compared to usual clinical management. For many of the studies patients were

not being treated with beta blocker therapy, and the effect of this form of therapy on BNP or NT-proBNP concentrations has been observed to be variable. Thus the results from these studies should be considered as pilot data, they provide the rational for larger studies of hormone-guided treatment including the use of beta blocker therapy. These larger studies would more reliably answer the question of whether BNP or NT-proBNP measurement can be used to monitor a response to therapy for HF patients. Four large studies are ongoing and include the United Kingdom Natriuretic Peptide Study (UKNPS), BNP-Assisted Treatment To Lessen Serial Cardiovascular Readmissions and Death (BATTLE-SCARRED), Rapid Assessment of Bedside BNP in Treatment of Heart Failure (RABBIT) and Suivi du Traitement dans l-innsuffisAnce caRdiaque Systolique (STARS) or treatment monitoring of systolic cardiac insufficiency.[210] The STARS trial in an abstract has reported preliminary findings on 220 patients showing HF events (death or hospitalizations) were reduced and delayed in the BNP guided therapy group compared to the clinically guided therapy group ($p = 0.001$, median follow up time was 15 months).[211]

Monitoring therapy with BNP or NT-proBNP requires serial measurements. Therefore knowledge of their biological variation is needed to know when a change in concentration signals a change in the pathophysiological process of the disease. Several studies have looked at the within day, day to day and week to week variation of these peptides in healthy individuals and patients with stable chronic HF.[212-216] The biological variation for individuals (CV_I) was found to increase with time between measurements for both BNP and NT-proBNP. The within-day day variation was 8.4 percent and 8.6 percent, the day-to-day was 25 percent and 20 percent and the week-to-week variation was 44 percent and 35 percent, for BNP and NT-proBNP, respectively.[212] There is also a slight increase in BNP and NT-proBNP from morning to early afternoon (approximately, 10 percent and 20 percent, respectively).[212]

Other studies looked at only week to week variation but found similar results for healthy individuals and patients with stable chronic HF.[213,215,216] There was also no difference between assay methods (BNP methods included Abbott, Bayer and Biosite while only the Roche method was used for NT-proBNP). Ultimately, the parameter that is used to monitor serial measurements is the reference change value (RCV) and includes both the analytical variation (CV_A) and individual variation (CV_I). At a 95 percent CI the formula is: $RCV = 1.96 \times 2^{1/2} (CV_A^2 + CV_I^2)^{1/2}$.[217] The RCV values calculated for these studies[212,213,215,216] showed that the RCV for BNP was slightly higher than for NT-proBNP (about 120 percent and 100 percent, respectively), but very similar among methods and between healthy and stable HF patients. These large RCV's indicate that a substantial change (about double or half) in serial measurements is required to indicate a significant change in concentration.

There is therefore a need to know if there are relevant and easily modifiable determinants that can be reduced such that the CV_I, since this is by far the largest component to the RCV (CV_A's are less than 25 percent of CV_I's). Standardized protocols (e.g., time of day, exercise, fluid intake) or taking replicate samples may help to reduce the RCV. Interestingly, the Melzi d'Eril study[214] found a much lower CV_I using the NT-proBNP method (9.1 percent). Although data analysis in this study was done using log-transformed data this would not account for the value being almost 75 percent lower. Although collection time could be a factor (since there is some diurnal variation), the collection times varied among studies. This observation merits further investigation since a lower CV_I would make monitoring of B-type natriuretic peptides more feasible. Since BNP is a hormone that is highly responsive to hemodynamic change this likely explains why biological variation is high.

The reduction in B-type natriuretic peptide concentration is variable among treated HF patients and rarely does it fall back into the normal reference range. Most treatment studies in this review reported decreases of about 40 percent and none exceeded 80 percent for any medication or B-type natriuretic peptide. Considering the large CV_I for both BNP (44 percent) and NT-proBNP (35 percent) this poses a major limitation for their use in monitoring therapy. However, there is good evidence, as described in Question 3 of this review that the risk of adverse events increases with higher concentrations of B-type natriuretic peptides. In view of this, and the association of decreasing B-type natriuretic peptide concentration with drug therapy, B-type natriuretic peptides show promise for use in optimizing therapy in a more objective way then querying symptoms. An analogy of B-type natriuretic peptide measurement in HF may be that of HbA1c in diabetes. The goal of therapy would be to stabilize the B-type natriuretic peptide levels and readjust therapy when significant changes occur. The results of the larger trials will provide more information on how the B-type natriuretic peptides can be used and possible target levels.

Limitations to this Systematic Review

The studies selected for this systematic review are English-language only. The budget and timelines available were a limiting factor to obtaining, translating, and abstracting non-English trials. In addition, we did not undertake to collect additional unpublished studies or to provide results/data that were not presented in the published articles. Although contact with the original authors of the studies (to supplement the missing information from the included publications) could have compensated for many of the reporting challenges we encountered, this strategy was not feasible given the timeline of this systematic review. Our experience at the McMaster University Evidence-based Practice Center suggests that the majority of authors do not respond in a timely fashion, if at all. Additionally, efforts were not made to contact industry for unpublished studies. Not contacting authors of eligible studies for additional data and not attempting to locate unpublished studies (either by other authors/ experts or by industry) may introduce publication bias in this systematic review.

Another possible limitation to this systematic review was the restriction of the BNP and NT-proBNP methods to a subset; our rationale was to reduce heterogeneity amongst studies to assay. Also, we wished to maximize external validity of the findings of this study by selecting predominately assays that are widely available for use in clinical laboratories. Lastly, we limited the collection of determinants to only studies included for research Questions 2, 3, and 4 due to issues of feasibility and relevance.

Comparison of Test Methods

Although this systematic review did not address the question of method differences it is important to note that differences do exist even among the methods selected for this review. All BNP methods included for this systematic review can be traced back to the original BNP method produced by Shionogi & Company in 1993. However, they vary in assay design and type of antibody (recognition to different epitopes) which results in quantitative measurement differences both systematically and randomly. Similarly, differences among the NT-proBNP methods include antibodies recognizing different epitopes and assay design. A systematic

difference refers to a consistent difference between methods, independent of test sample or concentration, which can be applied without condition. However, there are also random differences between methods that cannot be clearly described and can vary with test sample and concentration. As a consequence these differences demonstrate a lack of standardization among B-type natriuretic peptide methods.

For example, the Triage BNP assay when compared to the Shionoria assay gives consistently higher values and the magnitude of difference increases with both concentration and severity of HF.[218,219] One study found that at 100 pg/mL using the Triage system, there was a bias of -26 pg/mL, -10 pg/mL and +7 pg/mL compared to the ADVIA Centaur and Access, and AxSYM assays, respectively.[220]

Comparisons among NT-proBNP methods show considerably higher values for the Roche Diagnostics method versus the Biomedica method.[164,218] In a healthy population the difference is about 20 fold but decreases with severity of HF.[164] Similarly, the Christchurch method also produces lower values compared to the Roche Diagnostics method but not of the same magnitude (about 20 percent lower).[147] The bias between the early generation of the Roche assay (manual) and the present assay (Elecsys) is 2.7 fold.[221]

A review of the issues that need to be addressed regarding standardization have been presented in the publication "Quality specifications for B-type natriuretic peptide assays".[198] Consideration of these quality specifications and action to fulfill them will improve the comparability between assay methods. This will result in reduced heterogeneity among clinical studies especially with respect to cut point.

Conclusions

The volume of literature that has been published on B-type natriuretic peptides in such a short period of time exceeds that of any other biomarker. The rate of publication is unprecedented and as such many publications did not fall within the timeline established for this systematic review. However, the number of studies included in this review exceeds those in other reviews published on B-type natriuretic peptides as well as including a wider range of questions and interpretations.

In this systematic review we were cognizant that the setting, test type, and method were important considerations when evaluating the applicability of B-type natriuretic peptides. Therefore, this review, in contrast to the few that have been published so far, established these criteria at the outset and groups studies accordingly.

Determinants

Numerous determinants have been found to be associated with the B-type natriuretic peptides. However, the value of these associations for clinical use is not clear.

Future recommendations

- Further studies are required to assess the independent association of B-type natriuretic peptides with determinants, particularly as a function of HF severity.

- There is a need to design clinical studies to assess the magnitude of the effect determinants have on the diagnostic, prognostic and monitoring treatment roles of the B-type natriuretic peptides.

Diagnostic Properties for HF

In all settings (ED, clinics, and primary care) both BNP and NT-proBNP have high sensitivity and lower specificity, suggesting these measurements could play a role in ruling out cardiac dysfunction. In addition, the measurement of B-type natriuretic peptide levels adds independent information to traditional diagnostic measures for ruling out cardiac dysfunction.

Future recommendations

- Future research is required to explore the variation in optimum cut points for clinical applications. In particular, the potential influence of clinical determinants and population subgroups should be evaluated with respect to these optimum cut points for ruling out the presence of disease.
- The reporting of diagnostic metrics requires standardization to enable consistent comparisons. Ideally, all studies could report diagnostic characteristics based on a common sensitivity, specificity, likelihood value or cut point.
- Further studies are needed to evaluate the diagnostic value of B-type natriuretic peptides in diastolic HF.
- Large multicentre studies with sufficient sample size are needed to allow for adequate multivariate analysis to understand the variables that account for low specificity.
- Further studies evaluating NT-proBNP in all settings are needed to more clearly establish its role for diagnosis.
- There is a need to evaluate the B-type natriuretic peptides in long term care settings as this has been identified as a significant gap in the literature.
- Future research should increase the number of studies evaluating both NT-proBNP and BNP within the same study to compare their relative merits.
- Further studies are needed that are designed to compare B-type natriuretic peptides with other diagnostic tests, particularly echocardiography.
- Future studies should address the subset of patients who present to the ED with complex clinical pictures or atypical clinical findings.

Prognosis

BNP and NT-proBNP are consistent independent predictors of mortality and other cardiac composite endpoints for populations with risk of CAD, diagnosed CAD, and diagnosed HF.

There is insufficient evidence to make any conclusion as to the value of B-type natriuretic peptides for screening for HF.

Future recommendations

- Future research should compare the relative merits of BNP and NT-proBNP, as well as focus on whether there are differences in prognostic value for persons with HF.

- Conduct studies in acutely ill HF patients and compare predictive abilities of B-natriuretic type peptides at baseline relative to predischarge levels.
- Compare the relative merits of BNP and NT-proBNP, as well as focus on whether there are differences in prognostic value for persons with and without prior cardiac surgery in populations who are at risk for CAD or who have CAD.
- 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.
- Large multicentre studies with sufficient sample size are needed to allow for adequate multivariate analysis and adjustment of determinants.
- As more studies become available that can be grouped together, meta-analysis of these would be useful to provide information on the overall predictive effect of B-type natriuretic peptides for cardiac events.

Monitoring Treatment

There is insufficient evidence to demonstrate that BNP or NT-proBNP levels show change in response to therapies to manage stable chronic HF patients.

Future recommendations

- There is a need for large randomized trials to show whether therapy guided by increases and decreases in B-type natriuretic peptides affect outcome.
- Studies should be conducted to assess optimal timing for B-type natriuretic peptide testing for serial monitoring in stable chronic HF patients.
- Further research is needed to investigate if there are determinants of the biological variation that can be controlled for.

Table 24. Hypothetical analysis using BNP and NT-proBNP as first line tests and demonstrating the potential for reduction in subsequent requirement for further confirmatory testing for HF*

Report	Population	Prevalence %	Index test^	% of population with positive test	% of positive tests subsequently confirmed negative	% of population with negative test	% of population with outcome missed (negative screening test, but positive outcome)
Hobbs[63] 2004	primary care general population	1.6	BNP(1)	13	90	87	20
	primary care Clinical Dx of HF	20.3		53	72	74	28
	primary care, on diuretics	33.3		39	82	61	14
	primary care, high risk HF	7.5		34	89	66	50
Redfield[5] 2004	≥ 45 yrs, random sample of pop'n	1.9	BNP(2)	24	96	76	10
Groenning[145] 2004	primary care recruit from GP, 50 -90 y, exclude nursing homes	5.6	NT-proBNP(7)	35	87	65	7.8
Gustafsson[68] 2003	primary care with dyspnea referred for echo	8.9	NT proBNP(9)	63	78	37	3
Hobbs[63] 2004	primary care general population	1.6	NT-proBNP(9)	28	95	72	20
	primary care Clinincal Dx of HF	20.3		85	76	15	0
	primary care, on diuretics	33.3		62	88.8	38	14
	primary care, high risk HF	7.5		57	86	43	0
Wright[64] 2003	> 40 y, Present to GP with dyspnea/edema	25	NT-proBNP(6)	47	28	53	17

Abbreviations: Dx=diagnosis, GP=general practitioner, HF=heart failure, y=years.

* Based on Redfield et al.[5]).

^ Number in bracket refers to row number in Table 1 or Table 2 describing method used to measure B-type natriuretic peptide.

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List of Acronyms/Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Coverting Enzyme
ACID	Automatic Implantable Cardiac Defibrillator
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research Quality
AMED	Allied and Complementary Medicine
ANP	A-Type Natriuretic Peptide
AR	Aortic Regurgitation
AS	Aortic Stenosis
AUC	Area Under the (plasma time) Curve
BMI	Body Mass Index
BNP	B-Type Natriuretic Peptide
CAD	Coronary Artery Disease
CAGB	Coronary Artery Bypass Graft
CHF	Congestive Heart Failure
CCS	Canadian Cardiovascular Society
cGMP	Cyclic guanosine mononucleotide phosphate
CI	Confidence Interval
CPE	Cardiogenic pulmonary edema
CRP	C-reactive protein
CRT	Cardiac Resynchronization Therapy
CT	Computerized Tomography
CVD	Cardiovascular Disease
DOR	Diagnostic Odds Ratio
E/A	Early to late(atrial) echocardiographic phases of ventricular filling
ECG	Electrocardiogram
ECP	Enhanced Counterpulsation
ED	Emergency Department
EF	Ejection Fraction
ELISA	Enzyme Linked ImmunoSorbent Assay
FDA	Food and Drug Administration
FN	False Negative
FPR	False-Positive Rates
HbA1c	Hemoglobin A1c
HF	Heart Failure
HR	Hazard Ratio
IABP	Intra-Aortic Balloon Pump
IHD	Idiopathic Heart Disease
JVP	Jugular Venous Pressure
LAD	Left Anterior Descending
LR	Likelihood Ratio

LR-	Negative Likelihood Ratio
LR+	Positive Likelihood Ratio
LV	Left Ventricular
LVD	Left Ventricular Dysfunction
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Dimension
LVSD	Left Ventricular Systolic Dysfunction
MIBG	^{123}I-metaiodobenzylguanidine
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MRNA	Myocardial Radionuclide Angiogram
MS	Mitral Stenosis
NHANES	National Health and Nutrition Examination Survey
NPV	Negative Predictive Value
NSTEMI	Non ST-Elevation Myocardial Infarction
NT-proBNP	N-Terminal proBNP
NYHA	New York Heart Association
PCI	Percutaneous Coronary Interventions
PTCA	Percutaneous Transluminal Coronary Angioplasty
PCWP	Pulmocapillary wedge pressure
QoL	Quality of Life
QUADS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
RNA	Radionuclide Angiogram
ROC	Receiver Operator Characteristic
RR	Relative Risk
SROC	Summary Receiver Operator Characteristic
SRS	Systematic Review Software
STEMI	ST-Elevation Myocardial Infarction
TEP	Technical Expert Panel
TIA	Transient ischemic attack
TN	True Negative
TOO	Task Order Officer
TP	True Positive
TPR	True-Positive Rates
UKNPS	United Kingdom Natriuretic Peptide Study
VAD	Ventricular Assist Device

Glossary

Statistical/Methodological Terms Defined

ANOVA. Analysis of Variance. A test of the statistical significance of the differences among the mean scores of two or more groups on one or more variables

Backward selection logistic regression. See stepwise regression (variables are removed one at a time)

Chi-square χ^2 test. Any statistical hypothesis test in which the test statistic has a chi-square distribution if the null hypothesis is true. For example, it is used to compute the probability that there is no significant difference between the expected frequency of an occurrence with the observed frequency of that occurrence.

Cochranes's Q test. A test for statistical heterogeneity between studies, calculated as the sum of the squared differences between each study's effect estimate and the overall effect estimate, weighted for the information provided by the study. Under the null hypothesis, it follows a chi-squared distribution with degrees of freedom equal to the total number of studies less one

Correlation Coefficient. The correlation coefficient measures the strength of a linear relationship between two variables. Commonly designated as r, its values range from -1 to +1, indicating a strong negative relationship to a strong positive relationship with 0 (zero) as neutral

Cox Regression Model. A regression technique that allows adjustment for known differences in baseline characteristics between experimental and control groups as applied to survival data

Diagnostic Odds Ratio. This is a useful measure when combining studies in a systematic review. The DOR describes the odds of positive test results in participants with disease compared with the odds of positive test results in those without disease. A single diagnostic odds ratio corresponds to a set of sensitivities and specificities depicted by a receiver operating characteristic curve

Fisher's exact test. A test which can be used to determine if there are nonrandom associations between two categorical variables. It is an alternative to the Chi-square test. The test is based on exact probabilities from a specific distribution. The Chi-square test relies on a large sample approximation. Therefore, Fisher's test may be used in situations where a large sample approximation is inappropriate

Forest Plots. A graphical display tool that presents individual studies (black squares) with confidence interval lines through them, stacked upon each other, and summarized in a pooled effect estimate (black diamond)

Forward logistic regression. See stepwise regression. (variables are added one at a time)

Hazard Ratio. The weighted relative risk over the entire period of the study

Kaplan Meier Survival Analysis. Often shown as a curve that starts at 100% of the study population and shows the percentage of the population still surviving (or free of disease or some other outcome) at successive times for as long as information is available. Synonymous with Survival Curve

Kruskal Wallis. This is a non-parametric test for assessing differences between the medians of two or more samples to determine if the samples have come from different populations. It is useful for situations where the ANOVA normality assumptions may not apply.

Likelihood ratio. This statistic incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive**.** The likelihood ratio for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative

Logistic regression. A term used for a regression analysis in which the dependent or target variable is dichotomous.

Multiple linear mixed effects. These fit linear relationships between dependent and independent variables using mixed-effects models. Mixed effects models provide a powerful and flexible tool for the analysis of balanced and unbalanced grouped data in the presence of fixed and random effects.

Multiple linear regression. This aim of this analysis is to find a linear relationship between one dependent variable, and multiple independent variables

Multiple logistic regression. An extension of logistic regression to accommodate a dependent variable with more than 2 levels or categories (i.e. polytomous or multinomial variable)

Negative predictive value. The probability that the patient will not have the disease when restricted to all patients who test negative

Odds Ratio. This term differs from risk in that it involves two probabilities instead of just one and these are expressed in terms of a ratio. Specifically, odds are the ratio of the probability of an event occurring to the probability of the event not occurring

Pearson product-moment correlation coefficient. It is one example of a correlation coefficient. It is a measure of the linear association between two variables that have been measured on interval or ratio scales. It is calculated by dividing the covariance of the two variables by the product of their standard deviations

Positive Predictive Value. The probability that the patient has the disease when restricted to those patients who test positive

Relative Risk. A measure of the number of outcome events in the treatment group vs. the number in the control group. An RR = 1 indicates that the outcome rate is the same in both groups, i.e. the treatment group is no better or worse than the control group. An RR < 1 indicates that the event rate is less in the treatment group and an RR > 1 indicates that the event rate is more in the treatment group. The further that the RR is from 1, the greater the difference in event rates between the treatment and control

ROC. Receiver Operating Characteristic Curves. Used as a measure to assess the accuracy of diagnostic tests. They display the relationship between sensitivity (true positive rate) and 1-specificity (false positive rate) across all possible threshold values that define the positivity of a disease or condition. Summary measures i.e., the area under the curve (AUC) can explain the capacity of a test to discriminate a diseased from a non-diseased subject. An ROC curve for a perfect test has an area under the curve = 1.0 while a test that performs no better than by chance has an area under the curve of only 0.5

Sensitivity. The probability that the test is positive when given to a group of patients with the disease. A large sensitivity means that a negative test can rule out the disease

Simple (univariate) linear regression. This analysis aims to find a linear relationship between a response variable and a possible predictor variable by the method of least squares (the most common method of defining a straight line through a set of points on a scatterplot)

Simultaneous logistic regression. See multiple logistic regression.

Spearman's rank correlation coefficient. The nonparametric equivalent to the standard correlation coefficient (an expression of the relationship between two variables with one another)

Specificity. The probability that the test will be negative among patients who do not have the disease. A large specificity means that a positive test can rule in the disease

Standard Error (SE). The standard deviation of an estimate of a population parameter (thus, the standard error of the mean is the standard deviation of the estimate of the population mean value)

Stepwise Regression. Related to multiple regression analysis, but differs in that variables are entered into or removed from computational analysis one at a time to determine how much is "gained" or "lost" by each variable

Wilcoxon Mann-Whitney Test. This test does not require the assumption that the differences between the two samples are normally distributed. It is one of the most powerful of the non-parametric tests for comparing two populations. The *t*-test for independent samples (between groups), would be the comparable parametric test

Appendix A: Search terms for Peptides review

Main Review

MEDLINE® February 2005

natriuretic peptide, brain/
2. bnp.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. nt-probnp.mp.
4. brain-type natriuretic peptide.mp.
5. bnp1-32.mp.
6. bnp-32.mp.
7. bnp77-108.mp.
8. probnp.mp.
9. nt-probnp1-76.mp.
10. natriuretic factor-32.mp.
11. natriuretic peptide type-b.mp.
12. type-b natriuretic peptide.mp.
13. ventricular natriuretic peptide.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 14
16. limit 15 to yr=1989 – 2005

EMBASE 2005 Week 08

1 Brain Natriuretic Peptide/ct, ec, an, dv [Clinical Trial, Endogenous Compound, Drug Analysis, Drug Development] (2172)
2 bnp.tw. (1838)
3 nt-probnp.tw. (150)
4 brain-type natriuretic peptide.tw. (9)
5 bnp 1-32.tw. (4)
6 bnp1-32.tw. (1)
7 bnp-32.tw. (44)
8 bnp77-108.tw. (0)
9 bnp 77-108.tw. (2)
10 probnp.tw. (195)
11 nt-probnp1-76.tw. (0)
12 nt-probnp 1-76.tw. (1)
13 natriuretic factor-32.tw. (0)
14 natriuretic peptide type-b.tw. (3)
15 type-b natriuretic peptide.tw. (16)
16 ventricular natriuretic peptide.tw. (24)
17 or/1-16 (2895)

18 limit 17 to yr=1989-2005 (2881)
19 from 18 keep 1-1000 (1000)

CINAHL February 2005 Week 3

1 exp Peptides/an, me, bl, ph, st, df, du, ur [Analysis, Metabolism, Blood, Physiology, Standards, Deficiency, Diagnostic Use, Urine] (657)
2 nt-probnp.tw. (3)
3 brain-type natriuretic peptide.tw. (1)
4 bnp 1-32.tw. (0)
5 bnp-32.tw. (0)
6 bnp77-108.tw. (0)
7 probnp.tw. (3)
8 nt-probnp1-76.tw. (0)
9 natriuretic factor-32.tw. (0)
10 natriuretic peptide type-b.tw. (0)
11 type-b natriuretic peptide.tw. (0)
12 ventricular natriuretic peptide.tw. (0)
13 or/1-12 (659)
14 limit 13 to yr=1989-2005 (654)
15 from 14 keep 1-654 (654)

AMED February 2005

1 exp peptides/ (142)
2 bnp.tw. (2)
3 nt-probnp.tw. (0)
4 brain-type natriuretic peptide.tw. (0)
5 bnp 1-32.tw. (0)
6 bnp-32.tw. (0)
7 bnp77-108.tw. (0)
8 probnp.tw. (0)
9 nt-probnp1-76.tw. (0)
10 natriuretic factor-32.tw. (0)
11 natriuretic peptide type-b.tw. (0)
12 type-b natriuretic peptide.tw. (0)
13 ventricular natriuretic peptide.tw. (0)
14 or/1-13 (143)
15 limit 14 to yr=1989-2005 (143)
16 from 15 keep 1-143 (143)

Cochrane 2005 CDSR, ACP Journal Club, DARE

1 [Natriuretic Peptide, Brain/me, bi, bl, se, du [Metabolism, Biosynthesis, Blood, Secretion, Diagnostic Use]] (0)
2 bnp.mp. [mp=ti, ab, tx, kw, ct] (10)
3 nt-probnp.mp. [mp=ti, ab, tx, kw, ct] (0)
4 brain-type natriuretic peptide.tw. (0)
5 bnp1-32.tw. (0)
6 bnp-32.tw. (0)
7 bnp77-108.tw. (0)
8 probnp.tw. (0)
9 nt-probnp1-76.tw. (0)
10 natriuretic factor-32.tw. (0)
11 natriuretic peptide type-b.tw. (0)
12 type-b natriuretic peptide.tw. (0)
13 ventricular natriuretic peptide.tw. (0)
14 or/1-13 (10)
15 limit 14 to yr=1989-2005 [Limit not valid in: DARE; records were retained] (10)
17 from 15 keep 1-10 (10)

Review of Reviews

EMBASE 2005 Week 45

1 meta-analysis.sh,pt. or meta-analy:.tw. or metaanaly:.tw. (23869)
2 ((systematic: or quantitativ:) adj (review: or overview:)).tw. (7475)
3 (chochrane or medline or cinahl or embase or scisearch or psychinfo or psycinfo or psychlit or psyclit or (national and library)).tw. (12680)
4 ((handsearch: or search:) and (cochrane or medline or cinahl or embase or scisearch or psychinfo or psychlit or psyclit or (national and library) or (hand: or manual: or electronic: or bibliograph: or database:))).tw. (18474)
5 ((review or guideline).pt. or consensus.ti. or guideline:.ti. or literature.ti. or overview.ti. or review.ti.) and (3 and 4) (6533)
6 ((synthesis or overview or review or survey) and (systematic or critical or methodologic or quantitative or qualitative or literature or evidence or evidence-based)).ti. (21933)
7 1 or 2 or 3 or 4 or 5 or 6 (62142)
8 heart failure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (43809)
9 exp heart failure/ (54121)

10 8 or 9 (58713)
11 7 and 10 (1802)
12 diagnosis/ (1735)
13 diagnos:.ti. (75557)
14 12 or 13 (77064)
15 11 and 14 (27)
16 15 (27)
17 limit 16 to (english language and yr="2000 - 2005") (17)
18 from 17 keep 1-10 (10)

Ovid MEDLINE(R) October 2005 Week 4

1 meta-analysis.sh,pt. or meta-analy:.tw. or metaanaly:.tw. (17167)
2 ((systematic: or quantitativ:) adj (review: or overview:)).tw. (7963)
3 (chochrane or medline or cinahl or embase or scisearch or psychinfo or psycinfo or psychlit or psyclit or (national and library)).tw. (15249)
4 ((handsearch: or search:) and (cochrane or medline or cinahl or embase or scisearch or psychinfo or psychlit or psyclit or (national and library) or (hand: or manual: or electronic: or bibliograph: or database:))).tw. (22660)
5 ((review or guideline).pt. or consensus.ti. or guideline:.ti. or literature.ti. or overview.ti. or review.ti.) and (3 and 4) (9900)
6 ((synthesis or overview or review or survey) and (systematic or critical or methodologic or quantitative or qualitative or literature or evidence or evidence-based)).ti. (22940)
7 1 or 2 or 3 or 4 or 5 or 6 (59490)
8 heart failure.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (32938)
9 exp heart failure/ (23361)
10 8 or 9 (35572)
11 7 and 10 (683)
12 diagnos:.ti,ab. (402579)
13 diagnosis/ (1065)
14 12 or 13 (403061)
15 11 and 14 (121)
16 15 (121)
17 limit 16 to (english language and yr="2000 - 2005") (81)
18 [from 17 keep 1-159] (0)
19 from 17 keep 1-81 (81)

Appendix B: LEVEL 1 – TITLE & ABSTRACT SCREENING

1. Does citation evaluate BNP in any way? (using any related term: BNP, NT-proBNP, proBNP, BNP77-108, nt-proBNP1-76, brain type natriuretic peptide, natriuretic factor, natriuretic peptide type-b, type-b natriuretic peptide, ventricular natriuretic peptide B-type)

- (•) No
- ( ) Yes
- ( ) Unsure

Clear Selection

Submit Data

LEVEL 2 - LANGUAGE

1. Is this article published in English?

☐ YES

☐ NO (specify language)

☐ UNSURE

Clear Selection

Save to finish later | Submit Data

LEVEL 3 – FULL-TEXT SCREENING

	YES	NO (STOP NOW)	UNSURE (continue)	
1. **This report is published in English.**	☐	☐	☐	Clear
2. **The publication date is 1989 or later.**	☐	☐	☐	Clear
3. **This report describes a primary study.** (contains original data and is not an editorial, letter, comment, opinion, thesis, abstact only, or conference proceeding)	☐	☐	☐	Clear
4. **Samples evaluated include separately analyzed: serum or plasma or whole blood of adult (>/= 18 yr) humans (not cultured cells or urine).**	☐	☐	☐	Clear
5. **Test method is one of the following:** For BNP - Abbott laboratories - AxSYM - Bayer Healthcare - ADVIA Centaur - Beckman Couldter - Access or Access (Biosite) - Biosite Diagnostics - Triage - Shionogi & Co. Ltd.- No instrument, Shionoria-IRMA (manual assay) For NT-proBNP - Biomedica Grupe - No instrument, EIA (manual assay) - Dade Behring - Dimension - Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular - Manual method referencing: Karl J, Borgya A, Gallusser A, et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81 - New Zealand (Christchurch) - No instrument, manual assay (Author may be Mark Richards)	☐	☐	☐	Clear

	YES (STOP NOW)	NO (continue)	UNSURE (continue)	
6. **This is a case report or a case series with </= 10 subjects.**	☐	☐	☐	Clear
7. **This is a report of a trial of effectiveness of Nesiritide (Natrecor) or any natriuretic peptide?**	☐	☐	☐	Clear

8. **Report examines any aspect of health status of subjects who had BNP or NT-proBNP level measured.**

Examples of aspects of health status include:
cardiac events
cardiac testing
blood pressure
blood levels of substances other than BNP
chest x-ray
etc

☐ YES

☐ NO (STOP NOW)

☐ UNSURE

9. **Is a diagnosis of Heart Failure or a marker for Heart Failure an outcome?**

(they must have used one of these terms for Heart Failure, Congestive Heart Failure, HF, CHF, NYHA criteria, NYHA functional class, cardiac dysfunction) or analyzed one of the following markers for HF:
Anginal pain

Anginal syndrome
Ankle swelling
Bilateral leg edema
Breathlessness
Cardiac dysfunction
Cardiac insufficiency
Cardiomegaly on chest x-ray
Diastolic distensibility
Diastolic dysfunction
Diastolic dysfunction on cardiac catheterization
Diastolic stiffness
Dyspnea
EF
Elevated jugular venous pressure
Fatigue
Fluid retention
Hepatomegaly
Left Ventricular (LV) relaxation, filling
Left Ventricular (LV) systolic function (or dysfunction)
Nocturnal cough
Orthopnea
Palpitation
Paroxysmal nocturnal dyspnea
Peripheral edema
Pleural effusion
Pulmonary congestion
Pulmonary rales
Tachycardia (heart rate >/= 120 beats/min
Third heart sound
Ventricular dysfunction
Weight loss

☐ YES

☐ NO

☐ UNSURE

10. **Was one of the following tests performed?**

Chest X-ray
Echocardiography
Myocardial radionuclide angiogram (MRNA)
Dobutamine echo
Cardiac catheter
MRI
CT
pulmonary / vascular measures

☐ YES

☐ NO

☐ UNSURE

11. **Were either of the two previous questions answered with a 'NO'?**

☐ YES

☐ NO

12. **Are cardiac events presented as outcomes? (see list below)**

CARIOVASCULAR EVENTS
Admission to hospital for any of the relevant outcomes below:

Angina requiring a minimum 24 hour hospitalization (Acute Coronary Syndrome)
Angiographic percutaneous coronary interventions (PCI) including terms:
Angioplasty

Bypass surgery
CABG (Coronary Artery Bypass Graft)
Cardiac revascularization
PCTA (Percutaneous Transluminal Coronary Angioplasty)
Stent
Atrial fibrillation (arrhythmias)
Cerebrovascular event (e.g. Stroke)
Composite endpoint
Congestive heart failure (CHF)
Isolated diastolic ventricular dysfunction
Mortality (all cause)
Myocardial infarction (MI)

☐ YES

☐ NO

☐ UNSURE

13. **Do subjects who had BNP or NT-proBNP measured have a diagnosis of heart failure? (stable heart failure)**
By Criteria of:
American College of Cardiology (ACC) / American Heart Association (AHA)
New York Heart Association (NYHA)
Canadian Cardiovascular Society (CCS)
Modified Framingham Clinical Criteria for the Diagnosis of Heart Failure
European Study Group on Diastolic Heart Failure

☐ YES

☐ NO

☐ UNSURE

14.
Are subjects who have BNP or NT-proBNP measured being evaluated for the effect of a treatment (medication, lifestyle intervention, surgery or therapy) intended to improve symptoms of heart failure?
Treatments
Medications:
Angiotensin Converting Enzyme (ACE) Inhibitors
Angiotensin Receptor Blocker Therapy
Beta Blockers
Cardiac Glycosides
Diuretics
Nitrates
Spironolactone

Surgeries, Procedures and Medical Devices:
Balloon Valvuloplasty Catheter
Enhanced Counterpulsation (ECP)
Heart Valve Replacement Surgery
Intra-Aortic Balloon Pump (IABP) Insertion
Prosthetic Heart Valve
Ventricular Assist Device(VAD)
Valvuloplasty (Balloon or Surgical)

Healthy Lifestyles:
Exercise
Maintain A Healthy Weight
Eat A Healthy Diet
Control Blood Pressure

Control Blood Cholesterol

Prevent And Manage Diabetes Mellitus

Quit Smoking

Manage Stress

- YES
- NO
- UNSURE

15. Were either of the two previous questions answered with a 'NO"?

- YES
- NO

LEVEL 5 – Q1 SCREENING

1. Is a biological or analytical determinant described?

☐ YES

☐ NO

☐ Paper should be excluded overall

Save to finish later | Submit Data

LEVEL 6 – Q2a SCREENING

1. Is BNP evaluated as a marker of heart failure (or synonyms)?

☐ YES - HF as defined by criteria of NYHA, ACC/AHA, CCS, Modified Framingham Clinical Criteria for the Diagnosis of HF, European Study Group on Diastolic HF

☐ Compared to Left ventricular ejection fraction , (Left) ventricular dysfunction, Cardiac dysfunction, Reduced left ventricular function

☐ Compared to other signs or symptoms of HF

☐ NO

2. Is the population an included one? (i.e. not heart transplant, renal disease patients)

☐ NO

☐ YES

3. Has paper been excluded by either of the two previous questions?

☐ YES

☐ NO

4. What is the setting of the study? (Use of text box not required)

- [ ] Emergency Department
- [ ] Specialized clinic or outpatient setting (cardiovascular)
- [ ] Primary care physician
- [ ] Long-term care setting
- [ ] Other

Save to finish later | Submit Data

LEVEL 7 – Q2b SCREENING

1. Does the paper report results of multiple linear regression or multiple logistic regression of variables that can be used in the diagnosis of HF?

☐ YES

☐ NO

Clear Selection

Save to finish later | Submit Data

LEVEL 8 – Q3 SCREENING

1. Does this report present data which uses BNP or NT-ProBNP to predict one or more cardiac events? (Use of text box is not required)

- ☐ NO
- ☐ YES - CAD
- ☐ YES - RISK FOR CAD
- ☐ YES - SCREEN
- ☐ YES - HF
- ☐ YES - OTHER

LEVEL 9 – Q4 SCREENING

1.

Does study include separately analyzed (for BNP or NT-proBNP and other outcomes) subjects with Heart Failure diagnosed by the criteria of one of the following: (it is not required to use text boxes)

American College of Cardiology (ACC) / American Heart Association (AHA)

New York Heart Association (NYHA)

Canadian Cardiovascular Society (CCS)

Modified Framingham Clinical Criteria for the Diagnosis of Heart Failure

European Study Group on Diastolic Heart Failure

☐ Yes

☐ No

2. At what timepoints were reported BNP measures taken?

☐ Baseline only

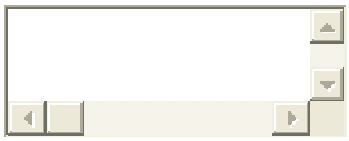
☐ Baseline plus one other

☐ Multiple timepoints (more than two)

☐ Other

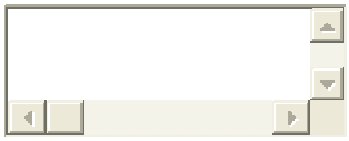
LEVEL 10 – Q1 DATA

1. What population type by inclusion criteria was the determinant assessed in?



Enlarge Shrink

2. What population type by exclusion criteria was the determinant assessed in?



Enlarge Shrink

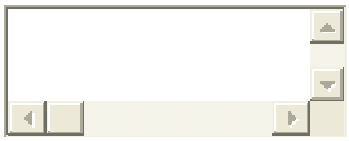
	1	2	3	4	5
3. Determinant name (use checkbox to indicate determinant)	☐	☐	☐	☐	☐
4. Determinant category (PF; PV; DC; DN; TN; TD; AP; AI)	☐	☐	☐	☐	☐
5. Effect of determinant (inc; dec; none)	☐	☐	☐	☐	☐
6. Briefly describe effect	☐	☐	☐	☐	☐

Question 4.	

Determinant category	Code
Physiologic-Fixed	PF
Physiologic-Variable	PV
Disease-Cardiac	DC
Disease - Noncardiac	DN
Treatment - Nondrug	TN
Treatment - Drug	TD
Analytical - Processing	AP
Analytical - Interference	AI
Question 5.	
Effect of Determinant	**Code**
Increase	Inc
Decrease	Dec
No effect	None

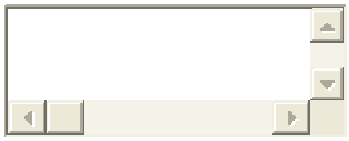
LEVEL 11 – Q2a DATA

1. Number of subjects



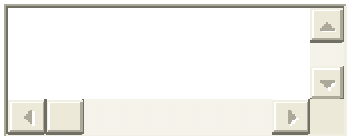
Enlarge Shrink

2. Prevalence



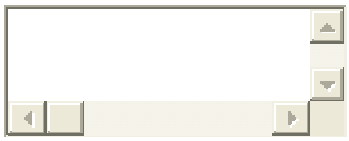
Enlarge Shrink

3. Description of study population



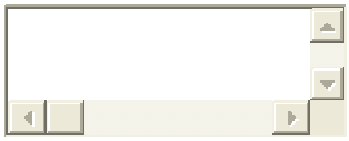
Enlarge Shrink

4. Reference test



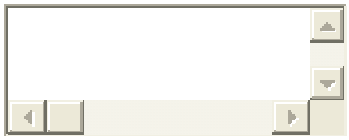
Enlarge Shrink

5. Reference decision point



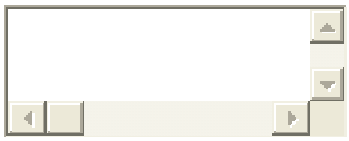
Enlarge Shrink

6. Index test



Enlarge Shrink

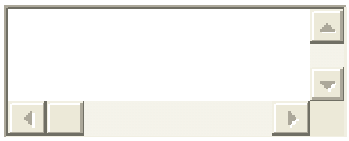
7. Index decision point



Enlarge Shrink

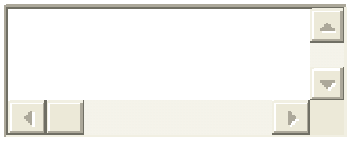
	Outcome positive	Outcome negative
8. Test positive		
9. Test negative		

10. Sensitivity



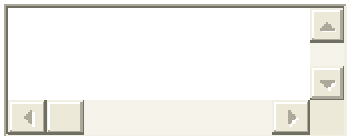
Enlarge Shrink

11. Specificity



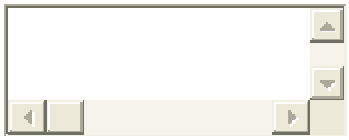
Enlarge Shrink

12. Accuracy



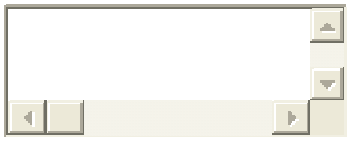
Enlarge Shrink

13. Likelihood Ratio +ve



Enlarge Shrink

14. Likelihood Ratio -ve



Enlarge Shrink

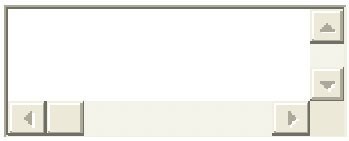
15. Area under ROC

Enlarge Shrink

Save to finish later | Submit Data

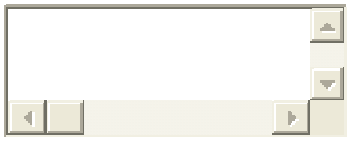
LEVEL 13 – Q3 DATA

1. PC Risk factors (CAD/Other)



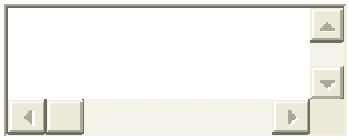
Enlarge Shrink

2. Number of subjects (control/treatment)



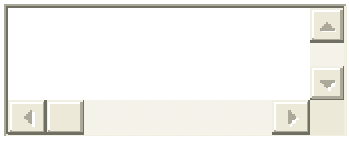
Enlarge Shrink

3. Diagnosis criteria



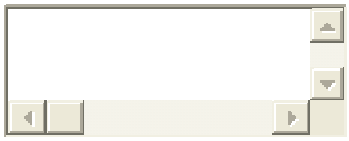
Enlarge Shrink

4. Unit /BNP threshold



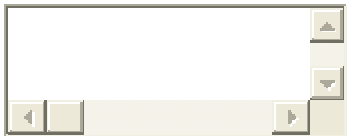
Enlarge Shrink

5. Primary outcomes



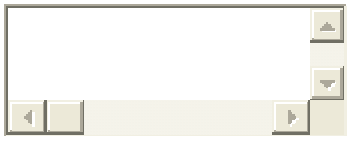
Enlarge Shrink

6. Secondary outcomes



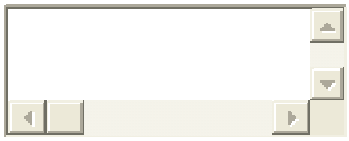
Enlarge Shrink

7. Ascertainment outcome



Enlarge Shrink

8. Number of events

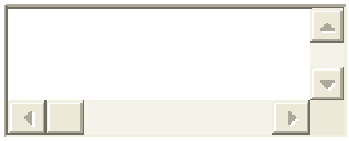


Enlarge Shrink

9. Follow-up (average time)

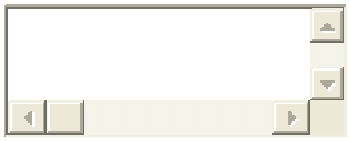
Enlarge Shrink

10. Analysis / model (adjusted / unadjusted)



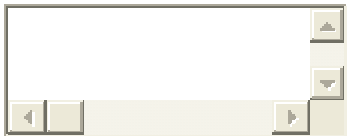
Enlarge Shrink

11. Variables (multivariate)



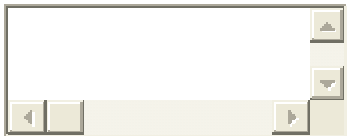
Enlarge Shrink

12. Risk estimate (RR or OR or HR)(CI)



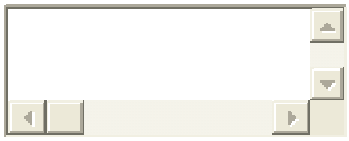
Enlarge Shrink

13. Other measures of association (means/proportions)



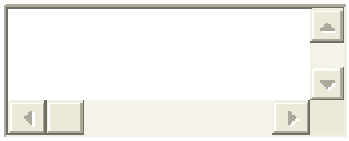
Enlarge Shrink

14. Quality assessment score



Enlarge Shrink

15. COMMENTS



Enlarge Shrink

16. Were subjects a consecutive cohort?

YES

NO

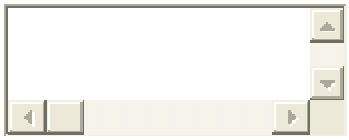
OTHER

17. Was blinding reported?

YES

Not Reported

18. Prior surgery?



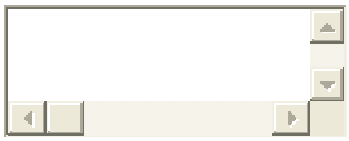
Enlarge Shrink

Save to finish later Submit Data

Bottom of Form

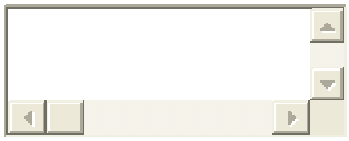
LEVEL 14 – Q4 DATA

1. Patient population



Enlarge Shrink

2. Which treatment(s) are being monitored by BNP or NT-proBNP.



Enlarge Shrink

3. What outcomes are being correlated to BNP or NT-proBNP?

- [ ] CV death
- [ ] Hospital admission for heart failure
- [ ] QOL questionnaire score
- [ ] Blood pressure
- [ ] LEV change
- [ ] All-cause Mortality
- [ ] Cardiac volumes (or dimensions)
- [ ] Pulmonary capillary wedge pressure
- [ ] Cardiac output
- [ ] Right atrial pressure
- [ ] Other hemodynamic outcome
- [ ] Exercise test results
- [ ] 6 minute wald test distance
- [ ] NYHA class

- [ ] Other

4. Describe the effect of the treatment.

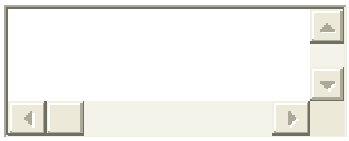
- ☐ CV death
- ☐ Hospital admission for heart failure
- ☐ Correlation between BNP and other parameter
- ☐ Blood pressure
- ☐ LEV change
- ☐ All-cause mortality
- ☐ Cardiac volumes (or dimensions)
- ☐ Pulmonary capillary wedge pressure
- ☐ Cardiac output
- ☐ Right atrial pressure
- ☐ Other hemodynamic outcome
- ☐ Exercise test results
- ☐ 6 minute wald test distance
- ☐ NYHA class

- ☐ Other

Save to finish later | Submit Data

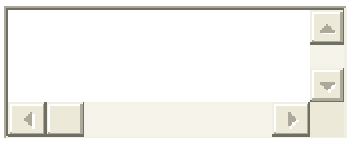
LEVEL 15 – GENERAL DATA

1. What is first author's surname?



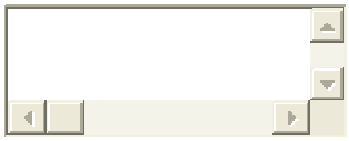
Enlarge Shrink

2. In what country was study carried out? (If not stated clearly, in what country did authors usually work?)



Enlarge Shrink

3. What is the study name (cohort identifier)? (enter none, if one does not exist)



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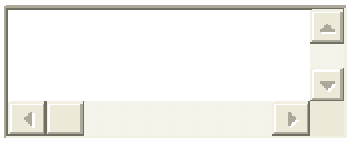
4. What is the sample size? (Choose the number of subjects originally included in the trial, for all conditions)

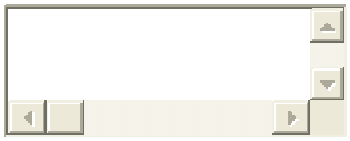


Enlarge Shrink

5. What is the mean age of subjects? (Provide whatever information is available)

- ☐ All subjects mean age
- ☐ Condition 1 mean age
- ☐ Condition 2 mean age
- ☐ All subjects age range
- ☐ Condition 1 age range
- ☐ Condition 2 age range
- ☐ Condition 3 mean age
- ☐ Condition 3 age range
- ☐ Condition 4 mean age
- ☐ Condition 4 age range
- ☐ Not stated

6. What is the % male subjects in the entire population?



Enlarge Shrink

7. What test method was used to measure BNP or NT-proBNP?

- [ ] [BNP] Abbott Labs - AxSYM
- [ ] [BNP] Bayer Healthcare - ADVIA Centaur
- [ ] [BNP] Beckman Coulter - Access or Access (Biosite)
- [ ] [BNP] Biosite Diagnostics - Triage
- [ ] [BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay)
- [ ] [NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay)
- [ ] [NT-proBNP] Dade Behring - Dimension
- [ ] [NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular
- [ ] [NT-proBNP] Manual method referencing - Carl J., Borgya A., Gallusser A. et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81
- [ ] [NT-proBNP] New Zealand (Christchurch) - no instrument, manual assay
- [ ] None of the above

8. Name the funding source for the trial?

- [ ] Funding support
- [ ] Supplies
- [ ] Direct involvement (analysis, authorship etc)
- [ ] Unstated

9. What is the study design?

- [ ] Diagnostic

- [ ] Randomized trial
- [ ] Non-randomized trial
- [ ] Prospective cohort
- [ ] Retrospective cohort
- [ ] Case-control
- [ ] Time series
- [ ] Before-after
- [ ] Cross-sectional
- [ ] Other (specify)
- [ ] Not reported

Save to finish later | Submit Data

Critical Appraisal of Systematic Reviews

Are the results of the study valid? (Internal Validity)

1. Did the systematic review address a focused clinical question?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The clinical population, the diagnostic test, and relevant comparators.	The *Title, Abstract or final paragraph of the Introduction* should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
2. Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, tests and compartors. In many cases the type of study design will also be a key component of the eligibility criteria.	The *Methods* section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
3. Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for a comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, EMBASE, etc) but should also include a search of reference lists from relevant studies, use of Science Citation Index, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The *Methods* section should describe the search strategy, including the terms used, in some detail. The *Results* section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
4. Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., consecutive patients, blinding of tests and reference standards, and completeness of verification).	The *Methods* section should describe the assessment of quality and the criteria used. The *Results* section should provide information on the quality of the individual studies.

This paper: Yes □ No □ Unclear □

Comment:

5. Were assessments of studies reproducible?

What is best?	Where do I find the information?
The studies should be assessed independently by at least 2 reviewers and the procedure to deal with disagreement should be provided.	*Methods* section should describe the how the assessments was done and by whom.

This paper: Yes □ No □ Unclear □

Comment:

6. Were the results similar from study to study?

What is best?	Where do I find the information?
The results of the different studies may be similar or homogeneous. The authors may estimate whether there is statistically significant heterogeneity. Possible reasons for the heterogeneity (population characteristics or study methods) should be explored.	The *Results* section should state whether the results are heterogeneous and discuss possible reasons. The SROC should illustrate the heterogeneity due to differences in threshold (spread along the SROC line), discrimination (spread around the SROC line) and the extent to which the SROC varies by population characteristics or study quality.

This paper: Yes □ No □ Unclear □

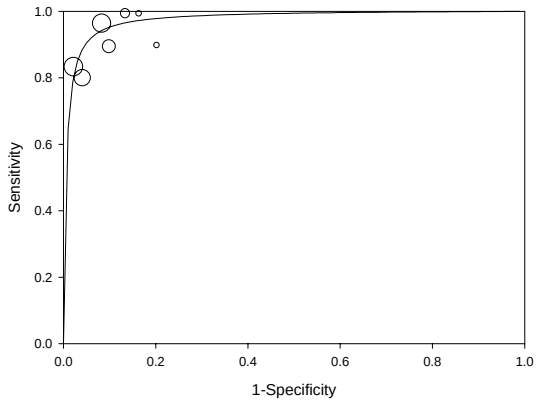
Comment:

What were the results?

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. Results are traditionally displayed in a figure, like the one below, called a SROC plot.

The SROC plot depicted above represents a meta-analysis of 5 studies that assessed the accuracy of the whispered



voice test.

Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for scatter of the studies compared to the summary ROC . In the example above note that the solid line is the SROC and the points are well placed along this indicating little heterogeneity.

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity.

RCT QUALITY ASSESSMENT
Systematic Review of Sport and Recreational Injury Prevention Strategies

Reference ID/RM # _____ Date of Review _____
Reviewer_____

Q1. Was the study described as randomized?
A trial reporting that it is "randomized" is to receive one point.

Yes	1
No	0

Q2. If randomized, was the randomization appropriate?
Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) a point is deducted.
If no information on randomization is given, no point is given or deducted (i.e. "0").

Yes	1
No	-1

Randomization = ___ / 2

Q3. Was the study described as double-blind?
A trial reporting that it is "double blind", it is to receive one point.

Yes	1
No	0

Q4. If double-blind, was the blinding appropriate?
Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to receive an additional point. However, if the report describes the trial as double blind and uses an inappropriate method (comparison of tablets versus injection with no double dummy), a point is deducted.
If no information on blinding is given, no point is given or deducted (i.e. "0").

Yes	1
No	-1

Double-blind = ___ / 2

Q5. Was there a description of withdrawals and drop-outs?
A trial reporting the number and reasons for withdrawals are to receive one point. If there is no statement, no point is given.

Yes	1

No	0

Withdrawals and drop-outs = ___ / 1

Total = ___ / 5

Poor Quality < 3

QUADAS Quality Screening

From:
Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003, 3:25-.

Users' guide to QUADAS

1. Was the spectrum of patients representative of the patients who will receive the test in practice?

a. What is meant by this item

Differences in demographic and clinical features between populations may produce measures of diagnostic accuracy that vary considerably, this is known as spectrum bias. It refers more to the generalisability of results than to the possibility that the study may produce biased results. Reported estimates of diagnostic accuracy may have limited clinical applicability (generalisability) if the spectrum of tested patients is not similar to the patients in whom the test will be used in practice. The spectrum of patients refers not only to the severity of the underlying target condition, but also to demographic features and to the presence of differential diagnosis and/or co-morbidity. It is therefore important that diagnostic test evaluations include an appropriate spectrum of patients for the test under investigation and also that a clear description is provided of the population actually included in the study.

b. Situations in which this item does not apply

This item is relevant to all studies of diagnostic accuracy and should always be included in the quality assessment tool.

c. How to score this item

Studies should score "yes" for this item if you believe, based on the information reported or obtained from the study's authors, that the spectrum of patients included in the study was representative of those in whom the test will be used in practice. The judgement should be based on both the method of recruitment and the characteristics of those recruited. Studies which recruit a group of healthy controls and a group known to have the target disorder will be coded as "no" on this item in nearly all circumstances. Reviewers should pre-specify in the protocol of the review what spectrum of patients would be acceptable taking factors such as disease prevalence and severity, age, and sex, into account. If you think that the population studied does not fit into what you specified as acceptable, the item should be scored as "no". If there is insufficient information available to make a judgement then it should be scored as "unclear".

2. Were selection criteria clearly described?

a. What is meant by this item

This refers to whether studies have provided a clear definition of the criteria used as in- and exclusion criteria for entry into the study.

b. Situations in which this item does not apply

This item is relevant to all studies of diagnostic accuracy and should always be included in the quality assessment tool.

c. How to score this item

If you think that all relevant information regarding how participants were selected for inclusion in the study has been provided then this item should be scored as "yes". If study selection criteria are not clearly reported then this item should be scored as "no". In situations where selection criteria are partially reported and you feel that you do not have enough information to score this item as "yes", then it should be scored as "unclear".

3. Is the reference standard likely to correctly classify the target condition?

a. What is meant by this item

The reference standard is the method used to determine the presence or absence of the target condition. To assess the diagnostic accuracy of the index test its results are compared with the results of the reference standard; subsequently indicators of diagnostic accuracy can be calculated. The reference standard is therefore an important determinant of the diagnostic accuracy of a test. Estimates of test performance are based on the assumption that the index test is being compared to a reference standard which is 100% sensitive and specific. If there are any disagreements between the reference standard and the index test then it is assumed that the index test is incorrect. Thus, from a theoretical point of view the choice of an appropriate reference standard is very important.

b. Situations in which this item does not apply

This item is relevant to all studies of diagnostic accuracy and should always be included in the quality assessment tool.

c. How to score this item

If you believe that the reference standard is likely to correctly classify the target condition or is the best method available, then this item should be scored "yes". Making a judgement as to the accuracy of the reference standard may not be straightforward. You may need experience of the topic area to know whether a test is an appropriate reference standard, or if a combination of tests are used you may have to consider carefully whether these were appropriate. If you do not think that the reference standard was likely to have correctly classified the target condition then this item should be scored as "no". If there is insufficient information to make a judgement then this should be scored as "unclear".

4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

a. What is meant by this item

Ideally the results of the index test and the reference standard are collected on the same patients at the same time. If this is not possible and a delay occurs, misclassification due to spontaneous recovery or to progression to a more advanced stage of disease may occur. This is known as disease progression bias. The length of the time period which may cause such bias will vary between conditions. For example a delay of a few days is unlikely to be a problem for chronic conditions, however, for many infectious diseases a delay between performance of index and reference standard of only a few days may be important. This type of bias may occur in chronic conditions in which the reference standard involves clinical follow-up of several years.

b. Situations in which this item does not apply

This item is likely to apply in most situations.

c. How to score this item

When to score this item as "yes" is related to the target condition. For conditions that progress rapidly even a delay of several days may be important. For such conditions this item should be scored "yes" if the delay between the performance of the index and reference standard is very short, a matter of hours or days. However, for chronic conditions disease status is unlikely to change in a week, or a month, or even longer. In such conditions longer delays between performance of the index and reference standard may be scored as "yes". You will have to make judgements regarding what is considered "short enough". You should think about this before starting work on a review, and define what you consider to be

"short enough" for the specific topic area that you are reviewing. If you think the time period between the performance of the index test and the reference standard was sufficiently long that disease status may have changed between the performance of the two tests then this item should be scored as "no". If insufficient information is provided this should be scored as "unclear".

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard?

a. What is meant by this item

Partial verification bias (also known as work-up bias, (primary) selection bias, or sequential ordering bias) occurs when not all of the study group receive confirmation of the diagnosis by the reference standard. If the results of the index test influence the decision to perform the reference standard then biased estimates of test performance may arise. If patients are randomly selected to receive the reference standard the overall diagnostic performance of the test is, in theory, unchanged. In most cases however, this selection is not random, possibly leading to biased estimates of the overall diagnostic accuracy.

b. Situations in which this item does not apply

Partial verification bias generally only occurs in diagnostic cohort studies in which patients are tested by the index test prior to the reference standard. In situations where the reference standard is assessed before the index test, you should firstly decide whether there is a possibility that verification bias could occur, and if not how to score this item. This may depend on how quality will be incorporated in the review. There are two options: either to score this item as 'yes', or to remove it from the quality assessment tool.

c. How to score this item

If it is clear from the study that all patients, or a random selection of patients, who received the index test went on to receive verification of their disease status using a reference standard then this item should be scored as "yes". This item should be scored as yes even if the reference standard was not the same for all patients. If some of the patients who received the index test did not receive verification of their true disease state, and the selection of patients to receive the reference standard was not random, then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

6. Did patients receive the same reference standard regardless of the index test result?

a. What is meant by this item

Differential verification bias occurs when some of the index test results are verified by a different reference standard. This is especially a problem if these reference standards differ in their definition of the target condition, for example histopathology of the appendix and natural history for the detection of appendicitis. This usually occurs when patients testing positive on the index test receive a more accurate, often invasive, reference standard than those with a negative test result. The link (correlation) between a particular (negative) test result and being verified by a less accurate reference standard will affect measures of test accuracy in a similar way as for partial verification, but less seriously.

b. Situations in which this item does not apply

Differential verification bias is possible in all types of diagnostic accuracy studies.

c. How to score this item

If it is clear that patients received verification of their true disease status using the same reference standard then this item should be scored as "yes". If some

patients received verification using a different reference standard this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

a. What is meant by this item

When the result of the index test is used in establishing the final diagnosis, incorporation bias may occur. This incorporation will probably increase the amount of agreement between index test results and the outcome of the reference standard, and hence overestimate the various measures of diagnostic accuracy. It is important to note that knowledge of the results of the index test alone does not automatically mean that these results are incorporated in the reference standard. For example, a study investigating MRI for the diagnosis of multiple sclerosis could have a reference standard composed of clinical follow-up, CSF analysis and MRI. In this case the index test forms part of the reference standard. If the same study used a reference standard of clinical follow-up and the results of the MRI were known when the clinical diagnosis was made but were not specifically included as part of the reference then the index test does not form part of the reference standard.

b. Situations in which this item does not apply

This item will only apply when a composite reference standard is used to verify disease status. In such cases it is essential that a full definition of how disease status is verified and which tests form part of the reference standard are provided. For studies in which a single reference standard is used this item will not be relevant and should either be scored as yes or be removed from the quality assessment tool.

c. How to score this item

If it is clear from the study that the index test did not form part of the reference standard then this item should be scored as "yes". If it appears that the index test formed part of the reference standard then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

8. Was the execution of the index test described in sufficient detail to permit replication of the test?

9. Was the execution of the reference standard described in sufficient detail to permit its replication?

a. What is meant by these items

A sufficient description of the execution of index test and the reference standard is important for two reasons. Firstly, variation in measures of diagnostic accuracy can sometimes be traced back to differences in the execution of index test or reference standard. Secondly, a clear and detailed description (or citations) is needed to implement a certain test in another setting. If tests are executed in different ways then this would be expected to impact on test performance. The extent to which this would be expected to affect results would depend on the type of test being investigated.

b. Situations in which these items do not apply

These items are likely to apply in most situations.

c. How to score these items

If the study reports sufficient details or citations to permit replication of the index test and reference standard then these items should be scored as "yes". In other cases these items should be scored as "no". In situations where details of test

performance are partially reported and you feel that you do not have enough information to score this item as "yes", then it should be scored as "unclear".

10. Were the index test results interpreted without knowledge of the results of the reference standard?

11. Were the reference standard results interpreted without knowledge of the results of the index test?

a. What is meant by these items

This item is similar to "blinding" in intervention studies. Interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This is known as review bias, and may lead to inflated measures of diagnostic accuracy. The extent to which this may affect test results will be related to the degree of subjectiveness in the interpretation of the test result. The more subjective the interpretation the more likely that the interpreter can be influenced by the results of the reference standard in interpreting the index test and vice versa. It is therefore important to consider the topic area that you are reviewing and to determine whether the interpretation of the index test or reference standard could be influenced by knowledge of the results of the other test.

b. Situations in which these items do not apply

If, in the topic area that you are reviewing, the index test is always performed first then interpretation of the results of the index test will usually be without knowledge of the results of the reference standard. Similarly, if the reference standard is always performed first (for example, in a diagnostic case-control study) then the results of the reference standard will be interpreted without knowledge of the index test. However, if test results can be interpreted at later date, after both the index test and reference standard have been completed, then

it is still important for a study to provide a description of whether the interpretation of each test was performed blind to the results of the other test. In situations where one form of review bias does not apply there are two possibilities: either score the relevant item as "yes" or remove this item from the list. If tests are entirely objective in their interpretation then test interpretation is not susceptible to review bias. In such situations review bias may not be a problem and these items can be omitted from the quality assessment tool. Another situation in which this form of bias may not apply is when tests results are interpreted in an independent laboratory. In such situations it is unlikely that the person interpreting the test results will have knowledge of the results of the other test (either index test or reference standard).

c. How to score these items

If the study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test then these items should be scored as "yes". If this does not appear to be the case they should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

a. What is meant by this item

The availability of clinical data during interpretation of test results may affect estimates of test performance. In this context clinical data is defined broadly to include any information relating to the patient obtained by direct observation such as age, sex and symptoms. The knowledge of such factors can influence the diagnostic test result if the test involves an interpretative component. If clinical data will be available when the test is interpreted in practice then this should also be available when the test is evaluated. If however, the index test is intended to replace other clinical tests then clinical data should not be available, or should be

available for all index tests. It is therefore important to determine what information will be available when test results are interpreted in practice before assessing studies for this item.

b. Situations in which this item does not apply

If the interpretation of the index test is fully automated and involves no interpretation then this item may not be relevant and can be omitted from the quality assessment tool.

c. How to score this item

If clinical data would normally be available when the test is interpreted in practice and similar data were available when interpreting the index test in the study then this item should be scored as "yes". Similarly, if clinical data would not be available in practice and these data were not available when the index test results were interpreted then this item should be scored as "yes". If this is not the case then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

13. Were uninterpretable/ intermediate test results reported?

a. What is meant by this item

A diagnostic test can produce an uninterpretable/indeterminate/intermediate result with varying frequency depending on the test. These problems are often not reported in diagnostic accuracy studies with the uninterpretable results simply removed from the analysis. This may lead to the biased assessment of the test characteristics. Whether bias will arise depends on the possible correlation between uninterpretable test results and the true disease status. If uninterpretable results occur randomly and are not related to the true disease status of the individual then, in theory, these should not have any effect on test performance. Whatever the cause of uninterpretable results it is important that

these are reported so that the impact of these results on test performance can be determined.

b. Situations in which this item does not apply

This item is relevant to all studies of diagnostic accuracy and should always be included in the quality assessment tool.

c. How to score this item

If it is clear that all test results, including uninterpretable/indeterminate/intermediate are reported then this item should be scored as "yes". If you think that such results occurred but have not been reported then this item should be scored as "no". If it is not clear whether all study results have been reported then this item should be scored as "unclear".

14. Were withdrawals from the study explained?

a. What is meant by this item

This occurs when patients withdraw from the study before the results of either or both of the index test and reference standard are known. If patients lost to follow-up differ systematically from those who remain, for whatever reason, then estimates of test performance may be biased.

b. Situations in which this item does not apply

This item is relevant to all studies of diagnostic accuracy and should always be included in the quality assessment tool.

c. How to score this item

If it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported, then this item should be scored as

"yes". If it appears that some of the participants who entered the study did not complete the study, i.e. did not receive both the index test and reference standard, and these patients were not accounted for then this item should be scored as "no". If it is not clear whether all patients who entered the study were accounted for then this item should be scored as "unclear".

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Palmer, 2003	ACE genotype DD		increase	NT-proBNP -Christchurch
Schnabel, 2005	ACS	No ACS	increase	NT-proBNP - Elecsys
Ueda, 2003	Activities of daily living score		increase	BNP - Shionogi
Ray, 2004	Acute right heart failure (no CPE group)	No acute right HF (no CPE group)	none	BNP - Triage
Richards, 1998	Adrenomedullin		increase	NT-proBNP - Christchurch
Maisel, 2004a	African-American	Caucasian	none	BNP - Triage
Bettencourt, 2000a	Age		increase	BNP - Shionogi
Grabowski, 2004	Age		increase	BNP - Triage
James, 2003	Age		increase	NT-proBNP - Elecsys
Lainchbury, 2003	Age		increase	NT-proBNP -Christchurch
Lindahl, 2005	Age		increase	NT-proBNP - Elecsys
Olsen, 2004	Age		increase	NT-proBNP - Elecsys
Omland, 1996	Age		increase	BNP - Shionogi
Redfield, 2004	Age		increase	BNP - Triage
Redfield, 2004	Age		increase	BNP - Triage
Suzuki, 2002	Age		increase	BNP - Shionogi
Tsutamoto, 1997	Age		increase	BNP - Shionogi
Ueda, 2003	Age		increase	BNP - Shionogi
Tarnow, 2005	Age (DN)		increase	NT-proBNP - Elecsys

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Latini, 2004a	Aldosterone		none	BNP - Shionogi
Shiga, 2003	Amiodarone	No Amiodarone	decrease	BNP - Shionogi
Shiga, 2003	Amiodarone	Baseline	decrease	BNP - Shionogi
James, 2003	Angina, stable		increase	NT-proBNP - Elecsys
Olsen, 2004	Angina, stable	without CV risk	none	NT-proBNP - Elecsys
Bertinchant, 2005	ANP		increase	BNP - Shionogi
Omland, 1996	ANP		increase	BNP - Shionogi
Richards, 1998	ANP		increase	NT-proBNP - Christchurch
Tsutamoto, 1997	ANP		increase	BNP - Shionogi
Weber, 2004	Aortic stenosis, mild	Normal LVF	increase	NT-proBNP - Elecsys
Weber, 2004	Aortic stenosis, moderate	Normal LVF	increase	NT-proBNP - Elecsys
Weber, 2004	Aortic stenosis, severe	Normal LVF	increase	NT-proBNP - Elecsys
Nielsen, L.S., 2004	Arrhythmia	Non-cardiac dyspnoea	increase	NT-proBNP - Roche (manual)
Stanek, 2001	Atenolol	Baseline	decrease	BNP - Shionogi
Dias, 2001	Atrial fibrillation	Sinus Rhythym	none	BNP - Shionogi
Fung, 2003	Beta-blocker (carvedilol, metoprolol)	Baseline	decrease	NT-proBNP - Roche (manual)
Yoshizawa, 2004	Beta-blocker (carvedilol, metoprolol)	Baseline	none	BNP - Shionogi
Latini, 2004a	Big endothelin-1		increase	BNP - Shionogi
Stanek, 2001	Big endothelin-1		increase	BNP - Shionogi
Bettencourt, 1999	Blood pressure	(hypertension group)	none	BNP - Shionogi
Tsutamoto, 1997	Blood pressure		none	BNP - Shionogi
Ueda, 2003	Blood pressure		none	BNP - Shionogi
Kawai, 2001	Blood pressure, systolic	Baseline	none	BNP - Shionogi
Olsen, 2004	Blood pressure, systolic		increase	NT-proBNP - Elecsys
Suzuki, 2002	Blood pressure, systolic		none	BNP - Shionogi

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Tarnow, 2005	Blood pressure, systolic (DN)		increase	NT-proBNP - Elecsys
Suzuki, 2002	BMI		none	BNP - Shionogi
Ueda, 2003	BMI		none	BNP - Shionogi
Taniguchi, 2004	Cardiac decompensation	No cardiac decompensation	increase	NT-proBNP - Roche (commercial)
Tsutamoto, 1997	Cardiac index		none	BNP - Shionogi
Ray, 2004	Cardiogenic pulmonary edema (CPE)	Obstructive lung disease	increase	BNP - Triage
Bettencourt, 2004	Carvedilol	No beta-blocker	decrease	BNP - Shionogi
Hartmann, 2004a	Carvedilol	Placebo	none	NT-proBNP - Roche (manual)
Kawai, 2001	Carvedilol	No carvedilol	none	BNP - Shionogi
Sliwa, 2004	Carvedilol	Perindopril	decrease	NT-proBNP - Roche (commercial)
Sliwa, 2004	Carvedilol	Baseline	decrease	NT-proBNP - Roche (commercial)
Yoshizawa, 2004	Carvedilol	Baseline	none	BNP - Shionogi
Sliwa, 2004	Carvedilol + Perindopril (6 months later)	Perindopril + Carvedilol (6 months later)	decrease	NT-proBNP - Roche (commercial)
Olsen, 2004	Cerebrovascular disease (stroke or TIA)	without CV risk	none	NT-proBNP - Elecsys
Richards, 1998	cGMP		increase	NT-proBNP - Christchurch
Tsutamoto, 1997	cGMP		increase	BNP - Shionogi
Tarnow, 2005	Cholesterol		none	NT-proBNP - Elecsys
Ueda, 2003	Cholesterol		none	BNP - Shionogi
Bazzino, 2004	C-reactive protein		increase	NT-proBNP - E170
James, 2003	C-reactive protein		increase	NT-proBNP - Elecsys
Lindahl, 2005	C-reactive protein		increase	NT-proBNP - Elecsys
Bettencourt, 2004	Creatinine		increase	BNP - Shionogi
Bettencourt, 1999	Creatinine	(hypertension group)	none	BNP - Shionogi
Galvani, 2004	Creatinine		increase	NT-proBNP - Elecsys

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
James, 2003	Creatinine		increase	NT-proBNP - Elecsys
Omland, 1996	Creatinine		increase	BNP - Shionogi
Panteghini, 2003	Creatinine		none	BNP - Triage
Ueda, 2003	Creatinine		increase	BNP - Shionogi
Zeller, 2004	Creatinine		increase	NT-proBNP - Elecsys
Wallen, 1997	Creatinine clearance		none	BNP - Shionogi
Taniguchi, 2004	Creatinine kinase		none	NT-proBNP - Roche (commercial)
Bazzino, 2004	Creatinine kinase, CK-MB		increase	NT-proBNP - E170
Mega, 2004	Creatinine kinase, CK-MB		none	BNP - Centaur
Morrow, 2003	Creatinine kinase, CK-MB		increase	BNP - Triage
Panteghini, 2003	Creatinine kinase, CK-MB		increase	BNP - Triage

	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
James, 2003	Diabetes		increase	NT-proBNP - Elecsys
Lindahl, 2005	Diabetes	No diabetes	none	NT-proBNP - Elecsys
Olsen, 2004	Diabetes	without CV risk	none	NT-proBNP - Elecsys
Schnabel, 2005	Diabetes	No diabetes	none	NT-proBNP - Elecsys
Tarnow, 2005	Diabetic nephropathy	Normoalbuminuric	increase	NT-proBNP - Elecsys
Tarnow, 2005	Diabetic retinopathy		none	NT-proBNP - Elecsys
Suzuki, 2002	Diastolic blood pressure		none	BNP - Shionogi
Bayes-Genis, 2004	Diastolic failure	Systolic LV dysfunction	decrease	NT-proBNP - Elecsys
Bettencourt, 2000c	Diastolic failure	Systolic dysfunction	decrease	BNP - Shionogi

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Bettencourt, 2000c	Diastolic failure	Normal ventricular function	increase	BNP - Shionogi
Bettencourt, 2000a	Diastolic failure	Systolic heart failure	decrease	BNP - Shionogi
Bettencourt, 1999	Diastolic failure	(hypertension group)	increase	BNP - Shionogi
Nielsen, L.S., 2004	Diastolic failure	Non-cardiac dyspnoea	increase	NT-proBNP - Roche (manual)
Redfield, 2004	Diastolic failure		increase	BNP - Triage
Hamada, 2005	Dilated cardiomyopathy	Old myocardial infarction	none	BNP - Shionogi
Bayes-Genis, 2004	Dyspnoea, non-cardiac	Control	increase	NT-proBNP - Elecsys
Logeart, 2002	Dyspnoea, non-cardiac	Control	increase	BNP - Triage
Maisel, 2002.	Dyspnoea, non-cardiac	No CHF	increase	BNP - Triage
Morrison, 2002	Dyspnoea, non-cardiac	CHF	decrease	BNP - Triage
Akioka, 2000	E/A ratio		none	BNP - Shionogi
Suzuki, 2002	E/A ratio		none	BNP - Shionogi
Yoshimura, 2002	Enalapril	Baseline	decrease	BNP - Shionogi
Yoshimura, 2002	Enalapril (15-mg)	Enalapril (5-mg)	decrease	BNP - Shionogi
Brunner-La Rocca, 1999	Enalapril (40-mg)	Enalapril (10-mg)	decrease	BNP - Shionogi
Taniguchi, 2004	End-diastolic dimension		none	NT-proBNP - Roche (commercial)
Latini, 2004a	Endothelin-1		increase	BNP - Shionogi
Richards, 1998	Epinephrine		increase	NT-proBNP - Christchurch
Koglin, 2001	Exercise		decrease	BNP - Shionogi
James, 2003	Female		increase	NT-proBNP - Elecsys
Lindahl, 2005	Female	Male	increase	NT-proBNP - Elecsys
Maisel, 2004a	Female	Male	none	BNP - Triage
Olsen, 2004	Female	Male	none	NT-proBNP - Elecsys
Redfield, 2004	Female	Male	increase	BNP - Triage
Schnabel, 2005	Female	Male	increase	NT-proBNP - Elecsys
Ueda, 2003	Female	Male	none	BNP - Shionogi
Weber, 2004	Female	Male	none	NT-proBNP - Elecsys
Wiviott, 2004	Female	Male	increase	BNP - Triage
Nielsen, O.W.,2004	Female (>74)	Male (>74)	none	NT-proBNP - Elecsys
Nielsen, O.W.,2004	Female (40-59)	Male (40-59)	none	NT-proBNP - Elecsys

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Nielsen, O.W.,2004	Female (60-74)	Male (60-74)	none	NT-proBNP - Elecsys
Tarnow, 2005	Female (DN)	Male	none	NT-proBNP - Elecsys
Kawai, 2001	Fibrosis	Baseline	none	BNP - Shionogi
Bettencourt, 1999	Fractional shortening	(hypertension group)	none	BNP - Shionogi
Bettencourt, 2004	Furosemide, dosage		none	BNP - Shionogi
Tarnow, 2005	Glomerular filtration rate (ND)		decrease	NT-proBNP - Elecsys
Tarnow, 2005	Glomerular filtration rate (No DN)		decrease	NT-proBNP - Elecsys
Tarnow, 2005	Glucose, fasting		none	NT-proBNP - Elecsys
O'Brien, 2003	Glucose, random		increase	NT-proBNP - Roche (manual)
Tarnow, 2005	HbA1c		none	NT-proBNP - Elecsys
Ueda, 2003	HbA1c		none	BNP - Shionogi
Bettencourt, 1999	Heart rate		none	BNP - Shionogi
James, 2003	Heart rate		increase	NT-proBNP - Elecsys
Kawai, 2001	Heart rate	Baseline	increase	BNP - Shionogi
Tsutamoto, 1997	Heart rate		increase	BNP - Shionogi
Ueda, 2003	Heart rate		none	BNP - Shionogi
Tarnow, 2005	Hemoglobin (DN)		decrease	NT-proBNP - Elecsys
Schnabel, 2005	Hyperlipidemia	No hyperlipidemia	decrease	NT-proBNP - Elecsys
James, 2003	Hyperlipidemia (hypercholesterolemia)		none	NT-proBNP - Elecsys
James, 2003	Hypertension		increase	NT-proBNP - Elecsys
Schnabel, 2005	Hypertension	No hypertension	none	NT-proBNP - Elecsys
Suzuki, 2002	Hypertension, duration		none	BNP - Shionogi
Suzuki, 2002	Hypertension, left ventricular hypertrophy	Normotensive	increase	BNP - Shionogi
Suzuki, 2002	Hypertension, normal left ventricular mass	Normotensive	increase	BNP - Shionogi
Bettencourt, 1999	Hypertension, with diastolic dysfunction	Hypertension, without diastolic dysfunction	increase	BNP - Shionogi

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Bettencourt, 1999	Hypertension, with diastolic dysfunction	Control & hypertension without diastolic dysfunction	increase	BNP - Shionogi
Bettencourt, 1999	Hypertension, without diastolic dysfunction	Control	increase	BNP - Shionogi
Richards, 2002	Hypertensive (MI)	Normotensive (MI)	increase	NT-proBNP - Christchurch
Richards, 2002	Hypertensive (OMI)	Normotensive (OMI)	increase	NT-proBNP - Christchurch
Jernberg, 2003	Interleukin-6		increase	NT-proBNP - Elecsys
Koglin, 2001	Ischemic heart disease	Nonischemic heart disease	none	BNP - Shionogi
Olsen, 2004	Ischemic heart disease	without CV risk	increase	NT-proBNP - Elecsys
Sadanandan, 2004	LAD culprit lesion	nonLAD culprit lesion	increase	BNP - Triage
Sadanandan, 2004	LAD lesion, proximal vs mid	Mid LAD lesion	increase	BNP - Triage
Thompson, 2005	Left ventricular assist device			BNP - Triage
		Baseline	decrease	
Kawai, 2001	Left ventricular diastolic dimension	Baseline	increase	BNP - Shionogi
Kawai, 2001	Left ventricular end-systolic diameter	Baseline	increase	BNP - Shionogi
Bettencourt, 2000c	Left ventricular mass index		increase	BNP - Shionogi
Bettencourt, 2000a	Left ventricular mass index		increase	BNP - Shionogi
Bettencourt, 1999	Left ventricular mass index	(hypertension group)	increase	BNP - Shionogi
Bettencourt, 1999	Left ventricular mass index		increase	BNP - Shionogi
Kawai, 2001	Left ventricular mass index	Baseline	increase	BNP - Shionogi
Suzuki, 2002	Left ventricular mass index		increase	BNP - Shionogi
Suzuki, 2002	Left ventricular relative wall thickness		none	BNP - Shionogi
Bettencourt, 2004	Lisinopril, dosage		decrease	BNP - Shionogi
Dao, 2001	Lung disease	CHF	decrease	BNP - Triage
Nielsen, L.S., 2004	Lung disease	CHF and CHF + lung disease	decrease	NT-proBNP - Roche (manual)
Sakatani, 2004	Lymphocytes (HHD, MS, AF, HC)		none	BNP - Shionogi
Sakatani, 2004	Lymphocytes (IHD, DC, AS, AR, MR)		decrease	BNP - Shionogi
Yoshizawa, 2004	Metoprolol	Baseline	none	BNP - Shionogi
Kyuma, 2004	MIBG activity		decrease	BNP - Shionogi

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Suzuki, 2002	Mid-wall left ventricular fractional shortening		none	BNP - Shionogi
Schnabel, 2005	Multi-vessel disease	No multi-vessel disease	increase	NT-proBNP - Elecsys
James, 2003	Myocardial infarction		increase	NT-proBNP - Elecsys
Olsen, 2004	Myocardial infarction	without CV risk	increase	NT-proBNP - Elecsys
Panteghini, 2003	Myocardial infarction		increase	BNP - Triage
Lindahl, 2005	Myocardial infarction, history	No previous MI	increase	NT-proBNP - Elecsys
Schnabel, 2005	Myocardial infarction, history	No myocardial infarction, history	increase	NT-proBNP - Elecsys
Bazzino, 2004	Myoglobin		increase	NT-proBNP - E170
Bertinchant, 2005	Norepinephrine		increase	BNP - Shionogi
Latini, 2004a	Norepinephrine		increase	BNP - Shionogi
Latini, 2002	Norepinephrine		increase	BNP - Shionogi
Richards, 1998	Norepinephrine		increase	NT-proBNP - Christchurch
Stanek, 2001	Norepinephrine		increase	BNP - Shionogi
Tsutamoto, 1997	Norepinephrine		increase	BNP - Shionogi
Jarai, 2005	NT-proANP		increase	NT-proBNP - Biomedica
Omland, 1996	NT-proANP		increase	BNP - Shionogi
Richards, 1998	NT-proANP		increase	NT-proBNP - Christchurch
Stanek, 2001	NT-proANP		increase	BNP - Shionogi
Wang, 2004	NT-proANP		increase	BNP - Shionogi
Vasan, 2002	NT-proANP (females)		increase	BNP - Shionogi
Vasan, 2002	NT-proANP (males)		increase	BNP - Shionogi

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Ueland, 2004	Osteoprotegerin		increase	NT-proBNP - Roche (manual)
Tsutamoto, 1997	PCWP		increase	BNP - Shionogi
Panteghini, 2003	Perfusion defect size		increase	BNP - Triage
Sliwa, 2004	Perindopril	Baseline	none	NT-proBNP - Roche (commercial)
Olsen, 2004	Peripheral vascular disease	without CV risk	none	NT-proBNP - Elecsys
Latini, 2004a	Plasma renin activity		decrease	BNP - Shionogi
Lindahl, 2005	Previous CHF	No previous CHF	increase	NT-proBNP - Elecsys
Tsutamoto, 1997	Pulmonary arterial pressure		increase	BNP - Shionogi
Suzuki, 2002	Pulse pressure		increase	BNP - Shionogi
Fisher, 2003	Relaxin		none	NT-proBNP - Roche (commercial)
Akioka, 2000	Restrictive filling pattern of deceleration time (DcT)		decrease	BNP - Shionogi
James, 2003	Revascularization		increase	NT-proBNP - Elecsys
Tsutamoto, 1997	Right atrial pressure		increase	BNP - Shionogi
Schnabel, 2005	Smoker, current	Non-smoker	none	NT-proBNP - Elecsys
James, 2003	Smoking, current		none	NT-proBNP - Elecsys
Shimpo, 2004	ST2, soluble receptor		none	BNP - Shionogi
James, 2003	Stroke		increase	NT-proBNP - Elecsys
Lindahl, 2005	ST-segment depression	No ST-segment depression	increase	NT-proBNP - Elecsys
James, 2003	ST-segment depression > 5mm		increase	NT-proBNP - Elecsys
Panteghini, 2003	Telesystolic volume		none	BNP - Triage
Ueda, 2003	Total protein		none	BNP - Shionogi
Grabowski, 2004	Troponin-I		increase	BNP - Triage

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	Determinant Name	Control or comparison group for categorical assocations	Effect	Method
Jarai, 2005	Troponin-I		none	NT-proBNP - Biomedica
Dokainish, 2005	Troponin-I (CAD)	Tn-I negative (CAD)	increase	BNP - Triage
Dokainish, 2005	Troponin-I (No CAD)	Tn-I negative (No CAD)	increase	BNP - Triage
Bayes-Genis, 2004	Troponin-T		increase	NT-proBNP - Elecsys
Bazzino, 2004	Troponin-T		increase	NT-proBNP - E170
Bertinchant, 2005	Troponin-T		increase	BNP - Shionogi
Ishii, 2003	Troponin-T		increase	BNP - Shionogi
James, 2003	Troponin-T		increase	NT-proBNP - Elecsys
Jernberg, 2003	Troponin-T		increase	NT-proBNP - Elecsys
Jernberg, 2002	Troponin-T		increase	NT-proBNP - Elecsys
Lindahl, 2005	Troponin-T		increase	NT-proBNP - Elecsys
Taniguchi, 2004	Troponin-T (> 0.01 ng/mL)	Troponin-T ($\leq$ 0.01 ng/mL)	increase	NT-proBNP - Roche (commercial)
Krum, 2004	Valsartan	Placebo	decrease	BNP - Shionogi
Latini, 2002	Valsartan	Placebo	decrease	BNP - Shionogi
Maggioni, 2002	Valsartan	Placebo	decrease	BNP - Shionogi
Krum, 2004	Valsartan (ACEi < median)	Placebo (ACEi < median)	decrease	BNP - Shionogi
Krum, 2004	Valsartan (ACEi > median)	Placebo (ACEi > median)	decrease	BNP - Shionogi
Baruch, 2004	Valsartan (age < 65 y)	Placebo (age < 65 y)	decrease	BNP - Shionogi
Baruch, 2004	Valsartan (age $\geq$ 65 y)	Placebo (age $\geq$ 65 y)	decrease	BNP - Shionogi
Krum, 2004	Valsartan (no ACEi)	Placebo (no ACEi)	decrease	BNP - Shionogi
Nielsen, L.S., 2004	Valvular disease	Non-cardiac dyspnoea	increase	NT-proBNP - Roche (manual)
James, 2003	Weight		decrease	NT-proBNP - Elecsys

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Palmer, 2003		196	522	28.6 +/-21.7	24.2 +/-13.8	pmol/L	Chi-square	0.007		
Schnabel, 2005	*904*			542.0 (161.43/1355.50)	192.0 (88.67/487.90)	pg/mL	Wilcoxon rank sum	<0.001		
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.0001/0.002	0.36	
Ray, 2004		52	115	125 (75 to 752)	59 (41 to 88)	pg/mL	Mann-Whitney		ns	
Richards, 1998	100					pmol/L	Pearson product moment	<0.001	0.4	
Maisel, 2004a		715	773			pg/mL	Kruskal-Wallis and Mann-Whitney *U* tests	<0.001		
Bettencourt, 2000a	85					pg/mL	Multiple regression	0.173	0.036	
Grabowski, 2004	126					pg/mL	Spearman correlation coefficient	0.01	0.23	
James, 2003	6809					ng/L	Multiple linear regression		0.46	0.04
Lainchbury, 2003	205					pmol/L	Pearson's correlation coefficient	<0.01		
Lindahl, 2005	1352 / 999					ng/L	not clear / Multiple linear mixed effects	<0.001 / <0.05		
Olsen, 2004	183					pmol/L	correlation, not specified	<0.001	0.4	
Omland, 1996	131					pmol/L	Linear regression analysis	<0.001	0.34	
Redfield, 2004	726					pg/mL	Least squares regression (controlled for diastolic dysfunction)	0.0003		
Redfield, 2004	2042					pg/mL	Least squares regression (controlled for EF)	0.0007		
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0001/0.0210	0.452/0.256	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	<0.0001	0.46	
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.001/0.05	0.31	
Tarnow, 2005	198					ng/L	na	<0.0001	0.42	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Latini, 2004a	4223					pg/mL	Spearman's coefficient	ns	0.0072	
Shiga, 2003		42	18	180 +/-30	282 +/-71	pg/mL	Mann-Whitney	<0.001		
Shiga, 2003		37	41	333 +/-107	146 +/-40	pg/mL	Mann-Whitney	<0.05		
James, 2003		3181				ng/L	Multiple linear regression			0.11
Olsen, 2004		15	123	29.7 +/- 136	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	ns		
Bertinchant, 2005	63					ug/L	Spearman rank correlation	<0.0001	0.85	
Omland, 1996	131					pmol/L	Linear regression analysis	<0.001	0.51	
Richards, 1998	100					pmol/L	Pearson product moment	<0.001	0.69	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	<0.0001	0.53	
Weber, 2004		26	32	612 +/- 151	140 +/- 27	pg/mL	Kruskal Wallis	<0.001		
Weber, 2004		29	32	1441 +/- 32	140 +/- 27	pg/mL	Kruskal Wallis	<0.001		
Weber, 2004		91	32	2579 +/- 13	140 +/- 27	pg/mL	Kruskal Wallis	<0.001		
Nielsen, L.S., 2004		10	264			pmol/L	*t* -test	<0.001		
Stanek, 2001	51					fmol/L	ANOVA	<0.01		
Dias, 2001		14	32	175.9 +/-39.5	215.3 +/-57.5	pg/mL	na	0.98		
Fung, 2003		43	43	- 37.0 +/-14.5		pmol/L	Student's *t* -test	0.015		
Yoshizawa, 2004		84	84	290 +/-384	177 +/-256	pg/mL	t-test	ns		
Latini, 2004a	2312					pg/mL	Spearman's coefficient	<0.001	0.4142	
Stanek, 2001	100					fmol/L	Spearman rank-correlation coefficient	0.0001	0.47	
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.445		0.013
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	0.044	0.018	
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.99	-0.001	
Kawai, 2001	21					pg/mL	Linear regression	0.28	0.25	
Olsen, 2004	183					pmol/L	regression, method not specified	<0.001	0.25	
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.1199	0.104	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Tarnow, 2005	198					ng/L	regression, method not specified	<0.0001	0.53	
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0002/0.0530	0.243/0.118	
Ueda, 2003	111					pg/mL	Univariate	0.47	-0.07	
Taniguchi, 2004		45	26	7233 +/-2369	1303 +/-291	pg/mL	na	<0.05		
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	ns	-0.11	
Ray, 2004		141	167	611 (370 to 709)	56 (48 to 97)	pg/mL	Mann-Whitney	<0.001		
Bettencourt, 2004		57	27			pg/mL		0.02		
Hartmann, 2004a	815	unknown	unknown	261.5	233.6	pmol/L	not given	ns		
Kawai, 2001		21	9			pg/mL	Repeated-measures analysis of variance	0.18		
Sliwa, 2004		27	30	-80		pg/mL	t-test	<0.01		
Sliwa, 2004		27	27	-125		pg/mL	t-test	<0.0005		
Yoshizawa, 2004		58	58	-44		pg/mL	t-test	ns		
Sliwa, 2004		27	30	-75		pg/mL	t-test	<0.01		
Olsen, 2004		19	123	28.5 +/- 36	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	ns		
Richards, 1998	100					pmol/L	Pearson product moment	<0.001	0.64	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	0.0002	0.4	
Tarnow, 2005	386					ng/L	na	ns		
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.72	0.03	
Bazzino, 2004	1483					pg/mL	Spearman correlation coefficient	0.01	0.28	
James, 2003	6809					ng/L	Multiple linear regression		0.34	0.19
Lindahl, 2005	1352 / 999			787 (696 to 890)	358 (327 to 390)	ng/L	Mann-Whitney / Multiple linear mixed effects	< 0.001 / 0.05		
Bettencourt, 2004	84					pg/mL	Spearman	0.01	0.3	
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.939		-0.004
Galvani, 2004	1756					ng/L	Spearman correlation coefficient	0.01	0.23	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
James, 2003	6809					ng/L	Multiple linear regression	na	0.2	0.0013
Omland, 1996	131					pmol/L	Linear regression analysis	<0.01	0.25	
Panteghini, 2003	64					pg/mL	Standard Linear regression	0.21	0.16	
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.02/0.002	0.23	
Zeller, 2004	101					pmol/L	Logistic regression	<0.01	0.481	
Wallen, 1997	200					pg/mL	na	0.126	-0.079	
Taniguchi, 2004	71					pg/mL	na	ns		
Bazzino, 2004	1483					pg/mL	Spearman correlation coefficient	<0.001	0.07	
Mega, 2004	436					pg/mL	Spearman correlation coefficient	0.19	-0.065	
Morrow, 2003	1676					pg/mL	Spearman correlation	<0.001	0.27	
Panteghini, 2003	64					pg/mL	Standard Linear regression	0.002	0.38	

	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
James, 2003		1420				ng/L	Multiple linear regression			0.08 (CI = 0.013 to 0.15)
Lindahl, 2005	1352 / 999			447 (366 to 546)	474 (438 to 512)	ng/L	Mann-Whitney / Multiple linear mixed effects	0.60 / ns		
Olsen, 2004		20	123	21 +/- 67	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	ns		
Schnabel, 2005	*904*	204	700	351.8 (107.35/875.00)	231.5 (101.00/691.90)	pg/mL	Wilcoxon rank sum	ns		
Tarnow, 2005		198	188	110 (5 to 79640)	27 (5 to 455)	ng/L	t-test	<0.0001		
Tarnow, 2005		320	66			ng/L	t-test	ns		
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0558	0.128	
Bayes-Genis, 2004		28	33	848 +/-297	1118 +/-199	pmol/L	Mann-Whitney	0.054		
Bettencourt, 2000c		31	36	168.0 +/-110.5	339.1 +/-249.9	pg/mL	t-test	0.001		

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Bettencourt, 2000c		36	33	339.1 +/-249.9	68.3 +/- 72.6	pg/mL	t-test	<0.001		
Bettencourt, 2000a		17	55	137.2 +/- 364.1	362 +/- 536.4	pg/mL	Chi-square	<0.03		
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.027		0.622
Nielsen, L.S., 2004		32	264			pmol/L	*t* -test	<0.001		
Redfield, 2004	726					pg/mL	Pearson' correlation coefficient	<0.0001	0.308	
Hamada, 2005		21	31	784 +/-682	688 +/-487	pg/mL	Chi-square	ns		
Bayes-Genis, 2004		15	86	50 +/-15	9 +/-3	pmol/L	Mann-Whitney	<0.05		
Logeart, 2002		48	30	187 +/-158	44 +/-39	pg/mL	t-test	<0.05		
Maisel, 2002.		72	770	346 +/-390	110 +/-225	pg/mL	t-test	<0.001		
Morrison, 2002		85	135	61 +/-92	759 +/-799	pg/mL	t-test	<0.001		
Akioka, 2000	33					pg/mL	Linear regression	ns		
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.7956	0.108	
Yoshimura, 2002		24	24			pg/mL	t-test	0.01		
Yoshimura, 2002		12	12	78 +/-58	139 +/-61	pg/mL	t-test	0.05		
Brunner-La Rocca, 1999		45	45	192	152	pg/mL		<0.005		
Taniguchi, 2004	71					pg/mL	na	ns		
Latini, 2004a	1929					pg/mL	Spearman's coefficient	<0.001	0.1955	
Richards, 1998	100					pmol/L	Pearson product moment	<0.01	0.17	
Koglin, 2001	78					pg/mL	Logistic regression	<0.0001		24.9
James, 2003		2597				ng/L	Multiple linear regression			0.26
Lindahl, 2005	1352 / 999			606 (529 to 693)	426 (391 to 463)	ng/L	Mann-Whitney / Multiple linear mixed effects	<0.001 / <0.05		
Maisel, 2004a		703	883			pg/mL	Kruskal-Wallis and Mann-Whitney *U* tests	0.756		
Olsen, 2004	183					pmol/L		ns		
Redfield, 2004		1058	984			pg/mL	Multivariate models	<0.0001		
Schnabel, 2005		208	696	354.5 (148.4/1288.0)	231.5 (94.66/662.30)	pg/mL	Wilcoxon rank sum	<0.001		
Ueda, 2003		88	23			pg/mL	Univariate / Multivariate	0.98	-0.003	
Weber, 2004		95	114	1852	1221.0	pg/mL	Mann-Whitney	0.59		
Wiviott, 2004		638	1227	68.4 +/-4.5	46.1 +/-2.4	ng/mL	Student t test	<0.0001		
Nielsen, O.W.,2004		85	23			pmol/L	t-test	0.74		
Nielsen, O.W.,2004		89	75			pmol/L	t-test	0.59		

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Nielsen, O.W.,2004		60	49			pmol/L	t-test			
Tarnow, 2005		150	236			ng/L	t-test	0.28		
Kawai, 2001	21					pg/mL	Linear regression	0.25	-0.28	
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.551		0.011
Bettencourt, 2004	84					pg/mL	Spearman	0.48	0.08	
Tarnow, 2005	198					ng/L	na	<0.0001	-0.6	
Tarnow, 2005	188					ng/L	na	0.002	-0.22	
Tarnow, 2005	386					ng/L	na	ns		
O'Brien, 2003	96					fmol/L	Pearson product moment correlation coefficient	0.011	0.27	
Tarnow, 2005	386					ng/L	na	ns		
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.87	-0.02	
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.825		-0.002
James, 2003	6809					ng/L	Multiple linear regression		0.14	0.07
Kawai, 2001	21					pg/mL	Linear regression	0.012	0.54	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	<0.0001	0.26	
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.46	0.07	
Tarnow, 2005	198					ng/L	na	<0.0001	-0.52	
Schnabel, 2005	*904*	645	259	214.5 (95.61/670.05)	361.5 (137.13/1011.75)	pg/mL	Wilcoxon rank sum	<0.001		
James, 2003		1995				ng/L	Multiple linear regression			-0.098
James, 2003		3515				ng/L	Multiple linear regression			0.082
Schnabel, 2005	*904*	695	209	261.8 (103.75/261.8)	213.8 (96.39/662.30)	pg/mL	Wilcoxon rank sum test	ns		
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0015/.1795	0.317/0.135	
Suzuki, 2002		89	44	57.3 +/-55.4	19.5 +/-24.0	pg/mL	One-way ANOVA	0.01		
Suzuki, 2002		96	44	29.7 +/-28.3	19.5 +/-24.0	pg/mL	One-way ANOVA	0.05		
Bettencourt, 1999		12	24			pg/mL	t-test	0.001		

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Bettencourt, 1999		36	11	61.16 +/-45.38	31.27 +/-18.10	pg/mL	t-test	0.001		
Bettencourt, 1999		24	11			pg/mL	t-test	0.0003		
Richards, 2002		436	657	192 +/-175	160 +/-150	pmol/L	Chi-square	0.034		
Richards, 2002		*436*	*657*	111 +/-134	76 +/-80	pmol/L	Chi-square	<0.001		
Jernberg, 2003	2019					ng/L	not found	<0.001	0.29	
Koglin, 2001		24	54	150.6 +/-25.7	158.9 +/-22.2	pg/mL	na	ns		
Olsen, 2004		26	123	67.3 +/- 118	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	< 0.05		
Sadanandan, 2004		88	188	40	24.0	pg/mL	Wilcoxon rank-sum test	0.005		
Sadanandan, 2004		83	6	41	10.0	pg/mL	Wilcoxon rank-sum test	0.03		
Thompson, 2005	19			221.1 +/-124.2	754.1 +/-261.1	pg/mL	t-test	<0.0001		
Kawai, 2001	21					pg/mL	Linear regression	<0.001	0.7	
Kawai, 2001	21					pg/mL	Linear regression	<0.001	0.86	
Bettencourt, 2000c						pg/mL	Pearson's correlation	0.008	0.27	
Bettencourt, 2000a	85					pg/mL	Multiple regression	<0.001	0.19	
Bettencourt, 1999	36					pg/mL	Multiple linear regression	0.041		0.006
Bettencourt, 1999	47					pg/mL	Pearson's correlation coefficient	<0.001	0.53	
Kawai, 2001	21					pg/mL	Linear regression	0.012	0.54	
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0001/0.0095	0.370/0.266	
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0159/0.4925	0.161/0.067	
Bettencourt, 2004	84					pg/mL	Spearman	<0.001	-0.41	
Dao, 2001		56	94	86 +/- 39	1076 +/- 138	pg/mL	t-test	<0.001		
Nielsen, L.S., 2004		136	81	2.19 +/- 0.97	4.39 +/- 1.31	pmol/L	*t* -test	<0.001		
Sakatani, 2004	30					pg/mL	Linear regression	0.393	-0.17	
Sakatani, 2004	40					pg/mL	Linear regression	0.011	-0.43	
Yoshizawa, 2004		26	26	-27		pg/mL	t-test	ns		
Kyuma, 2004	158					pg/mL	Linear regression	<0.0001	0.33	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.1014	0.109	
Schnabel, 2005	*904*	393	511	290.4 (127.6/873.2)	181.8 (86.91/659.6)	pg/mL	Wilcoxon rand sum	<0.001		
James, 2003		2067				ng/L	Multiple linear regression			0.35
Olsen, 2004		16	123	112.5 +/- 131	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	< 0.01		
Panteghini, 2003		64	28	119.5 (5-730)	6 (5-48)	pg/mL	Standard Linear regression	< 0.0001		
Lindahl, 2005	1352 / 999			651 (569 to 744)	414 (381 to 451)	ng/L	Mann-Whitney / Multiple linear mixed effects	< 0.001 / 0.05		
Schnabel, 2005	*904*			301.5 (135.0/714.8)	218.5 (90.38/727.95)	pg/mL	Wilcoxon rand sum	0.03		
Bazzino, 2004	1483					pg/mL	Spearman correlation coefficient	0.01	0.3	
Bertinchant, 2005	63					ug/L	Spearman rank correlation	<0.0001	0.62	
Latini, 2004a	4284					pg/mL	Spearman's coefficient	<0.001	0.2216	
Latini, 2002	4284					pg/mL	na	<0.001	0.26	
Richards, 1998	100					pmol/L	Pearson product moment	<0.001	0.33	
Stanek, 2001	100					fmol/L	Spearman rank-correlation coefficient	<0.05	0.2	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	<0.0001	0.67	
Jarai, 2005	120					nmol/L	Spearman rank correlation	<0.0001	0.63	
Omland, 1996	131					pmol/L	Linear regression analysis	<0.001	0.61	
Richards, 1998	100					pmol/L	Pearson product moment	<0.001	0.52	
Stanek, 2001	100					fmol/L	Spearman rank-correlation coefficient	0.0001	0.56	
Wang, 2004	3346					pg/mL	Spearman's coefficient	<0.001	0.67	
Vasan, 2002	1707					pg/mL	Spearman correlation coefficient	<0.001	0.62	
Vasan, 2002	1470					pg/mL	Spearman correlation coefficient	<0.001	0.7	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Ueland, 2004	234					pmol/L	na	<0.0001	0.51	
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	0.47	0.0045	
Panteghini, 2003	64					pg/mL	Standard Linear regression	0.001	0.4	
Sliwa, 2004		30	30	-45		pg/mL	t-test	ns		
Olsen, 2004		5	123	33.3 +/- 98	19.8 +/- 62.0	pmol/L	Unpaired Student's t-test	ns		
Latini, 2004a	4274					pg/mL	Spearman's coefficient	<0.001	-0.192	
Lindahl, 2005	1352 / 999			784 (552 to 1113)	460 (427 to 495)	ng/L	Mann-Whitney	0.004		
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	<0.0001	0.45	
Suzuki, 2002	185					pg/mL	Univariate/multivariate	0.0007/0.0176	0.224/0.231	
Fisher, 2003	87					pg/mL	NA	ns		
Akioka, 2000	33					pg/mL	Linear regression	0.003	-0.5	
James, 2003		1035				ng/L	Multiple linear regression			0.099
Tsutamoto, 1997	85					pg/mL	Linear regression analysis	0.31	ns	
Schnabel, 2005		592	312	252.9 (88.31/758.25)	243.6 (100.7/767.85)	pg/mL	Wilcoxon rank sum	ns		
James, 2003		1536				ng/L	Multiple linear regression			0.069 (CI = -0.001 to 0.14)
Shimpo, 2004	448					pg/mL	Spearman's coefficient	0.15	0.068	
James, 2003		153				ng/L	Multiple linear regression			0.14
Lindahl, 2005	1352 / 999			651 (587 to 723)	350 (318 to 385)	ng/L	Mann-Whitney / Multiple linear mixed effects	< 0.001 / 0.05		
James, 2003	6809					ng/L	Multiple linear regression			0.06
Panteghini, 2003	64					pg/mL	Standard Linear regression	0.083	0.22	
Ueda, 2003	111					pg/mL	Univariate / Multivariate	0.06/0.69	-0.18	
Grabowski, 2004	126					pg/mL	Spearman	<0.0001	0.39	

Evidence Table 1. Effect of clinical determinants on BNP and NT-proBNP listed by study

Study	n	Determinant n	Control or comparison group n	Determinant Concentration	Control or comparison group concentration	Units	Statistical Method	p	r	Beta or chi-square
Jarai, 2005	120					nmol/L	Spearman rank correlation	0.246	0.1	
Dokainish, 2005		454	252	38 (8/81)	16 (3/39)	pg/mL	Student t test	<0.0001		
Dokainish, 2005		29	65	19 (3/57)	15 (0/37)	pg/mL	Student t test	<0.0001		
Bayes-Genis, 2004	175					pmol/L	Spearman's rank correlation	<0.0001	0.6	
Bazzino, 2004	1483					pg/mL	Spearman correlation coefficient	0.01	0.23	
Bertinchant, 2005	63					ug/L	Spearman rank correlation	0.002	0.4	
Ishii, 2003	100					ng/L	Linear regression	<0.05	0.24	
James, 2003	6809					ng/L	Multiple linear regression		0.48	0.35
Jernberg, 2003	2019					ng/L	not found	<0.001	0.53	
Jernberg, 2002						ng/L	Spearman rank-correlation coefficient	0.01	0.49	
Lindahl, 2005	1352 / 999			797 (719 to 883)	293 (267 to 321)	ng/L	Mann-Whitney / Multiple linear mixed effects	< 0.001 / 0.05		
Taniguchi, 2004		20	51	13260 +/-5035	1847 +/-311	pg/mL	na	<0.001		
Krum, 2004		1532	1502	-21.56	27.2	pg/mL	Least squares mean change	<0.00001		
Latini, 2002		1940	1979	(-)21	(+)23	pg/mL	Least squares mean	<0.0001		
Maggioni, 2002	123					pg/mL	Least squares mean change	0.005		
Krum, 2004	*1024*					pg/mL	Least squares mean change	0.00006		
Krum, 2004	*1278*					pg/mL	Least squares mean change	0.00003		
Baruch, 2004	*2112*			-36.4		pg/mL	Placebo-subtracted least-squares mean difference	<0.001		
Baruch, 2004	*1807*			-51.4		pg/mL	Placebo-subtracted least-squares mean difference	<0.001		
Krum, 2004	*169*					pg/mL	Least squares mean change	0.05		
Nielsen, L.S., 2004		12	264			pmol/L	*t* -test	<0.001		
James, 2003	6809					ng/L	Multiple linear regression		-0.18	-0.012

Evidence Table 2. Summary of studies in patients with risk of CAD: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Bhalla 2004 USA	Cohort: N/A Age: Condition 1 mean age = 52 +/- 20 years (referred group) Condition 2 mean age = 61 +/- 12 years (not referred group) % Male: 96	482 Followup: 1) Condition 1 (referred group) :827 +/- 384 days 2) Condition 2 (non-referred group): 864 +/- 207 days	Subjects were either referred by physicians or nurse practitioner for echocardiography for clinical suspicion of cardiac dysfunction (referred group) or randomly selected and recruited from the diabetic clinic (not referred group). In this group of patients, there was no suspicion of cardiac dysfunction, no referrals to cardiologists, and no previous records of echocardiography with abnormalities of LV function (systolic or diastolic).	1) Cardiac mortality 2) All-cause mortality	NR/NR	1) Unadjusted: initial BNP = mortality (referred group) 2) Adjusted (non-referred) 3) Other variables used in regression analyses, but not statistically significant ($p<0.05$), were gender, type of diabetes, LV function, and ejection fraction.	Biosite Diagnostics – Triage Cut-off points: 20, 40, 60, 80, 100, 120 pg/ml	Likelihood ratio in non-referred group at BNP level of 120 pg/ml was 5.66.

Evidence Table 2. Summary of studies in patients with risk of CAD: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Kellett 2004 Ireland	Cohort: N/A Age: mean age = 73.7 +/- 11.9 (range 19-105) years % Male: 57	646 Followup: 1) Until discharge 8.3 +/- 6.9 days 2) Until death in hospital 12.2 +/- 9.9 days	Patients with suspected heart disease who were admitted for acute medical emergencies. Cardiac function was assessed by clinical exam, ECG, and chest X-ray.	In-hospital mortality	Yes/NR	Mortality = systolic blood pressure </= 90 mmHg, hemoglobin level </= 100 g/l, white blood cell count > 13000, being unwell before the current illness, BNP >/= 700 pg/ml	Biosite Diagnostics – Triage 700 pg/ml (200 pg/ml increments from 0 to 1199 pg/ml then >/=1200 pg/ml)	Adjusted odds ratio = 22.0
Suzuki 2002 Japan	Cohort: N/A Age: mean age = 66 +/- 11 years % Male: 50	229 Followup: 34.6 months	Hypertensive persons (systolic blood pressure >/= 140 mmHg or diastolic blood pressure >/= 90 mmHg).	Cardiovascular events (angina pectoris, myocardial infarction, arrhythmia, stroke, cardiovascular death, sudden death)	NR/NR	Univariate and multivariate analysis: age; systolic blood pressure; diastolic blood pressure; pulse pressure; left ventricular mass index ; left ventricular relative wall thickness; mid-wall left ventricular fractional shortening ; E/A ratio; ANP; BNP	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Cut-off point: 68pg/ml	Univariate analysis/Multivariate analysis (risk ratio [95% confidence interval]): BNP 1.015 (1.009–1.021)/1.011 (1.004–1.017)

Evidence Table 2. Summary of studies in patients with risk of CAD: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Ueda 2003 Japan	Cohort: N/A Age: mean age = 85.5 +/- 5.2 years % Male: 21	111 Followup: 2 years	Electrocardiographic abnormalities (presence of left bundle branch block, major Q waves according to the Minnesota code [Q111-Q128]; ST-J depression of 1mm or more or negative T waves in leads II, V2 to V6, AVL, and AVF; voltage criteria for left ventricular hypertrophy; or arrhythmias). Also, patients who had a clinical history of stroke or ischemic heart disease (without hospitalization).	1) Cardiac event 2) Death	NR/NR	Cox regression: plasma BNP = cardiac events, total mortality. Linear regression: plasma BNP = age, sex, body mass index, blood pressure, heart rate, serum total protein, serum creatinine, hemoglobin A1C, serum total cholesterol, ADL score.	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) 1) Cut-off point # 1: > 60 pg/ml (Kaplan-Meier) 2) Cut-off point # 2: >= 100 pg/ml (Cox regression)	Plasma BNP was significantly associated with cardiac events and total mortality. Each 50-pg/mL increase in plasma BNP concentration increased the rate of cardiac events by 1.6-fold, i.e, hazard ratio 1.6 (95% confidence interval: 1.2-2.1) and the rate of total mortality by 1.4-fold, i.e., hazard ratio 1.4 (1.2-1.6). Compared with subjects who had a normal BNP concentration (<18.4 pg/mL), those with BNP levels >=100 pg/mL had a 2.1-fold (1.3-3.4) greater rate of cardiac events and a 1.6-fold (1.3-2.1) greater mortality.

Evidence Table 2. Summary of studies in patients with risk of CAD: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Wang 2004 USA	Cohort: Framingham Offspring Study Age: Condition 1 mean age = 59 +/- 10 years Condition 2 mean age = 58 +/- 10 years % Male: 47	3346 Followup: 5.2 years	Readers are referred to another publication on the Framingham Study to obtain information on diagnostic criteria for cardiovascular events.	1) Death 2) Major cardiovascular events (myocardial infarction, coronary insufficiency, death from coronary heart disease, heart failure, stroke)	NR/Yes	Cox proportional hazards model	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) 1) 20.0 pg/ml (men) 2) 23.3 pg/ml (women)	Adjusted Hazard Ratio per 1 SD Increment in Log BNP Values (95% confidence interval): 1) Death: 1.27 (1.06–1.52) 2) First major cardiovascular event: 1.28 (1.03–1.59) 3) Heart failure: 1.77 (1.31–2.41) 4) Atrial fibrillation: 1.66 (1.30–2.11) 5) Stroke or transient ischemic attack: 1.53 (1.16–2.02) 6) Coronary heart disease events: 1.10 (0.89–1.37) Adjusted Hazard Ratio for BNP Values above 80th Percentile (95% confidence interval): 1) Death: 1.62 (1.08–2.42) 2) First major cardiovascular event: 1.76 (1.06–2.92) 3) Heart failure: 3.07 (1.51–6.26) 4) Atrial fibrillation: 1.91 (1.13–3.25) 5) Stroke or transient ischemic attack: 1.99 (1.09–3.62) 6) Coronary heart disease events: 1.30 (0.79–2.15)

Evidence Table 2. Summary of studies in patients with risk of CAD: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Nagao 2004 Japan	Cohort: N/A Age: Condition 1 mean age = 61.5 +/- 12.9 years Condition 2 mean age = 63.4 +/- 10.2 years Condition 3age range = 64.9 +/- 13.4 years Condition 4 age range = 65.4 +/- 10.6 years % Male: 80	401 Followup: Until discharge (specific length of time not provided)	Cardiac arrest prior to the arrival of emergency, with presumed cardiac origin of the arrest according to the Utstein Style.	Survival to hospital discharge	NR/NR	Survival to hospital discharge = cardiac arrest, age, gender, CPR, call-response interval, initial cardiac rhythm, ROSC	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) 1) Cut-off point: 100 pg/ml. 2) Analysis based on quartiles of BNP: 2.0-33.8 pg/ml (condition 1); 33.9-152.0 pg/ml (condition 2); 152.1-392.0 pg/ml (condition 3); 392.1-2620.0 pg/ml (condition 4).	Adjusted odds ratios with condition 1 as reference group: versus condition 2 = 0.13 (95% confidence interval: 0.04–0.46; versus condition 3 = 0.10 (0.03–0.41); versus condition 4 = 0.004 (0.00–0.16)

Abbreviations: N/A=not applicable, NR=not reported, ADL=activities of daily living, LV=left ventricular, ECG=electrocardiograph, E/A=early/atrial, ANP=atrial natriuretic peptide, IRMA=immunoradiometric assay, SD=standard deviation, CPR=cardiopulmonary resuscitation, ROSC=return of spontaneous circulation

Evidence Table 3: Summary of studies in patients with risk of CAD: NT-proBNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnosis criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Gaede 2005 Denmark	Cohort: Steno-2 study Age: mean age = 55.1 % Male: 74	160 Followup: 7.8 years	Diabetic patients between 40-65 years of age.	Combined mortality endpoint for cardiovascular disease: cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, percutaneous coronary interventions, coronary artery bypass graft, vascular surgery, amputations	NR/Yes	Model 1: CVD = diabetes duration, CVD, sex, age Model 2: CVD = diabetes duration, CVD, sex, age, systolic blood pressure, diastolic blood pressure, HbA1c, fasting serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, urinary AER	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Cut-off point: 33.5 pg/ml	Unadjusted hazard ratio: 4.4 (95% confidence interval: 2.3–8.4). Unadjusted hazard ratio: (42 patients whose BNP did not reach below the median in the first 2 years) 0.45 (0.12–1.65). Adjusted hazard ratio (model 1): 3.3 (1.7–6.5) Adjusted hazard ratio (model 2): 3.6 (1.7–7.5)
Jernberg 2002 Sweden	Cohort: N/A Age: Condition 1 mean age 55 (range 48-64) years Condition 2 mean age 70 (range 59-76) years Condition 3 mean age 75 (range 68-80) years Condition 4 mean age 77 (range 70-83) years	775 Followup: Median 40 months (range 35 to 47 months)	History of chest pain or other symptoms suggestive of an acute coronary syndrome.	Death	Yes/NR	Model 1: death = age, diabetes, ECG changes, elevated cTnT, P-creatinine Model 2: death = BNP, age, diabetes, ECG changes, elevated cTnT, P-creatinine	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Condition 1: </= 112 ng/l; condition 2: 113-400 ng/l; condition 3: 401-1653 ng/l; condition 4: >/= 1654 ng/l	Compared to condition 1 - adjusted rate ratios and 95% confidence intervals: Condition 2: 1.85 (0.67–5.08) Condition 3: 2.96 (1.12–7.81) Condition 4: 5.40 (2.02–14.4)

Evidence Table 3: Summary of studies in patients with risk of CAD: NT-proBNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnosis criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
	% Male: 60							
Olsen 2004 USA, Denmark, Norway	Cohort: Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study Age: Condition 1 mean age 66 +/- 7 years Condition 2 mean age 70 +/- 6 years % Male: 64	183 Followup: 60 +/- 5 months (range 54 to 68 months)	Electrocardiographic LV hypertrophy by the Cornell voltage-duration product or the Sokolow-Lyon voltage criterion	Composite endpoint: cardiovascular death, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke	NR/Yes	Composite endpoint = NT-proBNP, NT-proANP, cardiovascular risk, LV midwall fractional shortening, body weight, smoking, age, LV mass	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Cut-off point: 21.8 pmol/l	NT-proBNP > 21.8 pmol/l for incidence of composite endpoint (vs </= 21.8 pmol/l): unadjusted hazard ratio = 2.8 (1.19-5.70)

Evidence Table 3: Summary of studies in patients with risk of CAD: NT-proBNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnosis criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Tarnow 2005 Denmark	Cohort: N/A Age: Condition 1 (nephropathy) mean age 41 +/- 9.5 years Condition 2 (normoalbuminuria) mean age 42.5 +/-9.9 years % Male: 61	386 Followup: 9.3 years (range 0 to 9.5 years)	Diabetic nephropathy: persistent macroalbuminuria (>300 mg 24 h) in at least two out of three consecutive 24-h urine collections, in the presence of diabetic retinopathy and the absence of other kidney or urinary tract disease were recruited	All-cause mortality	Yes/NR	Mortality = BNP, smoking, antihypertensive medication, systolic blood pressure, serum cholesterol	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Cut-off point: 125 pg/l	NT-proBNP cutoff 125 pg/ml - adjusted hazard ratios and 95% confidence intervals: All-cause mortality: 2.68 (1.24–5.79) CV death: 4.09 (1.61–10.41) For each 10 fold increase in BNP as a continuous variable - adjusted hazard ratios and 95% confidence intervals: All-cause: 2.67 (1.62–4.42) CV death: 3.32 (1.90–5.81)
Weber 2004 Germany	Cohort: N/A Age: 60 (range 46-75) years % Male: 55	209 Followup: N/A (cross-sectional)	Degenerative aortic stenosis >/= 12 months. Aortic stenotic severity was assessed by the mean transvalvular pressure gradient obtained echocardiographically.	Severity of aortic stenosis	NR/Yes	Severity of aortic stenosis = NT-proBNP, NYHA class, left ventricular mass index, body mass index, ejection fraction (data in published report provided only for NT-proBNP and NYHA class)	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Cut-off point: 550 pg/ml	Chi-square, p-values only

Evidence Table 3: Summary of studies in patients with risk of CAD: NT-proBNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnosis criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Nielsen 2004 Denmark	Cohort: Copenhagen Hospital Heart Failure Study Age: age range 40-75 years % Male: not reported	2224 Followup: 1 year	No obvious heart disease: sinus rhythm, LV ejection fraction > 0.55, no valvular heart disease or dilated or congenital heart disease at referral	Major adverse cardiac events (MACEs): as LV ejection fraction < 0.35, valvular heart disease, pulmonary congestion on the chest X-ray at the time of admission or development of one of the following incidents during a 90 day follow up period: symptoms of heart failure, myocardial infarction, valvular disease, sudden death or cardiac death.	Yes/Yes	N/A	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Cut-off points: 40-59 years = 43.5 pmol/l; 60-74 years = 99 pmol/l; >/= 75 years = 250 pmol/l	No regression analysis

Abbreviations: NR=not reported, N/A=not applicable, CVD=cardiovascular disease, HDL=high density lipoprotein, LDL=low density lipoprotein, AER=albumin excretion rate, ECG=electrocardiograph, cTnT=cardiac tropinin T, LV=left ventricular, CV=cardiovascular, NYHA=New York Heart Association

Evidence Table 4. Summary of studies in patients with CAD with surgery: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Grabowski 2004 Poland	Mean age: 58.8 +/- 10.7 % Male: 45%	126 Followup: 42 days	Admission with acute STEMI, Clinical symptoms of ACS, or ST elevation >= 1 mm on at least 2 ECG at admission.	All-cause mortality	Yes/Yes	Simple and stepwise multiple logistic regression	Biosite Diagnostics – Triage Threshold: 100 pg/mL	BNP > 100 pg/mL: Unadj OR = 10.3(1.3-84.2) Adj OR = 16.3(1.4-186.7)
Jiang 2004 China, Saudi Arabia	Condition 1 - mean age: 52.8 +/- 9.8 Condition 2 - mean age: 51.8 +/- 9.9 % Male: 83%	949 completed followup (960 enrolled) Followup: 1 and 6 months	Current chest pain and unstable angina developed within 24 hours of admission. Patients with acute MI and at least 2 of the following: a) persistent chest pain over 20 minutes, b) elevation of ST segment in at least 2 related leads or developed a branch bundle blockade, c) new abnormal regional wall movement on Echocardiogram, d) elevation of biomarker of myocardium.	1) Mortality (1 and 6 months) 2) Heart failure 3) Acute MI 4) ACS 5) Death (all cause/ 6 months) 6) Acute MI (newly developed)	Yes/NR	1x1 variable comparisons using chi-square test Multiple logistic Regression (forward selection)	Biosite Diagnostics – Triage Threshold: 80 pg/mL	Appears that only delayed PCI was statistically significant for BNP > 80 pg/ml: Unadjusted odds ratio = 2.94 (95% confidence interval = 1.17-7.42) for mortality at 6 months. Early PCI group at 1 month --> Unadjusted odds ratio = 3.53 (1.35-9.21) Early PCI group at 6 month --> Unadjusted odds ratio = 2.96 (1.31-6.66)

Evidence Table 4. Summary of studies in patients with CAD with surgery: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Wiviott 2004 USA	TACTICS-TIMI 18 Condition 1 mean age 60.2 Condition 2 mean age 64.5, % Male: 66%	1,865 Followup: 6 months	Accelerated or prolonged angina, eligibility for PCI, and the presence of at least 1 objective marker of ischemia.	Combined incidence of death, myocardial infarction (MI), and rehospitalization for acute coronary syndrome (ACS)	NR/NR	Multiple logistic regression controlling for differences between genders	Biosite Diagnostics – Triage Threshold: 80 mg/dl	BNP for 6 month mortality (including interaction between gender and BNP): odds ratio = 2.1 (95% confidence interval = 0.64-7.20). For death or MI: odds ratio = 1.6 (0.70-3.8).
Morrow 2003 USA	Condition 1 - mean age: 60 Condition 2 - mean age: 69 % Male: 62.7%	1,676 Followup: 6 months	The index diagnosis was established by the investigator based on local electrocardiographic and laboratory data.	1) All cause death 2) New or recurrent MI 3) Rehospitalization for acute coronary syndrome (ACS) 4) New or worsening congested heart failure	NR/Yes	Simple logistic regression	Biosite Diagnostics – Triage BNP dichotomized > 80 pg/ml based on previous literature.	For 6 month mortality: Unadjusted odds ratio for BNP > 80 pg/ml = 3.7 Adjusted odds ratio = 3.3 (95% confidence interval = 1.7 to 6.3)

Evidence Table 4. Summary of studies in patients with CAD with surgery: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Takase 2004 Japan	Mean age: 67+/- 1, % Male: 70%	77 Followup: 25.9 ± 1.4 months	Positive results on an exercise myocardial single-photon-emission computed tomography scan using 99m technetium-sestamibi, 99m technetium-tetrofosmin, or 201 thallium-chloride, and had an angiographically significant coronary stenosis (75% stenosis of coronary artery).	Recurrence of anginal attacks.	Yes/NR	Simple Cox proportional hazards	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 68 pg/ml	The crude hazard ratio of incident anginal recurrence in patients with higher levels of BNP was 41·119 (95% confidence interval = 7·833–215·847).

Abbreviations: STEMI=ST-elevation myocardial infarction, ACS=acute coronary syndrome, ECG=electrocardiograph, UnAdj=unadjusted, Adj=adjusted, OR=odds ratio, MI=myocardial infarction, PCI=percutaneous coronary intervention, TIMI=thrombolysis in myocardial infarction, NR=not reported

Evidence Table 5. Summary of studies in patients with CAD no surgery: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Mega 2004 USA	Age range: 21-75 years % Male: 77	438 Followup: 30 days from angioplasty	ST segment elevation myocardial infarction	Mortality	NR/NR	Fisher's exact test and Chi Square test for simple comparisons between variables. Logistic regression	Bayer Healthcare - ADVIA Centaur Threshold: 80 pg/mL	Adjusted odds ratio = 7.2 (95% confidence interval = 2.1-24.5) No history of CHF: Adjusted odds ratio = 8.2, (2.3-to 28.4) The prognostic association between BNP and mortality was even stronger using a cut-point of 40 pg/mL: Adjusted odds ratio = 15.9 (3.1-81).
Omland 1996 Scandanavia	Mean age: 67.8 % Male: 74.8	131 Followup: Median = 1293 days	Unspecified	Mortality	NR/Yes	Simple and multiple Cox proportional hazards regression	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 115.22 pg/mL	Unadjusted odds ratio = 2.53 (2.14-2.92) Adjusted odds ratio = 1.99 (1.56-2.42)

Evidence Table 5. Summary of studies in patients with CAD no surgery: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Wylie 2004 USA	No data reported in the publication - readers are referred to another reference.	1124 Followup: periods at 30 days, 10 months	Ischemic discomfort at rest lasting >/= 5 minutes and associated with >/=1 of these features: new ST segment deviation >/= 0.5 mm, T-wave inversion >/= 3 mm in 3 leads or left bundle branch block, positive cardiac markers, or documented coronary artery disease.	Development of CHF or cardiogenic shock	NR/Yes	Backward selection logistic regression	Biosite Diagnostics – Triage Threshold: 80 pg/mL	Adjusted odds ratio (30 days) = 1.85 (1.04-3.28) Adjusted odds ratio (10 months) = 3.03 (1.25-7.35)

Evidence Table 5. Summary of studies in patients with CAD no surgery: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Sabatine 2002 USA	No data reported in the publication - readers are referred to another reference.	450 patients from OPUS-TIMI-16 trial 1635 patients from TACTICS-TIMI 18 trial (as part of validation cohort) Followup: periods at 6 months, 10 months	Non-ST elevation acute coronary syndromes (OPUS-TIMI-16)	1) All cause mortality 2) Non-fatal MI 3) Development of congestive heart failure 4) Composite of 1-3	NR/NR	Multiple Cox proportional hazards regression	Biosite Diagnostics – Triage Threshold: 80 pg/mL	For OPUS-TIMI 16 subjects at 10 months followup: Adjusted hazard ratio = 2.1, (p = 0.001) for composite endpoint (death, MI or CHF) For TACTIS-TIMI 18 through 6 months: BNP (OR 1.6, p = 0.019) for same endpoint

Evidence Table 5. Summary of studies in patients with CAD no surgery: BNP

Author	Sample Characteristics	Sample Size/ Followup	Diagnostic Criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Bettencourt 2000 Portugal	Mean age: 58.3 +/- 12.6 % Male: 84.2	101 Followup: 12 months	Admission to cardiac unit with acute myocardial infarction as defined by the presence of typical cardiac ischemic symptoms, presence of ischemic changes on ECG in two or more leads, and peak elevation of plasma creatinine kinase to at least level twice of normal.	1) Left ventricular dysfunction 2) Heart failure 3) Ischemia event	Yes/NR	Likelihood ratio-based forward stepwise logistic regression analysis	Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold values: 142.3 pg/mL for systolic dysfunction; 93.8 pg/mL for isolated diastolic dysfunction or systolic dysfunction; 259.1 pg/mL for heart failure; 380.5 pg/mL for death.	Adjusted odds ratio for outcome of left ventricular systolic dysfunction = 1.01 (p < 0.0001)Adjusted odds ratio for left ventricular dysfunction (systolic or isolated dyastolic) = 1.01 (p = 0.0002)

Abbreviations: NR=not reported ADVIA= CHF=congestive heart failure, IRMA= immuno radiometric assay, OPUS=Orbofiban in Patients with Unstable Coronary Syndromes, TIMI= thrombolysis in myocardial infarction, MI=myocardial infarction, ECG=electrocardiograph

Evidence Table 6: Summary of studies in patients with CAD not surgery: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
de Winter 2004 Netherlands	Condition 1 - mean age: 68 +/- 10 years Condition 2 - mean age: 60 +/- 11 years % Male: 70	1172 Followup: 12 to 14 months	Consecutive patients undergoing PTCA	1) Death 2) Myocardial infarction	Yes/NR	Simple logisitic regression (highest quartile as decision threshold for increased NT proBNP), Stepwise multiple logistic regression, Cox survival analysis	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 456 pg/mL	Mortality or myocardial infarction: unadjusted odds ratio = 7.06 (95% confidence interval 3.30-15.08) Mortality: unadjusted odds ratio = 13.47 (4.50-40.48) Myocardial infarction: unadjusted odds ratio = 2.53 (0.77-8.34) Event-free survival: adjusted odds ratio = 4.96 (2.25-10.94)
Galvani 2004 Italy	Condition 1 - mean age: 59 +/- 11 years Condition 2 - mean age: 65 +/- 11 years % Male: 71	1726 Followup: 30 days	Rest anginal pain lasting more than 10 minutes and occurring within 24 hours of admission to coronary care unit (angina was associated with ischemic ECG changes)	Mortality at 30 days	NR/NR	Simple and multiple logistic regression for 30 day mortality	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Threshold: Modular/Quartiles: </= 107 pg/mL, 108–353 pg/mL, 354–1357 pg/mL, >/= 1358 pg/mL	First quartile is reference category for predicting odds of 30 day mortality: 2nd quartile: Unadjusted odds ratio = 2.94 (1.15-7.52) Adjusted odds ratio = 1.33 (0.79-2.24) 3rd Quartile: Unadjusted odds ratio = 5.32 (2.19-12.91) Adjusted odds ratio = 1.89 (1.00-3.58) 4th quartile: Unadjusted odds ratio = 11.5 (4.90-26.87) Adjusted odds ratio = 3.91 (1.51-10.13)

Evidence Table 6: Summary of studies in patients with CAD not surgery: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Bazzino 2004 Argentina	Mean age: 66+/- 12 years % Male: 63.6	1483 Followup: From hospital admission to 180 days or death (which came first)	Resting chest pain within 24 hours of admission to coronary care unit	1) Combined endpoint of mortality or or non-fatal MI. 2) All cause mortality (in hospital and 180 day). 3) New non-fatal myocardial infarction (MI).	Yes/Yes	Stepwise multiple logistic regression	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 586 pg/mL	For 180 day mortality, the strongest independent predictor after adjusting for cardiac markers (treated as categorical) was NT-proBNP: adjusted odds ratio = 3.42 (1.95-5.98). After forward stepwise logistic regression, NT-proBNP remained in the model: For 180 day mortality, adjusted odds ratio = 1.67 (1.41–1.99) For 180 day mortlaity or new myocardial infarction, adjusted odds ratio = 1.43 (1.24–1.64) For in-hospital mortality, adjusted odds ratio = 1.70 (1.31–2.20)
James 2003 Sweden	Mean age: 65 +/- 11 years % Male: 61.9	6809 Followup:1) 30 days 2) 12 months	One or more episodes of angina lasting >/= 5 minutes, within 24 hours of admission, and either a positive cardiac troponin test or >/= 0.5 mm of ST-segment depression.	1) Myocardial Infarction 2) Mortality: 30 day and 12 month	NR/Yes	Multiple logistic regression	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: Quartiles: <= 237 pg/mL, 238–668 pg/mL, 669–1869 pg/mL, >1869 pg/mL	For the outcome of myocardial infarction at 30 days, the confidence intervals for all four quartiles overlap the null value of 1.00, thereby indicating that the adjusted odds ratios (depicted graphically) are not statistically significant at the 5% level. For mortality at 1 year, the adjusted odds ratios range from approximately 1.4 to 3.2 (depicted graphically). The odds ratios are statistically significant at the 5% level.

Evidence Table 6: Summary of studies in patients with CAD not surgery: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Richards 2003 New Zealand	Mean age: 62.4 +/- 10.4 (range 26-80) years % Male: 78.2	666 Followup:3 years (mean)	Myocardial infarction: ischemic change (including ST elevation or depression or dynamic T-wave changes; i.e., includes ST-elevation, non–ST elevation, Q-wave, and non–Q-wave infarcts) in 2 or more ECG leads and peak elevation of plasma creatinine kinase to at least twice the upper limit of normal.	1) Mortality 2) Re-admission to hospital with heart failure 3) New Myocardial Infarction 4) All recurrent acute coronary syndromes (ACS)	NR/NR	Stepwise Cox proportional hazards regression	[NT-proBNP] New Zealand (Christchurch) - no instrument, manual assay Threshold: 1370 pg/mL	Death: adjusted rate ratio = 6.63 (3.72-11.79); interaction between N-BNP and ejection fraction < 40%: adjusted rate ratio = 3.26 (2.04-5.22) Death or heart failure: adjusted rate ratio = 2.70 (1.65-4.41) Reinfarction: adjusted rate ratio = 3.51 (1.08-11.50); interaction between N-BNP and ejection fraction < 40%: adjusted rate ratio = 3.81 (1.01-13.52) Death, heart failure, or reinfarction: adjsuted rate ratio = 2.27 (1.54-3.33); interaction between N-BNP and ejection fraction < 40%: adjusted rate ratio = 1.59 (1.12-2.27) Death, heart failure, or acute coronary syndromes: adjusted rate ratio = 2.10 (1.57-2.83); interaction between N-BNP and ejection fraction < 40%: adjusted rate ratio = 1.57 (1.17-2.10)

Evidence Table 6: Summary of studies in patients with CAD not surgery: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Omland 2002 Sweden	Condition 1 - mean age: 62 Condition 2 - mean age: 69 % Male (NT-proBNP <=545 pmol/L): 73 % Male (NT-proBNP <545 pmol/L): 70	609 Followup:Median: 51 months (range 19-72 months)	Clinical diagnosis not specified	All-cause mortality	Yes/NR	Multiple Cox proportional hazards regression	Manual method referencing - Carl J., Borgya A., Gallusser A. et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81 Threshold: 4609 pg/mL	Unadjusted rate ratio = 3.9 (2.4-6.5) Adjusted rate ratio = 2.1 (1.1-3.9) (after adjustment for age and ejection fraction, rate ratio = 2.4 [1.1-5.4])

Abbreviations: PTCA= NR=not reported, ECG=electrocardiogram, MI=myocardial infarction, PCTA=percutaneous transluminal coronary angioplasty

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Squire 2004 U.K.	Mean age: 65 (range 32-95) years % Male: 75	403 Followup: Median = 462 (range 5-764) days	AMI was defined as presentation with at least two of three standard criteria, i.e. appropriate symptoms, acute ECG changes of infarction (ST elevation, new left bundle branch block) and a rise in creatine kinase to at least twice the upper limit of normal, i.e. > 400 international units/(200 nmol) in 0.1 mol/l phosphate buffer, and the tracer purified on reversed-phase HPLC. Acute MI pateints who presented with 2 or 3 criteria (i.e. appropriate symptoms, acute ECG changes [ST elevation, new left bundle branch block]) and a rise in creatine kinase to at least twice the upper limit of normal, i.e. >400 international units/l.	1) Mortality <30 days 2) Mortality > 30 days	Yes/NR	ANOVA, Cox proportional hazards (multiple), logisitic regression (multiple), Kaplan-Meier curves	Manual method referencing - Carl J., Borgya A., Gallusser A. et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81 Threshold: 7324 pg/mL	Adjusted odds ratio = 5.5 (95% confidence interval = 2.2-13.5) for predicting hospitalization due to HF. Adjusted odds ratio = 3.2 (1.7-6.2) for predicting outpaitent HF episodes. Adjusted hazard ratio = 4.2 (2.1-8.4) for all cause mortality. Adjusted odds ratio = 8.76 (2.48-30.90) for all-cause mortaliy < 30 days.

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Jernberg 2003 Sweden	Age range: 40-84 years % Male: Not reported	2019 Followup:</= 2 years	Myocardial ischemia had to be verified by an electrocardiogram (ST-segment depression =>0.10 mV or T-wave inversion =>0.10 mV) or by raised biochemical markers.	1) Mortality 2) Myocaridal infarction	NR/NR	Multiple logistic regression and multiple Cox proportional hazards	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 535 pg/mL (men) 672 pg/mL (women)	Adjusted rate ratio = 3.76 (1.95–7.25)
Palmer 2003 New Zealand	Mean age: 62.1 years % Male: 78	978 Followup: Median = 2.4 (range 2-2119) days	The presence of typical cardiac ischemic symptoms, ischemic change on the electrocardiogram in two or more contiguous leads, and peak elevation of plasma creatine kinase to at least twice normal (400 U/l). All patients were troponin T positive.	Mortality post-myocardial infarction	NR/Yes	Multiple Cox proportional hazards	New Zealand (Christchurch) - no instrument, manual assay Threshold: 186 pg/mL	Nt-proBNP interacts with angiotensin-converting enzyme: adjusted hazard ratio = 1.01 (1.00-1.02)

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Richards 1998 New Zealand	Mean age: 64 +/- 10 years % Male: 74	Control: 35 normal subjects not matched for age. Treatment: 121 patients with acute myocardial infarction. Followup: 24 months	Acute myocardial infarction was defined by the presence of typical cardiac ischemic symptoms, the presence of ischemic changes on the ECG in two or more ECG leads, and peak elevation of plasma creatine kinase to at least twice normal (400 U/L).	1) All-cause mortality 2) Left ventricular ejection	Yes/NR	Multiple logistic regression	New Zealand (Christchurch) - no instrument, manual assay Threshold: 254 pg/mL for death 1032 pg/mL for left ventricular failure	Mortality: 254 pg/mL adjusted odds ratio = 5.9 (1.8-19.0) 1032 pg/mL adjusted odds ratio = 19.7 (2.7-142.0), p < 0.001 (20 deaths above the median and 1 death below the median) Left ventricular failure: 254 pg/ml = 5.5 (2.3-13.3) 1032 pg/mL adjusted odds ratio = 5.5 (2.3-13.3)
Darbar 1996 USA	Mean age: 63.0 years % Male: 70.7	75 Followup: Median: 19.7 (range 14-31) months	Patients were assessed by clinical, echocardiographic, and neurohormonal methods to identify left ventricular dysfunction.	1) Cardiovascular death 2) Development of symptomatic heart failure	NR/Yes	Stepwise logistic regression	New Zealand (Christchurch) - no instrument, manual assay Threshold: 169 pg/mL	The estimated odds ratio for each 10 pmol/L increase in BNP concentrations was 7.33 (1.9-10.1).

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Jarai 2005 Austria	Mean age: 63 +/- 13 years % Male: Not reported	120 Followup: 2 years	Typical angina symptoms within the last 24 hours and signs of myocardial ischaemia in the 12 lead ECG (ST-depression of 0.1 mV in two continuous leads, T-wave inversion or both with concomitantly elevated TnI [>0.15 ng/mL] levels were diagnosed as non-ST-elevation myocardial infarction). Patients without TnI elevations were diagnosed with unstable angina.	Cardiovacular death	Yes/NR	Multiple logistic regression	Biomedica Grupe - No instrument, EIA (manual assay) Threshold: 2791 pg/mL (upper limit or normal range)	Adjusted odds ratio = 4.8 (2.84-6.76)
Latini 2004 Italy	Mean age: 31.9 % Male: 69	724 Followup: 3 months	Clinical persistent ST-segment elevation, maximal CK value exceeding 2X upper limit of reference range during the first hours after the index event.	1) All-cause mortality 2) Episodes of heart failure 3) Cardio residual ischemia 4) Combined death and heart failure	NR/Yes	Multiple logistic regression	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 1300 pg/mL	Not clearly reported in text.

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
James 2004 Europe, North America	Mean age: 65 % Male: 62	1381 Followup: 12 months	1 or more episodes of angina > 5 min and ST-depression > 5mm or Troponin or I test elevation.	1) Mortality at 12 months 2) Myocardial infarction 3) Death or MI	NR/Yes	Multiple logistic regression	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: Quartiles: <237 pg/mL, 237-669 pg/mL, 669-1869 pg/mL, and >1869 pg/mL	Graphical depiction of odds ratios shows that all odds ratios for myocardial infarction were not statistically significant at the 5% level. Graphical depiction shows that odds ratios for 3rd and 4th quartiles of NT-proBNP were statistically significant at the 5% level.

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Ueland 2004 U.K.	Condition 1 - mean age: 63 +/- 8 years (osteoprotegerin<2.1) Condition 2 - mean age: 67 +/- 10 years (OPG<3.0) Condition 3 - mean age: 69 +/- 10 years (OPG<4.1) Condition 4 - mean age: 72 +/- 11 years (OPG>4.1) % Male: 70.2	Control: 15 age and gender matched healthy controls Treatment: 234 patients with acute myocardial infarction complicated by heart failure Followup: Median 2.7 years	Left ventricular dysfunction (i.e., left ventricular ejection fraction [LVEF] <35% or a left ventricular end-diastolic dimension >65 mm) and/or HF during the acute phase as suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for HF, pulmonary rales, third heart sound, persistent sinus tachycardia (=/> 100 beats/min), or radiographic evidence of pulmonary congestion.	1) Non-fatal myocardial infarction 2) Cardiovascular death 3) Total mortality death	NR/NR	Simple Cox proportional hazards	Manual method referencing - Carl J., Borgya A., Gallusser A. et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81/ Threshold: 0537 pg/mL	All cause mortality: unadjusted rate ratio = 2.1 (1.0–4.4) Cardiovascular death: unadjusted rate ratio = 2.2 (1.0–5.0) Composite end point (all events combined): unadjusted rate ratio = 1.4 (0.8–2.6)

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Schnabel 2005 Germany	Condition 1 - mean age: 60.7 +/- 9.7 years Condition 2 - mean age: 62 +/- 11.2 years % Male: 77	904 Followup: Median 2 years (maximum 3.7 years)	Under coronary angiography: at least one stenosis >30% diagnosed in a major coronary artery, unstable angina classified by Braunwald classification (class B or C), acute myocardial infarction (ST-segment elevation in at least two corresponding leads plus troponin elevation - LVEF was determined by LV-angiography and off-line analysis according to the area–length method).	Cardiovascular events	NR/NR	Multiple Cox proportional hazards	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: In patients with stable angina: quartile 1 (<86.7 pg/ml) quartile 2 (86.7-192.0 pg/ml) quartile 3 (192.0–487.9 pg/ml) quartile 4 (>487.9 pg/ml) Hazard ratios according to quartiles of baseline NT-proBNP in patients with ACS: quartile 1 (<160.8 pg/ml) quartile 2 (160.8-538.1 pg/ml) quartile 3 (538.1–1356.0 pg/ml) quartile 4 (>156.0 pg/ml)	In patients with stable angina: quartile 1 (<86.7 pg/ml) adjusted hazard ratio=1.0 n=144 quartile 2 (86.7-192.0 pg/ml) adjusted hazard ratio=1.18, (0.30-4.58) quartile 3 (192.0–487.9 pg/ml) adjusted hazard ratio = 1.51 (0.40-5.64)quartile 4 (>487.9 pg/ml) adjusted hazard ratio = 3.96 (1.13-13.9). Hazard ratios according to quartiles of baseline NT-proBNP in patients with ACS: quartile 1 (<160.8 pg/ml) adjusted hazard ratio = 1.0 quartile 2 (160.8-538.1 pg/ml) adjusted hazard ratio = 0.64 (0.13-3.05)quartile 3 (538.1–1356.0 pg/ml) adjusted hazard ratio = 0.64 (0.14-2.95) quartile 4 (>156.0 pg/ml) adjusted hazard ratio = 1.2 (0.21-6.84)

Evidence Table 7: Summary of studies in patients with CAD no surgery: NT-proBNP

Author	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP Method /Units	Measure of Association
Heeschen 2004 Germany, New Zealand	Condition 1 - mean age: 59.9 +/- 10.9 years Condition 2 - mean age: 64.1 +/- 10.8 years % Male: 67%	1791 Followup: 30 days	Chest pain at rest or accelerating chest pain within the previous 24 hours. All patients had evidence of coronary artery disease as described in another article.	1) Mortality 2) Myocardial infarction	NR/NR	Multiple logistic regression	Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 246 pg/mL	Death or Nonfatal Myocardial Infarction During 30 Days of Followup: Adjusted odds ratio = 2.68 (1.66–4.34)

Abbreviations: LVEF=left ventricular ejection fraction, AMI=acute myocardial infarction, ECG=electrocardiogram, HPLC=high pressure liquid chromatography, MI=myocardial infarction, NR=not reported, HF=heart failure

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Dokainish 2005 USA	Condition 1 - mean age: 57.3 +/- 11.6 years Condition 2 - mean age: 60.6 +/- 13.3 years % Male: 57	895 Followup: NR	Angiographic CAD if >/= 50% stenosis in coronary artery	Death or Re-infarction	NR/Yes	Chi-square, Fisher exact test, t-test, Wilcoxon rank-sum, Kruskal-Wallis	[BNP] Biosite Diagnostics – Triage Threshold: BNP 80 pg/mL	Not Reported
Lindahl 2005 Sweden	Mean age: 67 years % Male: 71	961 Followup: 2 years if randomized to invasive vs non-invasive surgery 6 months if randomized to daltperin vs placebo	Non-ST-segment elevation. Both chest pain and signs of ischemia (ST-segment depression =>0.10 mV or T-wave inversion =>.10 mV or raised biochemical markers.	1) Changes in NT-proBNP after 5 serial measures expressed as a) median values b) mean rate of change per visit Outcomes for the FRISC-II trial 2) mortality 3) MI	NR/NR	Multiple linear and logistic regression	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: Baseline NT-proBNP median = 529 pg/mL, six months median = 238 pg/mL	Not Reported

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Panteghini 2003 Italy	All subjects mean age 52.5 years All subjects age range 33-78, 89%	Controls: 28 age-matched apparently healthy laboratory workers Treatment: 64 acute myocardial infarction patients Followup: 13 months median (range 4 to 23 months)	Made by cardiologist	1) All cause mortality 2) Unstable angina or recurrrent MI	NR/Yes	Linear regression, Kaplan-Meier survival curve	[BNP] Biosite Diagnostics – Triage Threshold: BNP 83 pg/ml	Not Reported
Richards 2002 New Zealand	Mean age: 63.6 years % Male: 72.6	747 Followup: 2 year mean (up to 1000 days)	Patients were categorized as having antecedent hypertension if this diagnosis was known by the patient to have been made by their family physician or after specialist referral, if the acute admission note indicated a history of hypertension and/or they were receiving antihypertensive medication.	1) Mortality 2) Pre-discharge heart failure 3) Re-admission for heart failure	NR/NR	Multiple Cox proportional hazards or logistic regression	NT-proBNP Threshold: 1015 pg/mL	Not Reported

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Sadanandan 2004 USA	Condition 1 - mean age: 61 years Condition 2 - mean age: 67 years % Male: 65%	276 Followup: 6 months	Subjects from TACTICS-TIMI-18 trial. All patients had unstable angina, non-ST elevated myocardial infarction (UA/NSTEMI), and cardiac cathertization within 4-48 hrs and revascularization.	Composite endpoint of death, non-fatal re-infarction, and repeat hospitalization for ACS (P)	NR/Yes	Chi square test	[BNP] Biosite Diagnostics – Triage Threshold: BNP 80 pg/mL	Not Reported
Shimpo 2004 USA	Mean age: 58 years % Male: 79.2	810 Followup: 30 days	Episode of ischemic discomfort of at least 30 minutes within 6 hours or 12 hours and exhibited at least 0.1-mV ST-segment elevation in 2 contiguous ECG leads.	1) Congestive heart faliure 2) Mortality 30 day 3) Mortality	NR/NR	Multiple logistic regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: BNP 80 pg/ml	Not Reported
Suzuki 2004 Japan	Condition 1 - mean age: 64.7 +/- 11.1 years Condition 2 - mean age: 66.7 +/- 7.9 years % Male: 73%	145 Followup: 58.6 month mean (range 1-158 months)	The diagnosis of AMI was made from clinical symptoms, including chest pain, ECG changes including ST elevation and ST depression, and an elevation of serum creatine kinase-MB isoenzyme to more than twice the normal upper level.	Cardiac related mortality	NR/NR	Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: BNP 180 pg/ml	Some chi-quare values for log BNP were given for Cox proportional hazards analysis: Log BNP univariate chi-square = 20.06, p<0.0001; multivairate chi-square = 7.003, p 0.008.

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Zeller 2004 France	Mean age: 69 (range 55-77) Years % Male: 69	101 Followup: NR	All patients with a diagnosis of MI exceeding the decision limit increase in troponin I (10.1 ng/ml) associated with either typical ischemic symptoms or ECG signs (ST-segment depression or negative T waves).	1) Death or recurrent MI 2) Death or recurrent MI or heart failure	NR/NR	Multiple logistic regression	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: NT-proBNP 136 pmol/L	Predictors of NT-proBNP > 136 pg/mL Univariate analysis (OR/95% CI): Age > 65 years 5.46/2.27–13.08 Killip > I 4.50/1.51–13.41 PURSUIT score >/= 7 4.25/1.85–9.76 Hypertension 2.75/1.23–6.15 LVEF < 50% 2.69/1.13–6.41 Female 0.29/0.12–0.72 Current smoker 0.20/0.08–0.61 Multivariate analysis LVEF < 50% 0.91/0.85–0.96 Age > 65 years 1.12 1.05–1.19 Hypertension 3.78/1.03–13.83

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Hutfless 2004 USA	Mean age: 63 +/- 9.1 years % Male: 100	98 Followup: NR	CAD included: 1) Myocardial infarction within 6 weeks preoperatively n=7. 2) CHF NYHA functional class III or IV n=9. 3) Insulin-dependent diabetes mellitus n=10. 4) Past cerebrovascular accident n=10. 5) Chronic renal insufficiency n=7. 6) Previous percutaneous transluminal coronary angioplasty/stent n=19. 7) Previous thoracotomy n=9. All male patients undergoing heart surgery at the VA hospital were eligible for inclusion	Clinical end points included: 1) intraoperative and postoperative cardiac events: significant STsegment change, significant arrhythmia, new Q-wave, or cardiac enzyme elevation; 2) ventilator dependence >48 h postoperatively; 3)intensive care unit stay longer than 5 days postoperatively; 4) hospital stay longer than 10 days postoperatively; 5) emergency reintubation other than for reoperation; 6)cardiothoracic reoperation within 2 weeks of initial surgery; 7) readmission within 30 days for cardiac reasons; 8) requirement for intra-aortic balloon pump (IABP); 9) mortality within 30 days and within 1 year postoperatively; and 10) postoperative requirement for epinephrine, lidocaine, and/or pressor doses of dopamine.	Yes/NR	None	[BNP] Biosite Diagnostics – Triage Threshold: 3 BNP cut-points: 120 pg/ml 280 pg/ml 385 pg/ml	Not Reported
Julier 2003 Switzerland	Mean age: 63.5 years % Male: 81.9	72 Followup: 72 hours	Scheduled for elective CABG surgery on CPB circuit with cardiac arrest.	NT-proBNP levels in treated vs. placebo patients postoperative cardiovascular and renal adverse events.	NR/Yes	None	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: None	Not Reported

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Kerbaul 2004 France	Condition 1 - mean age: 68 +/- 10 years Condition 2 - mean age: 67+/- 9 years % Male: 80%	60 Followup: Without complications: 2.6 +/- 0.9 days With complications: 6.9 +/- 3.8 days	1) Recent MI: acute coronary syndrome with or without ST modification or and with Tropinin I level modifications occurring within 6 weeks of the operation. 2) Unstable angina: associated with acute coronary sybdrome w/out modification in Tropinin I. 3) Peripheral arteriosclerosis: history of claudication or peripheral vascular surgery. patients undergoing elective OPCAB who were free of active preoperative infection and inflammation	1) Cardiovascular complications (myocardial infarction, cardiogenic shock, arrhythmias, CHF, and death occurring after the fourth postoperative hour) Abnormal post-operative cardiovascular course: ICU: (a) systolic arterial pressure < 90 mmHg with low cardiac output (cardiac index <2 l min^-1 m^-2) and signs of hypoperfusion such as oliguria; (b) need for catecholamines for cardiovascular support (dobutamine >5 ug kg^-1 min^-1 or any amount of epinephrine or norepinephrine >6 h); (c) postoperative myocardial infarction defined as a maximal creatine kinase MB fraction level >100 IU l^-1 associated electrocardiographic modifications and segmental hypokinesia at the echocardiography; (d) CHF defined by fluid retention and persistent chest infiltration; (e) atrial fibrillation >15 min with hemodynamic instability requiring electrical or pharmacological cardioversion; (f) ventricular fibrillation or tachycardia requiring electrical cardioversion; (f) operative mortality occurring within 30 days of the operation.	Yes/Yes	Unadjusted regression: BNP = preoperative left ventricular ejection fraction BNP = NYHA status	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: 0: 30 minutes after introduction of IV anesthesia before surgery --> 397 pg/ml. T1: 10 minutes after the end of surgery --> 430 pg/ml. T2: 4 hours after the end of surgery --> 491 pg/ml. (Various measures of NT-proBNP over time)	Not Reported

Evidence Table 8: Summary of studies in patients with CAD no regression analyses

Author	Sample Characteristics	Sample Size/Follow up	Diagnostic criteria	Outcomes	Consecutive Cohort / Outcome Blinding	Analysis/Model	BNP Method/Units	Measure of Association
Song 2004 Japan	Condition 1 - mean age: 66.7+/- 9.3 years (on-pump CABG) Condition 2 - mean age: 71.6 +/- 7.4 (off-pump CABG) % Male: 72.5%	40 Followup: 1 month	New York Heart Association	BNP levels Correlations between BNP and sample characteristics in both surgery groups.	NR/NR	Simple and multiple regression: BNP = CAB + pleural effusion BNP = CAB + atrial fibrillation	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 450 pg/ml	Peak BNP of > 450 pg/mL was found to be the most powerful predictor of post-operative pleural effusion and atrial fibrillation (no quantitative data are reported).
Watanabe 2003 Japan	Not Reported	14 Followup: 20 months	Undergoing elective CABG with cardiopulmonary bypass (CPB)	1) Clincal status: death, requiring intra-aortic balloon pump (IABP) support for left ventricular dysfunction, angina, graft failure, heart disease, cardiac scintingraphy, occlusion or critical stenosis of bypass grafts or progression of native coronary stenosis). 2) Presence of angina, NYHA class, positive cardiac scintigraphy, occlusion or critical stenosis of bypass grafts.	NR/NR	Simple linear regression: BNP = clinical status	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: None	Not reported

Abbreviations: CAD=cardiovascular artery disease, MI=myocardial infarction, NR=not reported, ECG=electrocardiogram, AMI=acute myocardial infarction, OR=odds ratio, CI=confidence interval, CHF=congestive heart disease, NYHA=New York Heart Association, ACS=acute coronary syndrome, CABG=coronary artery bypass graft

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Maisel 2004 USA	•Cohort: REDHOT •Age: Mean, 64 •Age: Range, 51 - 76 •% Male: 54%	464 Followup: 30 and 90 days	•REDHOT cohort enrolled only If had BNP > 100pg/mL NYHA (I-IV): 3.0% level I, 29% level II, 46% level III, 22.6% level IV. 45 % Level III •Clinical evaluation only. •LVEF Not Reported	Mortality	NR/Yes	Multivariate logistic regression	[BNP] Biosite Diagnostics – Triage Threshold:200 pg/mL (chosen retrospectively based on internal analysis)	Mortality 90 days:Multivariate: Baseline Exp(Beta) for logBNP = 4.531 (beta p = 0.001)
van der Meer 2004 Netherlands	•Cohort: NA •Age: Range, 26 to 90 •% Male: 80%	74 Followup: Deceased: mean 621 days (range 16 to 1,728 days) Survivors: mean 1100 days (range 844 to 1,934 days) and a median of 987 days (37 months)	•Stable mild to moderate CHF patients admitted to clinic (NYHA II - IV): 37% level II,32% level III, 31% level IV •Based on standard criteria from European Society for Cardiology (including echocardiography) and standard criteria (NYHA) •Used in regression analyses as a continuous variable to predict all cause mortality	All cause mortality	Yes/No	Uni and multivariate Cox backward Wald regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold:No threshold specified. Mean BNP 109.9 +/- 13.5 pmol/L [Conversion 380 pg/mL +/- 46.71]	All cause mortality: Univariate: Baseline BNP (pmol/L) H.R. =1.006, CI = 1.003–1.009, P = 0.001 All cause mortality: Multivariate: Baseline BNP did not remain independently associated

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Latini 2004 Italy	•Cohort: Val-HeFT •Age: Mean, No info •%Male: No info	4300 Followup: Not Specified (23 months outcomes are discussed in the results but not clear if this is total followup time)	•ValHeFT cohort: stable but symptomatic HF (NYHA I-IV) •LVEF < 40% and LV internal diameter in diastole adjusted for body surface area (LVIDd/BSA) of =>2.9 cm/m2. •LVEF < 40%	Mortality	NR/No	Uni and multivariate Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold:97 pg/mL (median sample)	Mortality: Univariate Baseline BNP >= 97 pg/mL HR = 2.47 [95% CI, 2.13-2.87] (significant) Mortality: Mulitvariate Baseline BNP >= 97 pg/mL 2.48 [95% CI, 2.13-2.88] (significant) Mortality: Multivarite Baseline BNP change = 10 pg/mL HR = 1.012 [95% CI, 1.010-1.014] p<0.0001 (adjusted for the other 3 neurohormones)
Kyuma 2004 Japan	•Cohort: N.A. •Age: Mean, 64+/-13, •% Male: 69.6%	158 Followup: 16 months +/-9 months	•NHYA (I-IV): 12% level I, 49% level 2, 25% level III, 14% level IV •Presence of symptoms, 2D echocardiogram, I-MIGB scintography •Pr34 % had </= 30% LVEF	Cardiac death due to pump failure	Yes/No	Uni and mulitvariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: >172 pg/mL (median of sample)	Cardiac mortality: Univariate: Baseline BNP HR = 1.0010 [95% CI, 1.0000-1.0021], p = 0.00018 Cardiac mortality: Multivariate: Baseline BNP HR = 1.0010 [95% CI, 1.0001-1.0019], p = 0.02404 (only variable significant) Cardiac mortality: Difference with Kaplan Meier curves: Baseline BNP >172 pg/mL HR = 7.2 [95% CI 1.6-32.1], p = 0.002

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Bettencourt 2004 Portugal	•Cohort: N.A. •Age: Mean, 69.4+/-9.3 •% Male: 71.4%	84 Followup: Median 1190 days (interquartile range 863–1572). 40 months	•Patients referred to a HF clinic and then followed on an outpatient basis. Note that those who did not survive to second scheduled measurement were excluded from the study. (NYHA I -III): 11.9% level I, 81% level II, 7% level III. •Clinical examination including ECG, chest X-ray, spirometry, echocardiogram, serum biochemical analyses. •Mean LVEF 31.2% +/- 12.0	Mortality	NR/Yes	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 260.4 pg/mL (median of sample); also compared subjects whose BNP levels increased versus those that decreased following treatment.	Mortality: Univariate: Baseline BNP > 260.4 pg/mL HR = 2.96 [95% CI, 1.06–8.26] Mortality: Univariate: 1) BNP increase (vs decrease) HR = 2.64 [95% CI, 1.00–7.00], 2) delta BNP (per increase in 100 pg/mL) HR = 1.28 (95% CI, 1.15– 1.43] Mortality: Multivariable: delta BNP (per increase in 100 pg/mL) HR = 1.34 [95% CI, 1.10 to 63]
Ishii 2003 Japan	•Cohort: N.A. •Age: Mean, 68 + 11 •% Male: 56%	100 Followup: Mean 391 days (range 16-884) 13 months	•Patients admitted to hospital for worsening CHF (NYHA III-IV): 54% level III and 46% level IV •Cardiologists not directly involved in the study determined if pateients met exclusion criteria. 2D Echocardiogram and venous blood samples were used to detrmine severity. •12% of patients had mean LVEF 36%	Cardiac death (death from worsening CHF, fatal MI or sudden death)	NR/Yes	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold:160 ng/L (based on ROC with best sensitivity). [Conversion 160 pg/mL]	Cardiac deaths: Univariate: Baseline Log BNP (10-fold increase), HR = 5.66 [95% CI 1.55–20.7], p = 0.006 Cardiac deaths: Multivariate model including cTnT and BNP concentrations: Baseline Log BNP (10-fold increase) HR = 3.11[95% CI, 1.61–6.01], p = 0.0005

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Vrtovec 2003 New Zealand	•Cohort: N.A. •Age: Mean, 67+/-14, •% Male: 59%	241 Followup: 6 months	•Patients referred with heart failure to single centre (Patients with BNP >400 pg/mL who had been NYHA class III-IV for at least 2 months before evaluation) (NYHA III-IV): 74% level III, 26% level IV. •Clinical evaluation and ECG. •Mean LVEF = 26% +/- 9%	All cause mortality	NR/No	Uni and multivariate Cox proportional hazard regression	[BNP] Biosite Diagnostics - Triage Threshold: Three categories (<700 pg/ml, 701-1000 pg/mL, > 1000 pg/mL)	All cause death: Univariate: Baseline BNP 400-700 pg/mL, p = 0.0003, Baseline BNP 701-1000 pg/mL, p = 0.0003, Baseline BNP >1000 pg/mL, p = 0.0001 All cause death: Multivariate Baseline BNP > 1000 pg/mL HR = 1.99 [95% CI, 1.18–3.36], p 0.0005 Cardiac death: Univariate: Baseline BNP 400-700 pg/mL, p = 0.0004, BNP 701-1000 pg/mL, p = 0.0004, BNP >1000 pg/mL, p = 0.0003 Cardiac death: Multivariate Baseline BNP HR = 1.76 [95% CI, 1.01–3.07], p 0.0007 Pump failure death: Univariate: Baseline BNP 400-700 pg/mL, p = 0.0003, Baseline BNP 701-1000 pg/mL, p = 0.0003, Baseline BNP >1000 pg/mL, p = 0.0001 Pump failure: Mutlivariate Baseline BNP HR = 3.78 [1.63–8.78], p = 0.0007 Sudden cardiac death: All were not significant

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Ishii 2002 Japan	•Cohort: N.A. •Age: Mean, All subjects, 69+/- 9 •Age: Mean, Condition 1: 71+/-10 •Age: Mean, Condition 2: 68+/-10 •Age Range, All subjects, 22-88 •% Male: 52%	98 Followup: Mean 451 +- 98 days (range 13 to 667 days) 15 months	•Patients were admitted to a coronary care unit due to worsening CHF. (NYHA mean 3.5 +/- 0.6) •2D echocardiography read by experts blinded to the study. •Mean LVEF = 42% +/- 17	1) Cardiac death (death from worsening chronic heart failure, fatal myocardial infarction, or sudden death)	Yes/No (but endpoints judged by independent researchers)	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: BNP 440 pg/ml (based on ROC analysis)	Cardiac death: Univariate: Baseline Log BNP, Chi Sq.= 6.66, p = 0.0098 Cardiac death: Multivariate: Baseline Log BNP Chi Sq. = 4.45, p = 0.034
Harrison 2002 USA	•Cohort: N.A. •Age: Mean, 65 •Age: Range, 29-83 •% Male: 95%	325 Followup: Mean followup time=682.2 +- 55.0 days 23 months	A convenience sample presenting with dyspnea to the emergency department (41% CHF) Diagnosis: Echocardiogram results from previous records was used to establish CHF. LVEF not reported	Mortality (any cardiac, noncardiac, and CHF)	No/Yes	Unadjusted Relative Risks	[BNP] Biosite Diagnostics - Triage Threshold: 480 pg/mL based on ROC; 230 pg/mL (provided few false negative values)	CHF death: Unadjusted: Baseline BNP>230 pg/mL vs. <=230 pg/mL: RR = 24.1 [95% CI, 6.3.5-491.1] Cardiac death: Unadjusted: Baseline BNP>230 pg/mL vs. <=230 pg/mL: RR = 37.9 [95% CI, 5.7.5-755.8]
Stanek 2001 Austria	Subjects with HF (LVEF < 25%) from a substudy of subjects from RCT evaluating those on atenolol versus placebo. (NYHA II-IV): 78% level II, 13% level III, 2% level IV.	SS = 91 Followup: 4 years	Radionuclide ventriculography and clinical evaluation	Cardiac mortality	NR/No	Uni and mulitvariate Cox proportional hazards regression	[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: 300 fmol/ml N-BNP (last available plasma level).	Death: Multivariate: Baseline LogBNP Chi Sq. = 13.9, p = 0.0002 Death: Multivariate: Last followup LogBNP Chi Sq. = 21.3, p = 0.0001 Death: Multivariate: Last followup LogNT-proBNP Chi Sq. = 8.9, p = 0.0027

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Imamura 2001 Japan	•Cohort: Ehime MIBG Heart Failure (EMIHEF Study) •Age: Mean, All subjects, 63 +/- 11 •Age: Mean, Condition 1: 64 +/- 11 (Event free) •Age: Mean, Condition 2: 65 +/- 12 (Cardiac death) •Age: Mean, Condition 3: 61 +/- 14 (hospitalization) •% Male: 73%	171 Followup: 27+/- 8 months	•Ehime MIBG Heart Failure Study (EMIHEF) randomized trial. (NYHA II-IV): 54% level II, 18% level III, 3% level IV. •Clinical evaluation, including NYHA, I-MIBG images, Chest x-ray, 2D echocardiography •Mean LVEF 27%+/- 10%	Cardiac mortality, defined as death from progressive CHF or sudden cardiac death	NR/No	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: <160 pg/ml (mean of sample)	Cardiac death: Univariate: Baseline BNP RR = 1.005 [95% CI,1.002-1.008], p = 0.0002 Cardiac death: Multivariate: Baseline BNP not statistically significant at 5% level (no quantitative data were reported).
Cheng 2001 USA	•Cohort: N.A. •Age: Mean, 68 +/- 1.6 •Age: Range, 28 - 110 •% Male: 100%	72 Followup: 30 days	•Convenience sample of veterans (NYHA III-IV) : mean level 3.64 +/- 0.07. •New-onset CHF: confirmed by at least one cardiologist using standard Framingham criteria or exacerbation of previously documented CHF, NYHA class. •LVEF < 50% (mean LVEF 37% +/-2%)	1) Death in hospital or death within 30 days after initial discharge	NR/No	Univariate logistic regression	[BNP] Biosite Diagnostics - Triage Threshold: Mean admission and discharge levels, and four categories of threshold (430 pg/mL, 840 pg/mL, 1090 pg/ml, 1220 pg/mL)	Mortality outcomes not reported

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Akioka 2000 Japan	•Cohort: N.A. •Age: Mean, 71 +/- 15 •% Male: 57%	33 Followup: 3 months	•Patients with chronic CHF admitted to the ER for episodes of acute decompensation. (NYHA III-IV): 23% level III, 73% level IV. •Clinical evaluation, chest X-ray, and 2D echocardiography. •Mean LVEF 41% +/- 13%	Cardiac mortality	NR/No	Univariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: > 700 pg/ml (median level)	Cardiac Mortality: Univariate: Baseline BNP Chi Sq. = 2.17, p = 0.141 Cardiac Mortality: Univariate: Deceleration time (DcT) < 120 and Baseline BNP > 700 pg/mL Chi Sq. = 5.87, p = 0.015
Bettencourt 2000 Portugal	•Cohort: N. A. •Age: Mean, 69.6 +/- 9.3 •% Male: 59%	139 Followup: 541.4+-346.5 days. 11.5 months	•Patients with mild to moderate heart failure who were referred to an outpatient HF clinic. (NYHA I-III): 11.5% level I, 82.7% level II, 5.8% level III. •Clinical examination, echocardiography, and doppler •Mean LVEF = 33.5% +/-13.2%.	All cause mortality	Yes/No	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 274 pg/mL (median of sample)	Mortality: Univariate:Baseline BNP Beta = 0.001, p < 0.0001 Mortality: Multivariate: Baseline BNP Beta = 0.0001, p = 0.002

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Maeda 2000 Japan	•Cohort: N.A. •Age: Mean, 63.6 +/- 1.5 •% Male: 64%	102 Followup: Mean: 807 days (+/- 42.3) Range: 120-1568 days (27 months)	•Patients hospitalized with chronic severe. (NYHA III-IV): 56% level III, 44% level IV. •Echocardiography at admission and 3 months. •Mean LVEF 23% +/- 0.9%	1) Cardiac death (worsening CHF, lethal MI, sudden death) or survival	Yes/No (but judged independently by researchers)	Uni and multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 170 pg/ml (median from sample) or 240 pg/ml (from ROC curve)	Mortality: Univariate: Baseline BNP Chi Sq. = 5.79, p = 0.0161; BNP 3 months post Tx Chi Sq. = 40.7, p < 0.0001 Mortality: Multivariate: Baseline BNP Chi Sq.= 2.61, p = 0.11, BNP 3 months post Tx Chi Sq. = 29.1, p < 0.0001
Tsutamoto 1999 Japan	•Cohort: N.A. •Age: Mean, 59 + 0.7 •Age: Range,18-82 •% Male: 76.6%	290 Followup: Mean = 502 days (range 31-1,619 days) in patients with an outcome Mean = 1,071 days (range 31-2,541 days) for event-free patients. 36 months	•Consecutive early-stage HF patients who subsequently underwent cardiac catheterization. (NYHA I-II):32% level I, 68% level II. •Clinical evaluation and LVEF demonstrated by ventriculography with contrast medium. •LVEF < 45%	Cardiac mortality	Yes/No	Linear regression Uni and multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 56 pg/mL (median of total sample)	Mortality: Multivariate: Baseline BNP HR = 1.004 [95% CI, 1.003-1.006], p < 0.001 (only high level of BNP was significant) Mortality: Univariate: Baseline BNP Chi Sq. = 100.5, p < 0.0001 Mortality: Multivariate: Baseline BNP Chi Sq. = 59.21, p < 0.001

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Tsutamoto 1997 Japan	•Cohort: N.A. •Age: Mean, 60 •Age: Range, 22 - 84 •% Male: 72%	85 Followup: > 1 year (mean 24 months)	•Chronic CHF pateints admitted to hospital. (NYHA II-IV): 54% level II, 21% level III, 25% level IV. •LVEF of <45% determined with ventriculography with radionuclide or contrast medium, and laboratory tests. •LVEF < 45% (Mean LVEF = 31.1% +/- 1.1%	Cardiac mortality	NR/No	Uni and multivariate Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 73 pg/mL (median plasma concentration)	Cardiac mortality: Univariate: Baseline BNP Chi Sq. = 60.83, p < 0.001 Cardiac mortality: Multivariate: Baseline BNP Chi Sq. = 19.68, p < 0.0001 Cardiac Mortality: Multivariate: Baseline BNP HR = 1.003 [95% CI, 1.001 to 1.004]
Wallén 1997 Sweden	•Cohort: 70 year old people in Gothenburg Sweden •Age: Mean, 85 •% Male: No info.	541 Followup: 60 months	•Sample from longitudinal study of those born in 1901 - 02 in Swedish city; the current study followed 85 year olds for 5 years. Not all patients had CHF. •Clinical evaluation and heart volume. •Not Reported	All cause mortality	NR/No	Multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Divided into quintiles: Q1=1.0 - 11.3 fmol/mL [39.8 pg/mL], Q5 = 61.5 - 1103.0 fmol/mL [212.8 pg/mL - 3816.4 pg/mL]	Mortality: Multivariate: Baseline BNP HR = 1.259 [95% CI, 1.088-1.457], p = 0.0020 (total population) Mortality: Multivariate: Baseline BNP HR = 1.240 [95% CI, 1.037-1.483], p = 0.0020 (cardiovascular disorder population) Mortality: Multivariate: Baseline BNP HR = 1.382 [95% CI, 1.046-1.826], p = 0.0020 (without defined cardiovascular disorder population)

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Watanabe 2005 Japan	•Cohort: CHART •Age: Mean, 64 •% Male: 69.4%	417 Followup: mean 26 months	•Hospital based cohort from the CHART study who represented CHF in real clinical situations as they had both impaired or preserved systolic dysfuntion. (NYHA III-IV): 19.3% had level III/IV. •Framingham criteria for HF, echocardiography and clinical evalution. •LVEF < 50% (mean LVEF 38% +/- 12%)	Mortality (due to exacerbation of HF) Sudden death (without unexpected worsening of HF) Mortality (all cause) Combined HF events (HF mortality of hospitalization due to exacerbation of HF)	NR/No	Multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Log BNP >=2.12 (median based on sample)	Mortality HF: Multivariate: Not included in model as not significant Sudden death: Multivariate: Baseline logBNP >=2.12 HR = = 3.46 [95% CI, 1.39-7.94], p = 0.005
Berger 2005 Austria		452 Followup: mean 592 days +/- 387 days 20 months	•Ambulatory patients recruited from a HF centre.(NYHA I -IV): 12% level I, 34% l3vel II, 33% level III, 21% level IV. •Clinical evaluation and LVEF (method not specified). •LVEF < 35% (Mean 20% +/- 7%)	Sudden death and heart failure death	NR/No	Uni and multivariate Cox proportional hazard regression	[BNP] Biosite Diagnostics - Triage Threshold: logBNP = 2.11 (approximated 130 pg/mL and based on ROC curve analysis (to discriminate between patients who succumbed to sudden death and survivors). Thresholds for BNP, N-BNP, logN-bnp were not reported but used inmultivariate analyses.	Pump Failure: Multivariate: Baseline BNP Chi Sq. = 7·4, p 0·007 Pump Failure: Univariate: Baseline Log BNP Chi Sq. = 33·4, p 0·0001 Pump Failure: Univariate: Baseline Log N-BNP Chi Sq. = 28·4, p 0·0001 Pump Failure: Multivariate: Baseline Log BNP Chi Sq. = 10·7, p 0·001

Evidence Table 9. Summary of studies in patients with HF and mortality outcomes: BNP

Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Van Beneden 2004 Belgium	•Cohort: N.A. •Age: Mean, 58 +/- 6 (Controls) •Age: Mean, Condition 1: 62 +/- 7 (Mild to moderate CHF) •Age: Mean, Condition 2: 67 +/- 8 (Severe CHF), •% Male: 84%	117 Followup: Severe CHF group survivors mean 81 +/- 15 months (range 60-91 months) Mild to moderate CHF group survivors mean 92 +/- 3 months (range 87–96)	•Three groups: Patients with mild to moderate CHF, severe CHF, and 30 healthy age and sex matched controls. (NYHA I-IV) •Clinical evaluation only. •Mean LVEF Mild /moderate group = 29.4% +/- 4%, mean LVEF severe CHF = 20.8% +/- 6%.	All cause mortality Cardiovascular mortality Urgent heart transplant	NR/No	Multivariate Cox regression analysis	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Median values of BNP, N-BNP, LogBNP, and LogN-BNP (values not reported) were used only if significant. Only logN-BNP was used as it had the highest statisitical significance. Mean values for mild to moderate CHF N-BNP = 491 fmol/mL [4152.3 pg/mL], and severe CHF N-BNP = 1,521 fmol/mL [8,457 pg/mL]	Mortality in severe CHF group: Univariate: Baseline N-BNP Log Likelihood Chi Sq. = 5.68, p = 0.017 Mortality in severe CHF group: Univariate: Baseline BNP RIA Log Likelihood Chi Sq. = 2.14, p = 0.143 Mortality in severe CHF group: Univariate: Baseline BNP IRMA Log Likelihood Chi Sq. = 0.71, p = 0.40

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Study	Sample Characteristics	Sample Size/Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method/Unit threshold	Measure of Association
Alehagen 2004 Sweden	•Cohort: N.A. •Age: Mean, 73 +/- 6 •Age: Range, 65 - 87 •% Male: 52%	458 Followup: 5.5 years median (range 242-2,222 days) all patients 3.8 years median non-survivors (range 242-2,156 days) 5.7 years median survivors (range 1,883-2,222 days) 68 months	•Patients referred to primary care with signs and symptoms attributed to HF. (NYHA I-III): 46% level I, 43% level II, 10% level III. •Cardiologist performed clinical evaluation, echocardiography. •Not reported but in multivariate analysis used LVEF < 40% as variable	All cause mortality and cardiovascular mortality	NR/No	Mutlivariate Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Two levels: 50-100 pmol/L and >100 pmol/L. [Conversion 173 - 346 pg/mL and > 346 pg/mL]	For step 1 (n = 458. excluded only those who who declined blood test or poor doppler) Cardiovascular mortality: Baseline BNP 50-100 pmol/L HR =1.58,p = 0.3 Cardiovascular mortality: Baseline BNP >100 pmol/L HR = 3.38, p = 0.002 All cause mortality: Baseline BNP 50-100 pmol/L HR=0.99,p = 0.99 All cause mortality: Baseline BNP >100 pmol/L HR=1.90,p = 0.18 For step 3 (n = 349, excluded those with no malignancy during followup and S-creatine < 200 mM) Cardiovascular mortality: Baseline BNP 50-100 pmol/L HR = 1.76, p = 0.33 Cardiovascular mortality: Baseline BNP >100 pmol/L HR=6.92,p = 0.01 All casue mortality: Baseline BNP 50-100 pmol/L HR = 1.20, p = 0.76 All cause mortality: Baseline BNP >100 HR = 3.23, p = 0.053

Abbreviations: NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, NR=not reported, HF=heart failure

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
de Groote 2004 France	•Cohort: N/A, •Age: Mean, 57 +/- 11, •% Male: No info.	407 Followup: median followup period of 787 days 26 months	•CHF patients referred to cardiology department (26% had NYHA III) •[Angiography, Echocardiography, Cardiopulmonary exercise test, 24 h halter monitoring] •LVEF <= 45%	1) Cardiac mortality (defined as cardiac related death or urgent cardiac transplantation 2) Cardiac event-free (defined as cardiac-related death or cardiac transplantation)	NR/No	Multivariate Cox proportional hazard analyses	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 109 pg/ml (median level of group)	Cardiac event free survival: Multivariate: Baseline BNP HR = 3.45 [95% CI 1.88 to 6.31], p = 0.0001
Barcarse 2004 USA	•Cohort: N/A •Age: Mean, 64.6 +/- 1.2 •% Male:100%	98 Followup: 90 day end point	•Convenience sample presenting to urgent care centre or emergency department (58% CHF) •Cardiologist blinded to the hemodynamic parameters reviewed the patient's medical record; Echocardiogram for every patient •Subgroup LVEF <= 45% to distinguish those with systolic dysfunction	1) Sensitivity and specificity predicting death or re-admission when BNP and Cardiac index elevated 2) Severity of CHF (include death, re-admission, and emergency visit within 90 days)	NR/No	Multivariate logistic regression	[BNP] Biosite Diagnostics - Triage Threshold: 100 pg/ml (Based on literature)	Multivariate analyses showed that thoracic fluid content, acceleration index, left cardiac work index were the best clinical predictors of more severe illness (cardiac deaths, readmissions, and emergency department visits within 90 days) in patients with baseline BNP levels > 100 pg/ml.

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Maisel 2004 USA	•Cohort: REDHOT •Age: Mean, 64 •Age: Range, 51 - 76 •% Male: 54%	464 Followup: 30 and 90 days	•REDHOT cohort enrolled only If had BNP > 100pg/mL NYHA (I-IV): 3.0% level I, 29% level II, 46% level III, 22.6% level IV. 45 % Level III •Clinical evaluation only. •LVEF Not Reported	Cardiac events (mortality, or cardiac related admission, or emergency room visit)	NR/Yes	Multivariate Logistic Regression	[BNP] Biosite Diagnostics - Triage Threshold: 200 pg/ml (chosen retrospectively based on internal analysis)	Cardiac events at 90 days: Multivariate: Baseline Exp(Beta) for logBNP = 2.030 (beta p = 0.005)
Gwechenberger 2003 Austria	Cohort: NA Age: Condition 1 mean 52.47+/- 9.69 Condition 2 mean 50.52+/- 11.0 % Male: 89%	SS = 100 Followup: mean 378 days (range 4 to 999 days) 13 months	Stable CHF (NYHA II-IV), 78% level II, 20% level III, 2% level IV Clinical Examination LVEF <=25%	Worsening Myocardial Failure (WHF) defined as any of the following: (1) Hospitalized for WHF; (2) need for IV therapy; (3) need for urgent CTx; or (4) death from pump failure as a consequence of WHF	NO (Clinical Trial)/ NO	Uni and Multivariate Cox proportional hazards regression	[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: 277 fmol/L (Median)	Worsening Heart Failure: Univariate: Log NT-proBNP Chi Sq. = 3.857, p = 0.0495 Worsening Heart Failure: Multivariate: LogNT-proBNP Chi Sq. not significant Worsening Heart Failure: Univariate: Log BNP Chi Sq. = 19.331, p = 0.0001 Worsening Heart Failure: Multivariate: LogBNP Chi Sq. = 14.165, p = 0.0002

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Sakatani 2004 Japan	•Cohort: N.A. •Age: Mean, All subjects, 72 +/- 12 •Age: Mean, Condition 1: 74 +/- 10 •Age: Mean, Condition 2: 71 +/- 12 •Age: Range, All subjects, 33-91 •% Male: 49%	80 Followup: 17 =/- 9 months	•CHF patients admitted to hospital (NYHA I-IV):6% level 1, 43% level 2, 43% level III, 8% level IV •Clinical evaluation only. •Not reported	Cardiac event (i.e. death or rehospitalization)	Yes/No	Multivariate Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: No threshold specified. Mean BNP in cardiac event group 402 +/-168 pg/ml; mean BNP in non-cardiac event group 153 +/-51 pg/ml.	Cardiac event: Multivariate Baseline BNP OR = 1.029 [95% CI, 0.984-1.075], p = 0.213
Latini 2004 Italy	•Cohort: Val-HeFT •Age: Mean, No info •%Male: No info	4300 Followup: Not Specified (23 months outcomes are discussed in the results but not clear if this is total followup time)	•ValHeFT cohort: stable but symptomatic HF (NYHA I-IV) •LVEF < 40% and LV internal diameter in diastole adjusted for body surface area (LVIDd/BSA) of =>2.9 cm/m2. •LVEF < 40%	Combined mortality and morbidity (morbidity defined as cardiac arrest with resuscitation, hospitalization for HF or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization)	NR/No	Uni and multivariate Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 97 pg/mL (median of same)	Mortality and Morbidity: Univariate Baseline BNP >= 97 pg/mL HR = 2.06 [95% CI 1.82-2.33]; demographics, clinical/echo variables) Mortality and morbidity: Multivariate Baseline BNP change = 10 pg/mL, HR = 1.012 [95% CI 1.010-1.013] p<0.0001

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Logeart 2004 France	•Cohort: N.A. •Age: Mean, Condition 1: 69.4+/- 14.4 (Derivation study) •Age: Mean, Condition 2: 70.9 +/- 13.3 (Validation study) •% Male: 60.5 %	223 (114 finally included (derivation study) and 109 from another centre included in validation study) Followup: 1 month and 6 months for 51/105 patients either dead or re-admitted; mean time from discharge to first event was 72 +/- 48 days	•Patients presenting to two hospitals (NYHA class IV) •The diagnosis of decompensated CHF was confirmed by two senior cardiologists using the generally accepted Framingham criteria and corroborative information including the hospital course and results of further cardiac tests. •Derivation group: LVEF 37.5% +/-14.9; Validation group 31.8% +/- 14.5	Combined death or first re-admission for CHF	Yes/No	Uni and multivariate Cox proportional hazards regression	[BNP] Biosite Diagnostics - Triage Threshold: Categorized into 3 predischarge level categories (<350 ng/L, 350-700 ng/L, >700 ng/L). [Conversion <350 pg/mL, 350-700 pg/mL, >700 pg/mL]	Death and readmission: Univariate: Baseline BNP per 100 ng/L increase HR = 1.06 [95% CI, 1.03-1.10], p = 0.0001 Death and readmission: Univariate: Predischarge per quartile HR 4th quartile = 13.77 [95% CI, 4.71-40.23], p = 0.0001 Death and readmission: Multivariate Pre-discharge BNP HR = 1.14 [95% CI, 1.02 to 1.28], p < 0.027, 2) at one month Death and readmission: Multivariate: Pre-discharge BNP HR = 1.17 [95% CI, 1.06 to 1.28], p = 0.002, 3) at six months Death and readmission: Multivariate: Pre-discharge BNP level >350 mg/L BNP HR = 12.6 [95% CI, 5.7-28.1], p = 0.0001 Death and readmission: Multivariate: Pre-discharge BNP 350-700 ng/L HR = 5.1 [95% CI, 2.8-9.1] Death and readmission: Multivariate: Predischarge BNP >700 ng/L HR = 15.2 [95% CI, 8.5-27.0], p=< 0.0001 Readmission: Multivariate: **at 6 months** Pre-discharge BNP HR = 1.25 [95% CI, 1.16 to 1.34], p = 0.001

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Ishii 2003 Japan	•Cohort: N.A. •Age: Mean, 68 + 11 •% Male: 56%	100 Followup: Mean 391 days (range 16-884) 13 months	•Patients admitted to hospital for worsening CHF (NYHA III-IV): 54% level III and 46% level IV •Cardiologists not directly involved in the study determined if patients met exclusion criteria. 2D Echocardiogram and venous blood samples were used to determine severity. •12% of patients had mean LVEF 36%	Cardiac events (death from worsening CHF, fatal MI or sudden death) and re-admission for worsening CHF or MI	NR/Yes	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 160 ng/L (based on ROC with best sensitivity). [Conversion 160 pg/mL]	Cardiac events: Univariate: Baseline Log BNP (10-fold increase), HR = 4.26 [95% CI 2.20–8.23], p < 0.0001 Cardiac events: Multivariate model including cTnT 0.01 (increase of 0.1 ug/L and Baseline BNP >160 mg/L as continuous variables: Baseline BNP > 160 ng/L, HR = 2.07 [95% CI, 1.43–3.01], p = 0.0001 Cardiac events: Multivariate model including cTnT 0.01 > 0.01 ug/L and Baseline BNP >160 mg/L as continuous variables: Baseline BNP > 160 ng/L, HR = 2.35 [95% CI, 1.14–4.84], p = 0.013

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Horwich 2003 USA	•Cohort: N.A. •Age: Mean, 52+/-13 •% Male: 71%	238 Followup: 18 months	•Patients with advanced heart failure referred for cardiac transplantation to a single centre (NYHA class III-IV): 50% were level IV. •Clinical evaluation only •Mean LVEF 0.25 +/- 0.09	All cause mortality or urgent cardiac transplantation.	Yes/No	Univariate and multivariate Cox regression	[BNP] Biosite Diagnostics - Triage Threshold: <485 pg/ml (based on ROC curve; BNP not considered independent of Troponin I levels).	Combined outcome: Multivariate: Baseline BNP < 485 pg/mL and Tropinin I < 0.04 ng/mL RR = 1.0 Combined outcome: Multivariate:Baseline BNP < 485 pg/mL and Tropinin I > 0.04 ng/mL RR= 2.1 [95% CI, 0.3-16.6] Combined outcome: Multivariate:Baseline BNP > 485 pg/mL and Tropinin I < 0.04 ng/mL RR= 4.7 [95% CI, 0.8-26.9] Combined outcome: Multivariate:Baseline BNP > 485 pg/mL and Tropinin I > 0.04 ng/mL RR 12.3 [95% CI, 2.4-64.0]
Anand 2003 USA	•Cohort: Valsartan Heart Failure Trial (Val-HeFT) •Age: Mean, No info. •% Male: No info.	4300 Followup: mean followup 2-3 years (at 4 months, year, and 2 years) 32 months	•ValHeFT cohort: stable but symptomatic HF (NHYA I-IV) •Patients with stable, symptomatic HF who were undergoing prescribed HF therapy and had left ventricular ejection fraction (LVEF) =/< 40% and P7 •LVEF < 40%	All cause mortality and first morbid event (death, sudden death with resuscitation, hospitalization for HF, or intravenous inotropic or vasodilator therapy for at least 4 hours)	NR/No	Multivariate Cox proportional hazard model [% change, quartile changes after 4 months]	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 97 pg/mL median (no range specified). Also evaluated using quartiles < 41pg/mL, 41-97 pg/mL, 97-238pg/mL, >238 pg/mL).	First morbid event: Univariate: Baseline BNP > 97 pg/mL HR = 2.2 [95% CI,1.98 to 2.52] First morbid event within 4 months: Controlling for Norepinephrine: % change 3rd vs 1st quartile Baseline BNP HR = 1.66 [95% CI, 1.36-2.04], p < 0.0001 First morbid event within 4 months: Controlling for Norepinephrine only: % change 4th vs 1st quartile Baseline BNP HR = 2.20 [95% CI, 1.80- 2.67], P = <0.0001

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Bettencourt 2002 Portugal	•Cohort: N.A. •Age: Mean, 71+/-44 •% Male: 44%	50 Followup: 6 months (time from discharge to first event ranged from 4 to 153 days (mean, 53 days))	•Patients admitted with decompensated heart failure to hospital (NYHA II-IV): 12% level II, 54% level III, 35% level IV. •Clinical evaluation only •Not reported	Death or hospital re-admission for cardiovascular causes	NR/No	Univariate Cox regression	[BNP] Biosite Diagnostics - Triage Threshold: No threshold specified. Admission median levels < 541 pg/mL, discharge median level < 321 pg/ml, and these that decreased by discharge.	Mortality or readmission: Univariate: Baseline BNP > 541 pg/mL HR = 1.0 [95% CI, 0.4 to 2.5] Mortality or readmission: Univariate: Increased BNP during hospital stay HR = 3.3 [95% CI, 1.3 to 8.8] Mortality or readmission: Univariate: DIscharge BNP level above the median (321 pg/mL) HR = 2.3 [95% CI, 0.9 to 5.8]

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Hulsmann 2002 Austria	•Cohort: N.A. •Age: Mean, 57 +/- 8 •% Male: 82%	96 Followup: 1 year	•Patients treated in clinic with documented HF based on LVEF function. Subjects were excluded from analysis if they underwent elective heart transplant. (NYHA I-III): 35% level I, 30% level II, 29% level III, 6% level IV. •HF based on LVEF level •Mean LVEF 26+/- 10%.	Death or worsening heart failure (decompensation, needing I.V. support and malignant arrhythmia)	Yes/No	Multivariate Cox proportional hazard regression	[BNP] Biosite Diagnostics - Triage Threshold: No thresholds specified for BNP and proBNP. Mean BNP: 182 +/- 264 fmol/mL [629.7 pg/mL] in patients no events and 688 +/- 423 fmol/ml [2380 pg/mL] in patients who either died or developed worsening heart failure within 1 year. Mean proBNP 325 +/- 198 fmol/ml [913.4 pg/mL] in patients with no events and 593 +/- 275 fmol/ml in patients who either died or developed worsening HF.	Death or worsening HF: Multivariate: Baseline BNP Chi Sq. = 8, p < 0·01 Death or worsening HF: Multivariate: Baseline proBNP Chi Sq. = 58, p < 0·0001

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Tsutsui 2002 Japan	•Cohort: N.A. •Age: Mean, All subjects 63 +/- 1.5 •Age: Mean, Condition 1: 58.9 +/- 3.1 •Age: Range, All subjects, 17-85 •Age: Range, Condition 1: 17-79 •% Male: 75% (subjects), 78% (controls)	84 + 18 Controls Followup: Survivors > 589 days (mean 780 +/- 15.6 days (range 589 to 984 days)). 26 months	•Patients with CHF with DCM or ischemic cardiomyopathy, LVEF < 45% (NYHA II-IV). •Serum blood tests and Echocardiogram • Mean LVEF = 30.7% +/- 1.0	Cardiac death (worsening CHF, lethal MI or sudden death) or hospitalization for worsening CHF, MI or fatal arrhythmia	Yes/No	Multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold not specified. Mean all patients 334 +/- 42 pg/mL.	Combined endpoint: Univariate: Baseline BNP Chi-Square = 36.77, p < 0.0001 Combined endpoint: Multivariate: Baseline BNP Chi-Square = 13.65, p 0.0002
Ishii 2002 Japan	•Cohort: N.A. •Age: Mean, All subjects, 69+/- 9 •Age: Mean, Condition 1: 71+/-10 •Age: Mean, Condition 2: 68+/-10 •Age Range, All subjects, 22-88 •% Male: 52%	98 Followup: Mean 451 +- 98 days (range 13 to 667 days) 15 months	•Patients were admitted to a coronary care unit due to worsening CHF. (NYHA mean 3.5 +/- 0.6) •2D echocardiography read by experts blinded to the study. •Mean LVEF = 42% +/- 17	1) Cardiac death (death from worsening chronic heart failure, fatal myocardial infarction, or sudden death); 2) Readmission for worsening chronic heart failure or myocardial infarction.	Yes/No (but endpoints judged by independent researchers)	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: >440 pg/mL (based on ROC)	Cardiac event: Univariate: Baseline Log BNP, Chi Sq = 8.79, p = 0.003 Cardiac event: Multivariate: Baseline Log BNP, Chi Sq = 6.73, p = 0.0095

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Harrison 2002 USA	•Cohort: N.A. •Age: Mean, 65 •Age: Range, 29-83 •% Male: 95%	325 Followup: Mean followup time=682.2 +-55.0 days 23 months	A convenience sample presenting with dyspnea to the emergency department (41% CHF) Diagnosis: Echocardiogram results from previous records was used to establish CHF. LVEF not reported	Hospital admissions (any cardiac and CHF), 3) repeat ED visits for CHF.	No/Yes	Unadjusted Relative Risks	[BNP] Biosite Diagnostics - Triage Threshold: 480 pg/mL based on ROC; 230 pg/mL (provided few false negative values)	CHF event (hospitalization, ED visit, or death for CHF): Unadjusted: Baseline BNP>230 pg/mL vs. <=230 pg/mL: RR = 15.5 [95% CI,6.2-43.7] CHF event (hospitalization, ED visit, or death for CHF): Unadjusted: Baseline BNP>480 pg/mL vs. <=230 pg/mL: RR = 8.2 [95% CI, 4.7-14.3] Cardiac Event (all CHF events plus the same for from ischemia or infarction): Unadjusted: Baseline BNP>230 pg/mL vs. <=230 pg/ml: RR = 5.5 [95% CI, 2.9-6.9]
Dias 2001 USA	•Cohort: N.A. •Age: Mean, 70.4+/-1.2 •% Male: 45.7%	46 Followup: 6 months	•A convenience sample presenting with dyspnea to the emergency department (41% CHF) •Echocardiogram results from previous records was used to establish CHF. •Not Reported	Death or hospitalization from cardiac cause	NR/Yes	Unadjusted relative risks	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: >480 pg/mL based on ROC curve of sample; 230 pg/mL (provided few false negative values)	Combined outcome:Univariate: Baseline BNP pg/mL (all patients) OR = 1.02 [95% CI not reported], p = 0.01 Combined outcome:Univariate: Baseline BNP pg/mL (patients in group II only) OR = 1.002 [95% CI not reported], p = 0.02

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Koglin 2001 Germany	•Cohort: N.A. •Age: Mean, 51 +/- 9 •Age: Range, 24 - 65, •% Male: 88%	78 Followup: Median 398 days (range 248-493). 13 months	•Patients with chronic CHF who were referred to a heart failure outpatient clinic; subjects were included after optimization of medical therapy. (NHYA I-IV): 12.8% level I, 42.3% level II, 33.3% level III, 11.5% level IV. •Clinical history and examination, ECG, echocardiogram, laboratory results cardiopulmonary exercise test. •Mean LVEF 36% +/-15 at admission	Changes in degree of cardiovascular disability: improvement, stabilization, deterioration (includes death)	NR/No	Logistic regression and Cox proportional hazard regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 107.5 pg/ml (based on 75th percentile) and BNP change (increase by 100 pg/ml).	Changes in limitations of physical activity: Baseline BNP was significantly related to deterioration of physical limitations Chi Sq. = 24.9, p = < 0.0001 Clinical event: Univariate: Baseline BNP per 100 pg/ML HR = 1.492 [95% CI, 1.221-1.819] Clinical event: Multivariate: Baseline BNP did not add prognostic information independent of HFSS (p = 0.748)

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Imamura 2001 Japan	•Cohort: Ehime MIBG Heart Failure (EMIHEF Study) •Age: Mean, All subjects, 63 +/- 11 •Age: Mean, Condition 1: 64 +/- 11 (Event free) •Age: Mean, Condition 2: 65 +/- 12 (Cardiac death) •Age: Mean, Condition 3: 61 +/- 14 (hospitalization) •% Male: 73%	171 Followup: 27+/- 8 months	•Ehime MIBG Heart Failure Study (EMIHEF) randomized trial. (NYHA II-IV): 54% level II, 18% level III, 3% level IV. •Clinical evaluation, including NYHA, I-MIBG images, Chest x-ray, 2D echocardiography •Mean LVEF 27%+/- 10%	Progressive CHF, (combined cardiac death and CHF requiring hospitalization)	NR/No	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: > 160 pg/mL ((based on mean of sample)	Hospitalization and death: Univariate: Baseline BNP RR = 1.006 [95% CI, 1.004-1.007], p <0.0001 Progressive CHF:Multivariate: Baseline RR = 1.005 (no CI reported), p <0.0001.

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Tamura 2001 Japan	•Cohort: N.A. •Age: Mean, All subjects, 78 +/- 1 •Age: Mean, Condition 1: 81 +/- 2 (Cardiac event) •Age: Mean, Condition 2: 77 +/- 1 (No cardiac event) •Age: Range, All subjects, 67-92 •% Male: 48%	48 Followup: 10.8+-1.1 months (range: 1-25 months)	•Patients aged >=65 admitted to hospital with their first episode of CHF (NYHA I-IV): 23% level I, 33% level II, 8% level III, 38% level IV. •Clinical evaluation, 2D echocardiography, radionuclide angiography and laboratory tests. •mean LVEF varied from 38.1% +/- 5.0 ((sample with cardiac events) and 49.2% +/- 2.4 (groups with non-cardiac events)	Cardiac event (readmission because of worsening CHF, angina pectoris or acute myocardial infarction or death from CHF or sudden cardiac death)	Yes/No	Uni and multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 132 pg/ml (median based on sample)	Cardiac event: Multivariate: Predischarge logBNP = 2.656 [No CI reported], p < 0.05
Cheng 2001 USA	•Cohort: N.A. •Age: Mean, 68 +/- 1.6 •Age: Range, 28 - 110 •% Male: 100%	72 Followup: 30 days	•Convenience sample of veterans (NYHA III-IV) : mean level 3.64 +/- 0.07. •New-onset CHF: confirmed by at least one cardiologist using standard Framingham criteria or exacerbation of previously documented CHF, NYHA class. •LVEF < 50% (mean LVEF 37% +/-2%)	1) readmission to the hospital facility for CHF within 30 days of initial discharge 2) All events (combined into a single dichotomous outcome (occurrence of death or re-admission vs. no occurrence of either event)).	NR/No	Univariate logistic regression	[BNP] Biosite Diagnostics - Triage Threshold: Mean admission and discharge levels, and four categories of threshold (430 pg/mL, 840 pg/mL, 1090 pg/mL, 1220 pg/mL)	All endpoints:Univariate: Admission BNP = p = 0.003; Admission Log BNP = p = 0.001 All endpoints:Univariate: Discharge BNP = p < 0.0001;Discharge Log BNP = p < 0.0001 30 day readmission:Univariate: Admission BNP = p = 0.03; Admission Log BNP = p = 0.01 30 day readmission:Univariate: Discharge BNP = p = 0.05;Discharge Log BNP = p = 0.02

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Maeda 2000 Japan	•Cohort: N.A. •Age: Mean, 63.6 +/- 1.5 •% Male: 64%	102 Followup: Mean: 807 days (+/- 42.3) Range: 120-1568 days (27 months)	•Patients hospitalized with chronic severe. (NYHA III-IV): 56% level III, 44% level IV. •Echocardiography at admission and 3 months. •Mean LVEF 23% +/- 0.9%	Hospitalization for worsening CHF or MI	Yes/No (but judged independently by researchers)	Uni and multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: >170 pg/mL (median from sample) or 240 pg/ml (from ROC)	
Tsutamoto 1999 Japan	•Cohort: N.A. •Age: Mean, 59 + 0.7 •Age: Range,18-82 •% Male: 76.6%	290 Followup: Mean = 502 days (range 31-1,619 days) in patients with an outcome Mean = 1,071 days (range 31-2,541 days) for event-free patients. 36 months	•Consecutive early-stage HF patients who subsequently underwent cardiac catheterization. (NYHA I-II):32% level I, 68% level II. •Clinical evaluation and LVEF demonstrated by ventriculography with contrast medium. •LVEF < 45%	Morbidity (hospitalization) or mortality due to cardiovascular causes	Yes/No	Linear regression Uni and multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: 56 pg/mL (median of total sample)	Morbidity and Mortality: Univariate: Baseline BNP Chi Sq. = 90.5, p < 0.0001 Morbidity and Mortality: Multivariate: Baseline BNP Chi Sq. = 23.83, p < 0.0001

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Watanabe 2005 Japan	•Cohort: CHART •Age: Mean, 64 •% Male: 69.4%	417 Followup: mean 26 months	•Hospital based cohort from the CHART study who represented CHF in real clinical situations as they had both impaired or preserved systolic dysfunction. (NYHA III-IV): 19.3% had level III/IV. •Framingham criteria for HF, echocardiography and clinical evaluation. •LVEF < 50% (mean LVEF 38% +/- 12%)	Combined HF events (HF mortality of hospitalization due to exacerbation of HF)	NR/No	Multivariate Cox regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Log BNP >=2.12 (median based on sample)	Combined HF events: Multivariate: Baseline logBNP >= 2.12 and low ejection fraction (<=38%) HR = 2.10 [95% CI, 1.14-3.85], p = 0.0168
Hamada 2005 Japan	•Cohort: N.A. •Age: Mean, Condition 1: 67 +/- 9 (old MI) •Age: Mean, Condition 2: 60 +/- 17 years (dilated cardiomyopathy) •% Male: 63%	52 Followup: 1 year (5.9 +/- 3.7 months)	•Patients with chronic CHF admitted for acute emergency decompensation. (NYHA III-IV) •Clinical evaluation, chest X-ray, and echocardiography. •LVEF <40	Re-hospitalization for acute decompensation of CHF or cardiac death	NR/No	Multivariate Cox proportional hazards regression	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: > 230 pg/ml (median pre-discharge BNP level)	Cardiac events: Multivariate: Baseline BNP Chi Sq.= 1.016, p = 0.314 Cardiac events: Multivariate: Baseline BNP & Decceleration time Chi Sq.= 0.282, p = 0.596 Cardiac events: Multivariate: Discharge BNP Chi Sq.= 6.899, p = 0.0086 (Exponential of coefficient = **15.758**) Cardiac events: Multivariate: Discharge BNP & Decceleration time Chi Sq.= 2.96, p = 0.853

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Bertinchant 2005 France	•Cohort: N.A. •Age: Median, 54 +/- 7.2 •% Male: 87%	63 Followup: median 22 months (range 1-45), median event-free survival time for all CHF patients was 33.8 months	•Acute and chronic CHF patients referred to the cardiology department. Those that were acute (n=19) required urgent hospital admission because of cardiac decompensation. All patients had been symptomatic withinthe previous 12 months. (NYHA I-IV): 36.6 levels I/II, 49.2 level III, 14.3 level IV. •Clinical evaluation only. •LVEF < 45% (mean 24% +/- 9.7%)	Worsening CHF and cardiac death	NR/No	Uni and multivariate Logistic Cox regression analysis	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: > 254 ng/l (optimal threshold from ROC analysis). [Conversion 254 pg/mL]	Mortality or HF: Univariate: Baseline BNP > 254 ng/L Chi Sq. = 7.33, p = 0.0068 Mortality or HF: Multivariate: Baseline BNP > 254 ng/L RR = 3.23 [95% CI, 1.32–7.94], p 0.01 (BNP was only significant independent predictor).

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Van Beneden 2004 Belgium	•Cohort: N.A. •Age: Mean, 58 +/- 6 (Controls) •Age: Mean, Condition 1: 62 +/- 7 (Mild to moderate CHF) •Age: Mean, Condition 2: 67 +/- 8 (Severe CHF), •% Male: 84%	117 Followup: Severe CHF group survivors mean 81 +/- 15 months (range 60-91 months) Mild to moderate CHF group survivors mean 92 +/- 3 months (range 87–96)	•Three groups: Patients with mild to moderate CHF, severe CHF, and 30 healthy age and sex matched controls. (NYHA I-IV) •Clinical evaluation only. •Mean LVEF Mild /moderate group = 29.4% +/- 4%, mean LVEF severe CHF = 20.8% +/- 6%.	Urgent heart transplant	NR/No	Multivariate Cox regression analysis	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay) Threshold: Median values of BNP, N-BNP, LogBNP, and LogN-BNP (values not reported) were used only if significant. Only logN-BNP was used as it had the highest statisitical significance. Mean values for mild to moderate CHF N-BNP = 491 fmol/mL [4152.3 pg/mL], and sever CHF N-BNP = 1,521 fmol/mL [8,457 pg/mL]	Not reported

Evidence Table 10. Summary of studies in patients with HF and mixed outcomes: BNP

Study	Sample Characteristics	Sample Size /Followup	Diagnostic criteria	Outcomes	Quality: Consecutive Cohort / Outcome Blinding	Analysis /Model	BNP method /Unit threshold	Measure of Association
Berger 2003 Austria	•Cohort: N.A. •Age: Mean, 54 +/- 10 •% Male: 87%	452 Followup: followed up at 1, 2, and 3 years. 36 months	•Ambulatory patients recruited from a HF centre.(NYHA I -IV): 12% level I, 34% l3vel II, 33% level III, 21% level IV. •Clinical evaluation and LVEF (method not specified •Not specified	Death or urgent heart transplantation	NR/NR	Multivariate Cox proportional hazard regression	[BNP] Biosite Diagnostics - Triage/Evaluated BNP and N-BNP Threshold: logBNP 2.11 (approximated 130 pg/mL) and was based on the highest sensitivity from ROC curve analysis (to discriminate between patients who succumbed to sudden death and survivors). Thresholds for BNP, N-BNP, logN-bnp were not reported but use dinmultivariate analyses.	For combined death and urgent cTx: Multivariate MILD CHF (Group A):Baseline Log BNP 2 yr Chi Sq. = 5, p < 0.05; 3 yr Chi Sq. = 8, p < 0.005 MODERATE CHF (Group B): Baseline Log BNP 3 yr Chi Sq. = 8, p < 0.001 ALL Subjects: Log BNP (not significant for any year) MILD CHF (Group A): Baseline Log N-BNP Not significant for any year MODERATE CHF (Group B):Log N-BNP 2 yr Chi Sq. = 19, p < 0.0001; LogN-BNP 3 yr Chi Sq. = 22, p < 0.0001 ALL Subjects: Baseline Log N-BNP 1 yr Chi Sq. = 4, p < 0.05; Log N-BNP 2 yr Chi Sq. = 10, p < 005; Log N-BNP 3 yr Chi Sq. = 11, p < 0.005

Abbreviations: NA=not applicable, NR=not reported, HF=heart failure, CHF=congestive heart failure, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, MI=myocardial infarction, ECG=electrocardiograph

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Rossig 2004 Germany	Cohort: NA Age: mean 57 +/- 1 % Male: 77%	48 Followup: Minimum followup of 30 months (median followup for survivors 1254 days). 42 months	Outpatient HF clinic (NYHA class II-IV): 42% level II, 44% level III, 14% level IV. Clinical evaluation and previous medical history. Mean LVEF 25% +/- 1%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: continuous variable (pg/mL)	No/No	All-cause mortality	Uni and multivariable Cox Proportional Hazard Regression	Mortality: Univariate: Baseline LogNT-proBNP HR = 7.76 (95% CI, 2.63-22.86), p < 0.001 Mortality: Multivariate with NYHA class: Step I: Baseline Log NT-proBNP per log (NT-proBNP), HR = 5.66 (95% CI, 1.69–18.95), p = 0.005 Mortality: Multivariate with serum creatinine: Baseline Log NT-proBNP per log (pro-BNP), HR =6.61 (95% CI, 2.05–21.29), p = 0.002 Mortality: Multivariate with blood pressure: Baseline Log NT-proBNP per log (pro-BNP), HR = 9.18 (95% CI, 2.52–33.41), p = 0.001 (When Log NT-proBNP and blood pressure were considered together, both parameters remained independent significant predictors of mortality) Mortality: Multivariate with blood pressure and apoptosis: Baseline Log NT-proBNP per log (pro-BNP), HR = 9.35 (95% CI, 2.42–36.10), p = 0.001

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Rothenburger 2004 Germany	Cohort: NA Age: Condition 1 mean age 55 +/- 11 Age: Condition 2 mean age 57 +/- 8 % Male: 75%	550 Followup: 2 yrs	Recruited to interdisciplinary Heart Failure Program (NYHA II-IV): Dilative Cardiomyopathy mean NYHA 2 +/- 1, CAD mean NYHA 3 +/- 1. Clinical, Echocardiography, ECG. Dilative Cardiomyopathy mean LVEF 32% +/- 13% CAD LVEF 31% +/- 11%.	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: > 1000 ng/mL	Yes/Yes	Prediction ability for selection of cardiac transplant by cardiologists blinded to NT-proBNP levels	Multivariate Cox Logistic Regression	Cardiac Transplantation selection: Univariate: Baseline NT-proBNP > 1000ng/mL OR = 10.6 [95% CI, 3.7- 14.5], p = 0.01
Hartmann 2004 Germany	Cohort: COPERNICUS Age: Mean 62.5 +/- 11.0 % Male: 81%	1048 Followup: 29 months	European patients with chronic severe HR enrolled in a Multicenter RCT (Copernicus) one treatment arm on carvedilol (NYHA not reported). Clinical evaluation, LVEF. Mean LVEF 20.4% +/- 3.6%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: specified as above and below median (value not reported) (pmol/L)	No/No	(1) all cause mortality (2) all cause mortality or heart failure hospitalisation (3) all cause mortality or hospitalisation for cardiovascular reasons (4) all cause mortality or hospitalisation for any reason	Univariate Cox proportional hazards regression	All cause mortality: UnivariateL NT-proBNP (10 pmol/L increase) RR = 1.005 [95% CI, 1.003–1.006], p = 0.0001 All cause mortality: Univariate: NT-proBNP (above and below median) > 1762 pmol/L RR = 3.13 [95% CI, 1.94–5.07], p = 0.0001

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Kirk 2004 Denmark	Cohort: CHHF (Copenhagen Hospital Heart Failure Study) Age: Condition 1 mean 73.0 years (no HF)Age: Condition 2 mean 78.0 years (HF) % Male: 41%	2230 Followup: 1 year	Patients admitted to general city hospital with HF (NYHA classification not reported) (Total sample contained subjects subsequently determined to not have HF). European Society of Cardiology criteria (clinical and echocardiography). mean LVEF HF group: 45.3% +/- 1.1%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: continuous variable (pmol/L)	Yes/No (Physician blinded to NT-proBNP levels)	All cause mortality	Multivariate logistic regression	Mortality in total sample: Univariate: NT-proBNP levels predicted mortality in total population (data not shown) Mortality in HF patients: Multivariate: ln(NT-proBNP) OR = 1.66 [95% CI, 1.25–2.2], was significant (p value not reported)
Gardner 2003 Scotland	Cohort: NA Age: mean 50.4+/-10.5 % Male: 82.4%	142 Followup: median time 374 days range (1-660 days)13 months	Patients with advanced CHF referred for consideration of heart transplant surgery (NYHA II-IV): 14.8% level II, 66.2% l3v3l III, 19% level IV. Clinical evaluation and radionuclide ventriculography. Mean LVEF = 14.9% +/- 7.1%; LVEF < 35%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: >1490 pg/mL (median of sample)	Yes/No	1) All cause mortality, (2) death from worsening HF, 3) Hospitalisation for CHF or Coronary syndromes	Uni and multivariate Cox proportional hazards analysis	All cause mortality:Univariate: NT-proBNP > 1490 pg/mL OR = 5.0 [95% CI, 1.6-15.9], p = 0.006 All cause mortality or urgent transplantation: Univariate: NT-proBNP > 1490 pg/mL OR = 6.8 [95% CI, 2.2-21.1], p = 0.001 All cause mortality: Multivariate: NT-proBNP > 1490 pg/mL Chi Sq. = 6.03, p = 0.01 ONLY independent predictor All cause mortality and urgent transplant: Multivariate: NT-proBNP > 1490 pg/mL Chi Sq. = 6.03, p = 0.01

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Stanek 2001 Austria	Cohort: NA Age: Condition 1 mean 51+/-11 years (Atenolol) Age: Condition 2 mean 52+/-10 years (Placebo) % Male: 97%	91 Followup: 4 years	Subjects with HF (LVEF < 25%) from a substudy of subjects from RCT evaluating those on atenolol versus placebo. (NYHA II-IV): 78% level II, 13% level III, 2% level IV. Radionuclide ventriculography and clinical evaluation. LVEF < 25% (mean 17%)	[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: continuous variable (fol/mL)	No (clinical trial)/No	Cardiac mortality	Uni and mulitvariate Cox proportional hazards regression	Death: Multivariate: Baseline LogBNP Chi Sq. = 13.9, p = 0.0002 Death: Multivariate: Last followup LogBNP Chi Sq. = 21.3, p = 0.0001 Death: Multivariate: Last followup LogNT-proBNP Chi Sq. = 8.9, p = 0.0027

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Richards 2001 New Zealand	Cohort NA: Age: Not reported % Male: Not reported	297 Followup: 18 months	Substudy of patients with chronic stable randomized to receive Atenolol or placebo. (NYHA II-IV). 30% level I at randomization, but 43% had been previously in level IV. Radionuclide ventriculography and clinical evaluation. LVEF < 45% (mean LVEF 29%)	[NT-proBNP] New Zealand (Christchurch) - no instrument, manual assay Threshold: continuous variable (pmol/L)	No(subset of clinical trial)/No	1) All-cause mortality 2) Death from worsening HF3) Episodes of worsening HF (defined as deterioration requiring an increase in nonstudy anti-HF treatments, an increase in NYHA functional class, hospital admission for worsening symptoms of HF or nonsudden death from progressive HF)4) Hospital admission for worsening HF and hospital admission for acute coronary syndromes	Multivariate Cox proportional hazards analysis	All cause mortality, Admission for worsening HF and episodes of worsening HF NT-proBNP (significant, p level not reported) [NT-proBNP not significant for admission with acute coronary syndrome]

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Taniguchi 2004 Japan	Cohort : NA Age: mean 68.4 +/- 1.4 % Male: 52%	71 Followup: 17 months	Patients hospitalized for acute HF (decompensated) (NYHA I-IV): 14% level I , 31% level II, 31% level III, 24% level IV. Clinical evaluation and roentgenographically apparent pulmonary eodema. LVEF Not reported	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: cardiac decompensation 1.050 pg/ml; cardiac events 2,000 pg/ml (based on ROC analysis)	Yes/No	Sudden death, CHF death, rehospitalization for CHF, adverse cardiac events (sudden death without apparent ischemia, death from CHF, or rehospitalisation for cardiac decompensation with pulmonary oedema)	Kaplan Meier's and ROC curves only	Not estimated

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
Hartmann 2004 Germany	Cohort: COPERNICUS Age: mean 62.7 +/- 10.9 % Male: 81%	1011 Followup: 24 months	European patients with chronic severe HF enrolled in a Multicenter RCT (Copernicus) one treatment arm on carvedilol (NYHA not reported). Clinical evaluation, LVEF. Mean LVEF 20.4% +/- 3.6%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: > 1767 pg/ml (median)	No/No	1) All cause mortality 2) death or hospitalized for HF 3) death or hospitalized for CV reasons specified in protocol 4) death or hospitalization for any reason	Uni and multivariate Cox proportional hazards regression	All cause mortality : Univariate: NT-proBNP > 1767 pg/mL RR = 2.7 [95% CI, 1.7 to 4.3], p < 0.0001All-cause mortality or hospitalization for heart failure: Univariate: NT-proBNP > 1767 pg/mL RR = 2.4 [95% CI 1.8 to 3.4], p< 0.0001 All-cause mortality or protocol specified CV hospitalizations: Univariate: NT-proBNP > 1767 pg/mL RR = 2.09 [95% CI, 1.57–2.77], p = 0.0001 All cause mortality : Multivariate: NT-proBNP > 1767 pg/mL RR = 2.17 [95% CI, 1.33 to 3.54], p < 0.02All-cause mortality or hospitalization for HF: Multivariate: NT-proBNP > 1767 pg/mL RR = 2.11 [95% CI, 1.54 to 2.90], p< 0.0001
Berger 2005 Austria	Cohort: none Age: mean 54 +/- 10 % Male: 87%	452 Followup: mean 592 days +/- 387 days 20 months	Ambulatory patients recruited from a HF centre. (NYHA I -IV): 12% level I, 34% l3vel II, 33% level III, 21% level IV. Clinical evaluation and LVEF (method not specified). LVEF < 35% (Mean 20% +/- 7%)	[BNP] Biosite Diagnostics - Triage [NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: continous variable (pg/mL)	No/No	Sudden death and heart failure death	Uni and multivariate Cox proportional hazard regression	Pump Failure: Multivariate: Baseline BNP Chi Sq. = 7·4, p 0·007 Pump Failure: Univariate: Baseline Log BNP Chi Sq. = 33·4, p 0·0001 Pump Failure: Univariate: Baseline Log N-BNP Chi Sq. = 28·4, p 0·0001 Pump Failure: Multivariate: Baseline Log BNP Chi Sq. = 10·7, p 0·001

Evidence Table 11. Summary of studies in patients with HF and mortality outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	BNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis / model	Measure of association
VAN BENEDEN 2004 Belgium	Cohort: none Age: All mean 58 +/- 6 years (Controls)Age: Condition 1 mean 62 +/- 7 years (Mild to moderate CHF)Age: Condition 2 mean 67 +/- 8 years (Severe CHF % Male: 84%	117 Followup: Severe CHF group survivors mean 81 +/- 15 months (range 60-91 months) Mild to moderate CHF group survivors mean 92 +/- 3 months (range 87–96)	Three groups: Patients with mild to moderate CHF, severe CHF, and 30 healthy age and sex matched controls. (NYHA I-IV). Clinical evaluation only. Mean LVEF Mild /moderate group = 29.4% +/- 4%, mean LVEF severe CHF = 20.8% +/- 6%.	[BNP] Shionogi & Co. Ltd - No instrument, Shionoria-IRMA (manual assay)[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: continous variable (pg/mL)	No/No	All cause mortality Cardiovascular mortalityUrgent heart transplant	Multivariate Cox regression analysis	Mortality in severe CHF group: Univariate: Baseline NT-BNP Log Likelihood Chi Sq. = 5.68, p = 0.017 Mortality in severe CHF group: Univariate: Baseline BNP RIA Log Likelihood Chi Sq. = 2.14, p = 0.143 Mortality in severe CHF group: Univariate: Baseline BNP IRMA Log Likelihood Chi Sq. = 0.71, p = 0.40

Abbreviations: HF=heart failure, LVEF=left ventricular ejection fraction, HR=hazards ratio, CI=confidence interval, NA=not applicable, NYHA=New York Heart Association, RIA=radioimmunoassay, CHF=congestive heart failure, ROC=receiver operator characteristic, CAD=coronary artery disease, ECG=electrocardiogram

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Gwechenberger 2004 Austria	Cohort: NA Age: Condition 1 mean 52.47+/- 9.69/ Condition 2 mean 50.52+/- 11.0 % Male: 89%	100 Followup: mean 378 days (range 4 to 999 days) 13 mon	Stable CHF (NYHA II-IV), 78% level II, 20% level III, 2% level IV. Clinical examination. LVEF <=25%	[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: not specified for NT-proBNP (fmol/L)	No/No	Worsening Myocardial Failure (WHF) defined as any of the following: (1) Hospitalised for WHF; (2) need for IV therapy; (3) need for urgent CTx; or (4) death from pump failure as a consequence of WHF	Uni and Multivariate Cox proportional hazards regression	Worsening HF: Univariate: Baseline Log NT-proBNP Chi Sq. = 3.857, p = 0.049 Worsening HF: Multivariate: Baseline LogNT-proBNP not significant predictor Worsening HF Univariate: Baseline LogBNP Chi Sq. = 19.331 p = 0.001 Worsening HF: Multivariate: Baseline LogBNP Chi Sq. = 14.163, p = 0.0002
Hartmann 2004 Germany	Cohort: COPERNICUS Age: Mean 62.5 +/- 11.0 % Male: 81%	1048 Followup: 29 months	European patients with chronic severe HR enrolled in a Multicentre RCT (Copernicus) one treatment arm on carvedilol (NYHA not reported). Clinical evaluation, LVEF. Mean LVEF 20.4% +/- 3.6%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: specified as above and below median (value not reported) (pmol/L)	No/No	(1) all cause mortality (2) all cause mortality or heart failure hospitalisation (3) all cause mortality or hospitalisation for cardiovascular reasons (4) all cause mortality or hospitalisation for any reason	Univariate Cox proportional hazards regression	Not reported

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Gardner 2003 Scotland	Cohort: NA Age: mean 50.4+/-10.5 % Male: 82.4%	142 Followup: median time 374 days range (1-660 days)13 months	Patients with advanced CHF referred for consideration of heart transplant surgery (NYHA II-IV): 14.8% level II, 66.2% l3v3l III, 19% level IV. Clinical evaluation and radionuclide ventriculography. Mean LVEF = 14.9% +/- 7.1%; LVEF < 35%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: >1490 pg/mL (median of sample)	Yes/No	1) All cause mortality, (2) death from worsening HF, 3) Hospitalisation for CHF or Coronary syndromes	Uni and multivariate Cox proportional hazards analysis	All cause mortality:Univariate: NT-proBNP > 1490 pg/mL OR = 5.0 [95% CI, 1.6-15.9], p = 0.006 All cause mortality or urgent transplantation: Univariate: NT-proBNP > 1490 pg/mL OR = 6.8 [95% CI, 2.2-21.1], p = 0.001 All cause mortality: Multivariate: NT-proBNP > 1490 pg/mL Chi Sq. = 6.03, p = 0.01 ONLY independent predictor All cause mortality and urgent transplant: Multivariate: NT-proBNP > 1490 pg/mL Chi Sq. = 6.03, p = 0.01
O'Brien 2003 UK	Cohort: NA Age: mean 74 % Male: 56%	96 Followup: median 350 days (2-762) 11.6 months	Patients admitted to coronary care unit with dianosis of acute left ventricular failure. (Killp class II-IV): 39% level II, 55% level III, 6% level IV. Clinical evalation. LVEF not reported	[NT-proBNP] Manual method referencing * Threshold: continuous variable (fmol/mL)	Yes/No	Combined endpoint of death, HF readmission, and worsening HF in an outpatient setting.	Univariate and multivariate analyses (type not specified)	Combined endpoint: Multivariate: Whole sample Baseline NT-proBNP OR = 1.84 [95% CI, 0.75–4.51], p = 0.185. Combined endpoint: Multivariate: Subset sample Predischarge NT-proBNP OR = 15.30 [95% CI, 1.4–168.9], p = 0.026
Fisher 2003 UK	Cohort: NA Age: mean 75 % Male: 58.6%	87 Followup: mean 12 months	Patients admitted on an emergency basis with CHF caused by left ventricular systolic dysfunction (NYHA II-IV): 24% level II, 32% level III, 44% level IV. Clinical evaluation. LVEF not reported	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: > 2994 pg/mL (median in	No (clinical trial)/Yes	Death or readmission with HF	Uni and multivariate regression analysis (type not specified)	Death or re-hospitalization: Multivariate: Predischarge NT-proBNP OR = 4.15, p = 0.003 Death: Multivariate: Predischarge NT-proBNP OR = 2.22, p = 0.03

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
				sample)				
Hulsmann 2002 Austria	Cohort: NA Age: mean age 57 +/- 8 % Male: 82%	96 Followup: 1 year	Patients treated in clinic with documented HF based on LVEF function. Subjects were excluded from analysis if they underwent elective cTx. (NYHA I-III): 35% level I, 30% level II, 29% level III, 6% level IV. HF based on LVEF level. Mean LVEF 26+/- 10%.	[BNP] Biosite Diagnostics - Triage [N-BNP] Biomedica Threshold: continuous variable (fmol/mL)	Yes/No	Death or worsening heart failure (decompensation, needing I.V. support and malignant arrhythmia)	Multivariate Cox proportional hazard regression	Death or worsening HF: Multivariate: Baseline BNP Chi Sq. = 8, p < 0·01Death or worsening HF: Multivariate: Baseline proBNP Chi Sq. = 58, p < 0·0001

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Zugck 2002 Germany	Cohort: NA Age: mean 55 +/11 % Male: 84%	408 Followup: 1 year	Ambulatory chronic CHF patients being treated with ACE inhibitor or angiotensin type 1 receptor antagonist. Subjects divided into 2 groups: those treated with Beta-blockers and those not treated with b-blockers. (NYHA I-IV). 15% level I, 41% level II, 42% level III, 2% level IV, and mean NYHA level 2.3 +/- 0.7. Clinical evaluation, Radionuclide ventriculography. LVEF < 45%. Mean LVEF = 22% +/- 10%	[NT-proBNP] Manual method referencing * Threshold: continuous variable (pmol/L)	Yes/No	Cardiac death or hospital admission for worsening HF or hospital admission with IV inotropic, diuretic, or mechanical support.	Uni and multivariate Cox regression analysis	Combined outcome: Univariate: All patients NT-proBNP Chi Sq. = 49.2, p = 0.0001 (also significant for groups treated with and without Beta-blockers)Combined outcome: Multivariate: All patients NT-proBNP Chi Sq. = 8.1, p = 0.0045 (significant only for patients NOT on Beta-blockers)

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Bettencourt 2004 Portugal	Cohort: NA Age: mean 73 +/- 11 % Male: 47%	156 Followup: 6 months	Patients admitted due to decompensated heart failure (NYHA III-IV): 33% level III, 67% level IV. Clinical diagnosis using European Society of Cardiology criteria or Framingham criteria for HF. LVEF not reported on admission	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: continuous variable but categorized into 1000 pg/mL and relative change of 30%	Yes/No	Death or hospital re-admission	Uni and multivariate Cox proportional hazard regression	Composite outcomes: ~ Univariate: Baseline NT-proBNP (per 1000 pg/mL increase) HR = 1.012, [95% CI, 1.005-1.020] p NR ~Univariate: Discharge NT-proBNP (per 1000 pg/mL increase) HR = 1.018, [95% CI, 1.012-1.024] p NR ~Univariate: Change in NT-proBNP (vs decrease > 30%) changed in either direction HR = 2.19, [95% CI, 1.23- 3.91] p NR 'Univariate: Change in NT-proBNP (vs decrease > 30%) increased > 30% HR = 6.64, [95% CI, 3.60- 12.23] p NR ~ Multivariate: Change in NT-proBNP (vs decrease > 30%) changed ineither direction HR = 2.03 [95% CI, 1.14 - 3.64], p NR ~ Multivariate: Change in NT-proBNP (vs decrease > 30%) increase > 30% HR = 5.96 [95% CI, 3.23–11.01], p NR Death: Multivariate Change in NT-proBNP (vs decrease > 30%) changed in either direction HR = 2.59 [95% CI, 0.98–6.87], p NR Death: Multivariate Change in NT-proBNP (vs decrease > 30%) increase > 30% HR = 3.67 [95% CI, 1.36–9.87], p NR

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Hartmann 2004 Germany	Cohort: COPERNICUS Age: mean 62.7 +/- 10.9 % Male: 81%	1011 Followup: 24 months	European patients with chronic severe HR enrolled in a Multicentre RCT (Copernicus) one treatment arm on carvedilol (NYHA not reported). Clinical evaluation, LVEF. Mean LVEF 20.4% +/- 3.6%	[NT-proBNP] Roche Diagnostics - Elecsys 1010, Elecsys 2010, E170 or Modular Threshold: > 1767 pg/ml (median)	No/No	1) All cause mortality 2) death or hospitalized for HF 3) death or hospitalized for CV reasons specified in protocol 4) death or hospitalization for any reason	Uni and multivariate Cox proportional hazards regression	All cause mortality : Univariate: NT-proBNP > 1767 pg/mL RR = 2.7 [95% CI, 1.7 to 4.3], p < 0.0001All-cause mortality or hospitalization for heart failure: Univariate: NT-proBNP > 1767 pg/mL RR = 2.4 [95% CI 1.8 to 3.4], p< 0.0001 All-cause mortality or protocol specified CV hospitalizations: Univariate: NT-proBNP > 1767 pg/mL RR = 2.09 [95% CI, 1.57–2.77], p = 0.0001 All cause mortality : Multivariate: NT-proBNP > 1767 pg/mL RR = 2.17 [95% CI, 1.33 to 3.54], p < 0.02All-cause mortality or hospitalization for HF: Multivariate: NT-proBNP > 1767 pg/mL RR = 2.11 [95% CI, 1.54 to 2.90], p< 0.0001

Evidence Table 12. Summary of studies in patients with HF and mixed outcomes: NT-proBNP

Study	Sample characteristics	Sample size /Followup	Diagnostic criteria	NT-proBNP method /Unit threshold	Quality Consecutive cohort /Outcome blinding	Outcomes	Analysis /model	Measure of Association
Berger 2003 Austria	Cohort: none Age: mean 54 +/-10 % Male: 87%	452 Followup: 1, 2, and 3 years. 36 months	Ambulatory patients recruited from a HF centre.(NYHA I -IV): 12% level I, 34% l3vel II, 33% level III, 21% level IV. Clinical evaluation and LVEF (method not specified). LVEF not specified	[BNP] Biosite Diagnostics - Triage[NT-proBNP] Biomedica Grupe - No instrument, EIA (manual assay) Threshold: continous variable (pg/mL)	No/No	death, urgent heart transplantation	Multivariate Cox proportional hazard regression	For combined death and urgent cTx: MultivariateMILD CHF (Group A):Baseline Log BNP 2 yr Chi Sq. = 5, p < 0.05; 3 yr Chi Sq. = 8, p < 0.005MODERATE CHF (Group B): Baseline Log BNP 3 yr Chi Sq. = 8, p < 0.001 ALL Subjects: Log BNP (not significant for any year)MILD CHF (Group A): Baseline Log N-BNP Not significant for any year MODERATE CHF (Group B):Log N-BNP 2 yr Chi Sq. = 19, p < 0.0001; LogNT-proBNP 3 yr Chi Sq. = 22, p < 0.0001 ALL Subjects: Baseline Log NT-proBNP 1 yr Chi Sq. = 4, p < 0.05; Log NT-proBNP 2 yr Chi Sq. = 10, p < 005; Log NT-proBNP 3 yr Chi Sq. = 11, p < 0.005

* Carl J., Borgya A., Gallusser A. et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999; 230:177-81

Abbreviations: LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, HF=heart failure, CHF=congestive heart failure, cTx=heart transplant, CV=cardiovascular, NR=not reported, NA=not applicable

Evidence Table 13: Tests for heterogeneity due to STUDY SETTINGS for BNP using the lowest cut point provided in each study (Figures 3 a-e).

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Clinic (n=1)	NA	NA	NA
ED (n=8)	8.55	0.286	18.2%
Primary Care (n=2)	9.03	0.003	88.9%
Overall (n=11)	47.77	0.000	79.1%
SPECIFICITY			
Clinic	NA	NA	NA
ED	335.03	0.000	97.9%
Primary Care	66.25	0.000	98.5%
Overall	508.63	0.000	98.0%
LR +			
Clinic	NA	NA	NA
ED	149.64	0.000	95.3%
Primary Care	0.64	0.425	0.0%
Overall	238.47	0.000	95.8%
LR -			
Clinic	NA	NA	NA
ED	22.36	0.002	68.7%
Primary Care	0.83	0.362	0.0%
Overall	108.45	0.00	90.8%
DOR			
Clinic	NA	NA	NA
ED	48.55	0.00	85.6%
Primary Care	0.13	0.713	0.0%
Overall	99.80	0.00	90.0%

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Evidence Table 14: Tests for heterogeneity due to STUDY SETTINGS for BNP using the lowest cut point provided in each study (Figures 4a-e).

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Clinic (n=1)	NA	NA	NA
ED (n=3)	6.86	0.032	70.8%
Primary Care (n=3)	6.17	0.046	67.6%
Overall (n=7)	24.15	0.000	75.2%
SPECIFICITY			
Clinic	NA	NA	NA
ED	15.99	0.000	87.5%
Primary Care	75.63	0.000	97.4%
Overall	121.61	0.000	95.1%
LR +			
Clinic	NA	NA	NA
ED	10.64	0.005	81.2%
Primary Care	25.22	0.000	92.1%
Overall	49.51	0.000	87.9%
LR -			
Clinic	NA	NA	NA
ED	7.31	0.026	72.6%
Primary Care	1.61	0.447	0.0%
Overall	11.55	0.073	48.1%
DOR			
Clinic	NA	NA	NA
ED	9.51	0.009	79.0%
Primary Care	0.20	0.904	0.0%
Overall	11.81	0.066	49.2%

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Evidence Table 15: Tests for heterogeneity due to STUDY SETTINGS for BNP in the ED using a cut point of 100 pg/mL (Figures 5a-e).

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
ED (n=6)	14.24	0.014	64.9%
SPECIFICITY			
ED	203.58	0.000	97.5%
LR +			
ED	152.93	0.000	96.7%
LR -			
ED	9.16	0.103	45.4%
DOR			
ED	33.56	0.00	85.1%

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio

Evidence Table 16: Tests for heterogeneity due to STUDY DESIGN for BNP using the lowest cut point provided in each study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Cross sectional (n=8)	35.68	0.000	80.4%
Diagnostic (n=2)	11.93	0.001	91.6%
Prospective Cohort (n=1)	NA	NA	NA
Overall (n=11)	47.77	0.000	79.1%
SPECIFICITY			
Cross sectional	424.00	0.000	98.3%
Diagnostic	14.94	0.00	93.37%
Prospective Cohort	NA	NA	NA
Overall	508.63	0.000	98.1%
LR +			
Cross sectional	219.52	0.000	96.8%
Diagnostic	0.16	0.689	0.0%
Prospective Cohort	NA	NA	NA
Overall	238.47	0.000	95.8%
LR -			
Cross sectional	78.89	0.00	91.2%
Diagnostic	9.93	0.002	89.9%
Prospective Cohort	NA	NA	NA
Overall	108.45	0.00	90.8%
DOR			
Cross sectional	76.71	0.000	90.9%
Diagnostic	6.78	0.009	85.3%
Prospective Cohort	NA	NA	NA
Overall	99.80	0.00	90.0%

Abbreviations: DOR = diagnostic odds ratio, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Evidence Table 17: Tests for heterogeneity due to STUDY DESIGN for NT-proBNP using the lowest cut point provided in each study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Cross sectional (n=3)	8.51	0.014	80.4%
Diagnostic (n=2)	0.76	0.382	0.0%
Prospective Cohort (n=1)	NA	NA	NA
Randomized Trial (n=1)	NA	NA	NA
Overall (n=7)	24.15	0.000	75.2%
SPECIFICITY			
Cross-sectional	72.43	0.000	97.2%
Diagnostic	17.79	0.000	94.4%
Prospective Cohort	NA	NA	NA
Randomized trial	NA	NA	NA
Overall	121.61	0.000	95.1%
LR +			
Cross-sectional	219.52	0.000	96.8%
Diagnostic	0.16	0.689	0.0%
Prospective Cohort	NA	NA	NA
Randomized Trial	NA	NA	NA
Overall	49.53	0.000	87.9%
LR -			
Cross-sectional	7.56	0.023	73.5%
Diagnostic	0.19	0.667	0.0%
Prospective Cohort	NA	NA	NA
Randomized Trial	NA	NA	NA
Overall	11.58	0.072	48.2%
DOR			
Cross-sectional	9.84	0.007	79.7%
Diagnostic	0.00	0.955	0.0%
Prospective Cohort	NA	NA	NA
Randomized Trial	NA	NA	NA
Overall	11.80	0.066	49.2%

Abbreviations: DOR = diagnostic odds ratio, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Table 18: Tests for heterogeneity due to STUDY DESIGN for BNP in the ED using a cut point of 100 pg/mL.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Cross sectional (n=5)	9.89	0.042	59.5%
Diagnostic (n=1)	NA	NA	NA
SPECIFICITY			
Cross sectional	159.97	0.000	97.5%
Diagnostic	NA	NA	NA
LR +			
Cross sectional	139.89	0.000	97.1%
Diagnostic	NA	NA	NA
LR -			
Cross sectional	7.90	0.095	49.4%
Diagnostic	NA	NA	NA
DOR			
Cross sectional	33.51	0.000	88.1%
Diagnostic	NA	NA	NA

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies:

Table 19: Tests for heterogeneity due to CUT POINT near or exactly 100 pg/mL BNP.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Exactly 100pg/mL (n=1)	NA	NA	NA
Greater than 100 pg/mL (n=4)	32.52	0.000	90.8%
Less than 100 pg/mL (n=6)	1.52	0.911	0.0%
Overall (n=11)	47.77	0.000	79.1%
SPECIFICITY			
Exactly 100pg/mL	NA	NA	NA
Greater than 100 pg/mL	41.19	0.000	92.7%
Less than 100 pg/mL	400.57	0.000	98.8%
Overall	508.63	0.000	98.0%
LR +			
Exactly 100pg/mL	NA	NA	NA
Greater than 100 pg/mL	19.28	0.000	84.4%
Less than 100 pg/mL	212.84	0.000	97.7%
Overall	238.47	0.000	95.8%
LR -			
Exactly 100pg/mL	NA	NA	NA
Greater than 100 pg/mL	19.50	0.006	69.5%
Less than 100 pg/mL	16.41	0.006	69.5%
Overall	108.45	0.00	90.8%
DOR			
Exactly 100pg/mL	NA	NA	NA
Greater than 100 pg/mL	31.23	0.000	88.8%
Less than 100 pg/mL	41.56	0.000	88.0%
Overall	99.80	0.00	90.0%

Abbreviations: DOR = diagnostic odds ratio, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies:

Table 20: Tests for heterogeneity due to CUT POINT exactly or greater than 100 pg/mL BNP studies in ED.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Exactly 100pg/mL (n=4)	9.28	0.026	67.7%
Greater than 100 pg/mL (n=2)	0.81	0.369	0.0%
Overall (n=6)	14.24	0.14	64.9%
SPECIFICITY			
Exactly 100pg/mL	154.28	0.000	98.1%
Greater than 100 pg/mL	48.26	0.000	97.9%
Overall	203.58	0.000	97.5%
LR +			
Exactly 100pg/mL	117.42	0.000	97.4%
Greater than 100 pg/mL	34.94	0.000	97.1%
Overall	152.93	0.000	96.7%
LR -			
Exactly 100pg/mL	4.89	0.180	38.6%
Greater than 100 pg/mL	0.08	0.777	0.0%
Overall	9.16	0.103	45.4%
DOR			
Exactly 100pg/mL	25.55	0.000	88.3%
Greater than 100 pg/mL	1.29	0.255	22.7%
Overall	33.56	0.00	85.1%

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio

Table 21: Heterogeneity for SAMPLE SIZE for the lowest cut point provided in each BNP study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Large [n>=500] (n=1)	NA	NA	NA
Small [n<500] (n=10)	46.55	0.000	80.7%
Overall (n=11)	47.77	0.000	79.1%
SPECIFICITY			
Large [n>=500]	NA	NA	NA
Small [n<500]	463.31	0.000	98.1%
Overall	508.63	0.000	98.0%
LR +			
Large [n>=500]	NA	NA	NA
Small [n<500]	191.11	0.000	95.3%
Overall	238.47	0.000	95.8%
LR -			
Large [n>=500]	NA	NA	NA
Small [n<500]	63.49	0.000	85.8%
Overall	108.45	0.00	90.8%
DOR			
Large [n>=500]	NA	NA	NA
Small [n<500]	83.41	0.000	89.2%
Overall	99.80	0.00	90.0%

Abbreviations: DOR = diagnostic odds ratio, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Table 22: Heterogeneity for SAMPLE SIZE for the lowest cut point provided in each NT-proBNP study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Small [n<500] (n= 7)	24.11	0.0000	75.2%
SPECIFICITY			
Small [n<500]	121.61	0.000	95.1%
LR +			
Small [n<500]	49.53	0.000	87.9%
LR -			
Small [n<500]	11.58	0.072	48.2%
DOR			
Small [n<500]	11.80	0.066	49.2%

Abbreviations: DOR = diagnostic odds ratio, LR- = negative likelihood ratio, LR+ = positive likelihood ratio

Table 23: Heterogeneity for SAMPLE SIZE for ED with a BNP cut point near 100 pg/mL.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Large [n≥500] (n=1)	NA	NA	NA
Small [n<500] (n=5)	5.12	0.275	21.9%
SPECIFICITY			
Large [n≥500]	NA	NA	NA
Small [n<500]	102.66	0.000	96.7%
LR +			
Large [n≥500]	NA	NA	NA
Small [n<500]	152.93	0.000	96.7%
LR -			
Large [n≥500]	NA	NA	NA
Small [n<500]	7.91	0.095	49.4%
DOR			
Large [n≥500]	NT	NT	NT
Small [n<500]	NT	NT	NT

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, NA = not able calculate because not enough studies

Table 24: Tests for heterogeneity due to REFERENCE used to diagnose HF for BNP using the lowest cut point provided in each study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Compared to LVEF (n=5)	15.21	0.004	73.7%
Compared to SS (n=4)	0.50	0.919	0.0%
HF to Clinical Scales (n=2)	26.02	0.00	96.2%
Overall (n=11)	47.77	0.000	79.1%
SPECIFICITY			
Compared to LVEF	206.99	0.000	98.1%
Compared to SS	216.40	0.00	98.6%
HF to Clinical Scales	4.44	0.035	77.5%
Overall	508.63	0.000	98.0%
LR +			
Compared to LVEF	53.03	0.000	92.5%
Compared to SS	87.43	0.000	96.6%
HF to Clinical Scales	11.16	0.001	91.0%
Overall	238.47	0.000	95.8%
LR -			
Compared to LVEF	24.44	0.000	83.6%
Compared to SS	4.10	0.251	26.9%
HF to Clinical Scales	19.95	0.000	95.0%
Overall	108.45	0.00	90.8%
DOR			
Compared to LVEF	53.03	0.000	92.5%
Compared to SS	87.43	0.000	96.6%
HF to Clinical Scales	11.16	0.001	91.0%
Overall	99.80	0.00	90.0%

Abbreviations: DOR = diagnostic odds ratio, HF = heart failure, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, LVEF = left ventricular ejection fraction, SS = suggestive symptoms

Table 25: Tests for heterogeneity due to REFERENCE used to diagnose HF for NT-proBNP using the lowest cut point provided in each study.

Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Compared to LVEF (n=5)	15.88	0.003	74.8%
HF to Clinical Scales (n=2)	7.96	0.005	87.4%
Overall (n=7)	24.15	0.000	75.2%
SPECIFICITY			
Compared to LVEF	85.52	0.000	95.3%
HF to Clinical Scales	5.13	0.024	80.5%
Overall	121.61	0.000	95.1%
LR +			
Compared to LVEF	33.13	0.000	88.1%
HF to Clinical Scales	4.92	0.0227	79.7%
Overall	49.53	0.000	87.9%
LR -			
Compared to LVEF	4.85	0.303	17.6%
HF to Clinical Scales	6.69	0.010	85.1%
Overall	11.58	0.072	48.2%
DOR			
Compared to LVEF	1.44	0.837	0.0%
HF to Clinical Scales	9.84	0.002	89.8%
Overall	11.80	0.066	49.2%

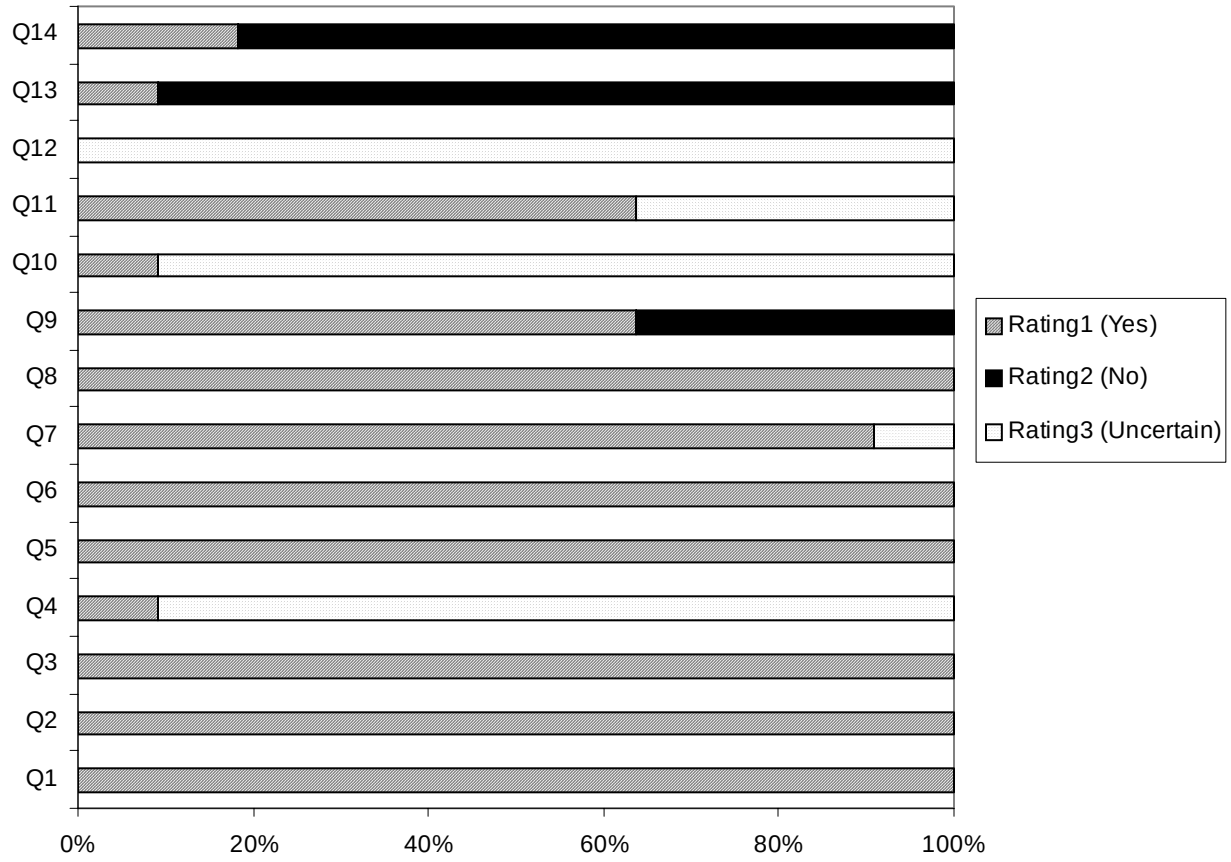
Abbreviations: DOR = diagnostic odds ratio, HF = heart failure, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, LVEF = left ventricular ejection fraction

Table 26: Tests for heterogeneity due to REFERENCE used to diagnose HF for BNP in the ED using a cut point of 100 pg/mL.

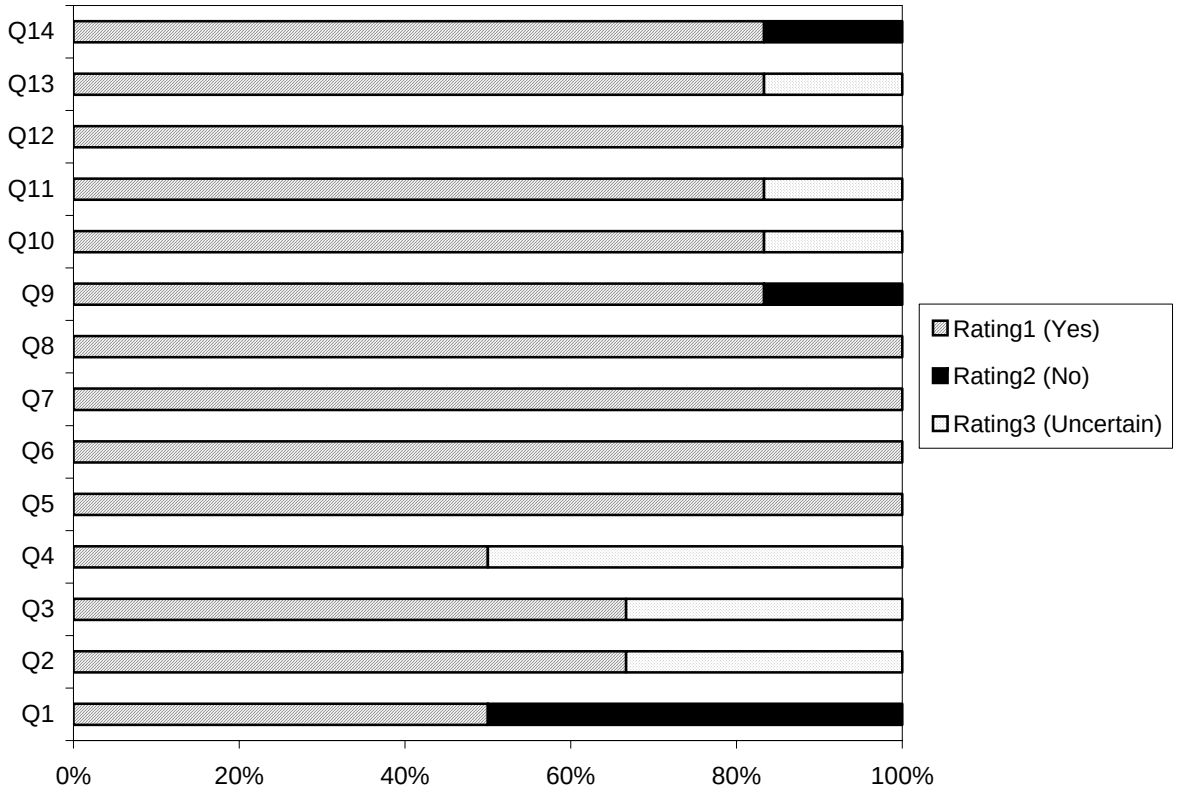
Study Setting	Heterogeneity Statistic (Q-test)	Probability	I-Squared
SENSITIVITY			
Compared to LVEF (n=2)	4.36	0.037	77.1%
Compared to SS (n=3)	8.68	0.013	77.0%
HF to Clinical Scales (n=1)	NA	NA	NA
Overall (n=6)	14.24	0.014	64.9%
SPECIFICITY			
Compared to LVEF	2.04	0.1530	51.0%
Compared to SS	124.18	0.000	98.4%
HF to Clinical Scales	NA	NA	NA
Overall	203.58	0.000	97.5%
LR +			
Compared to LVEF	0.65	0.420	0.0%
Compared to SS	111.88	0.000	98.2%
HF to Clinical Scales	NA	NA	NA
Overall	152.93	0.000	96.7%
LR -			
Compared to LVEF	2.15	0.143	53.4%
Compared to SS	3.79	0.151	47.2%
HF to Clinical Scales	NA	NA	NA
Overall	9.16	0.103	45.4%
DOR			
Compared to LVEF	1.51	0.219	33.8%
Compared to SS	19.69	0.000	89.8%
HF to Clinical Scales	NA	NA	NA
Overall	33.56	0.000	85.1%

Abbreviations: DOR = diagnostic odds ratio, ED = emergency department, HF = heart failure, LR- = negative likelihood ratio, LR+ = positive likelihood ratio, LVEF = left ventricular ejection fraction, NA = not able calculate because not enough studies, SS = suggestive symptoms

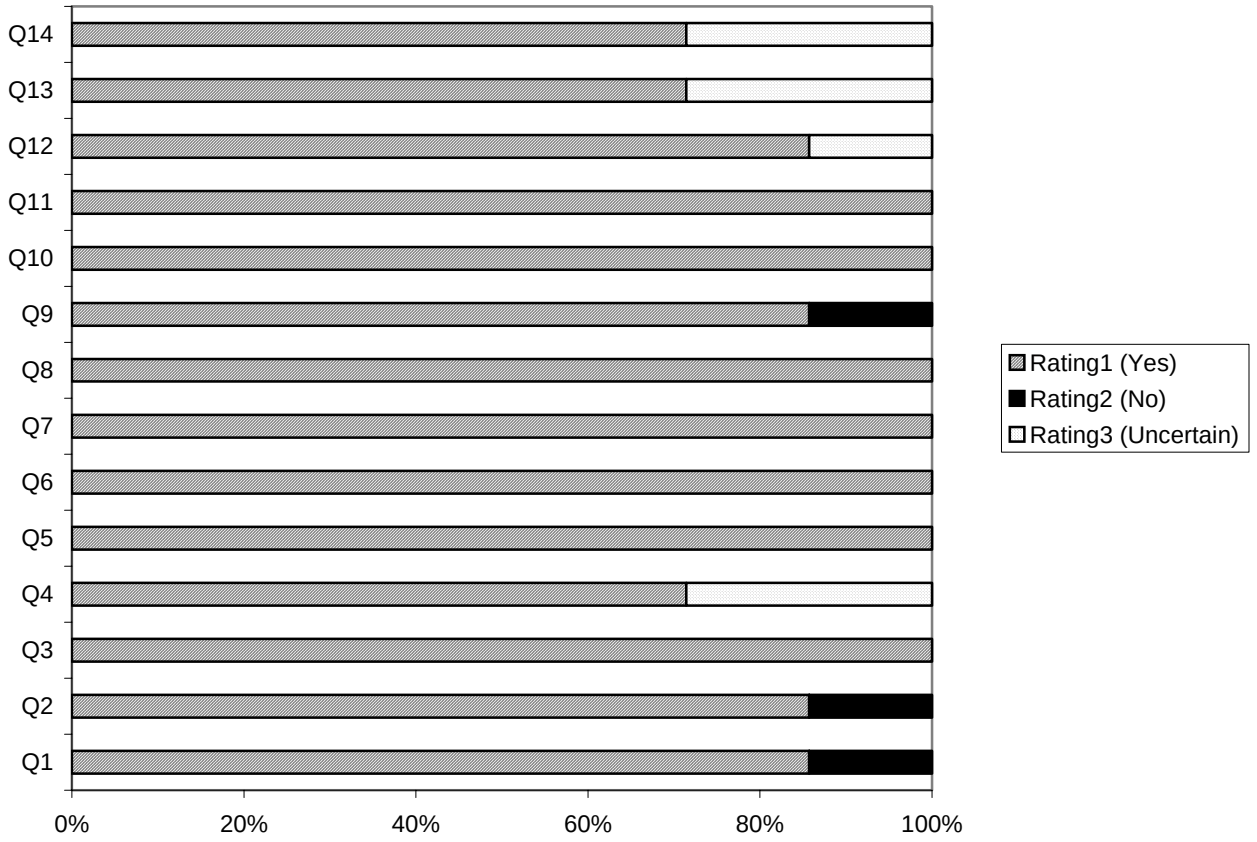
Evidence Figure 1. QUADAS results for question 2ai papers



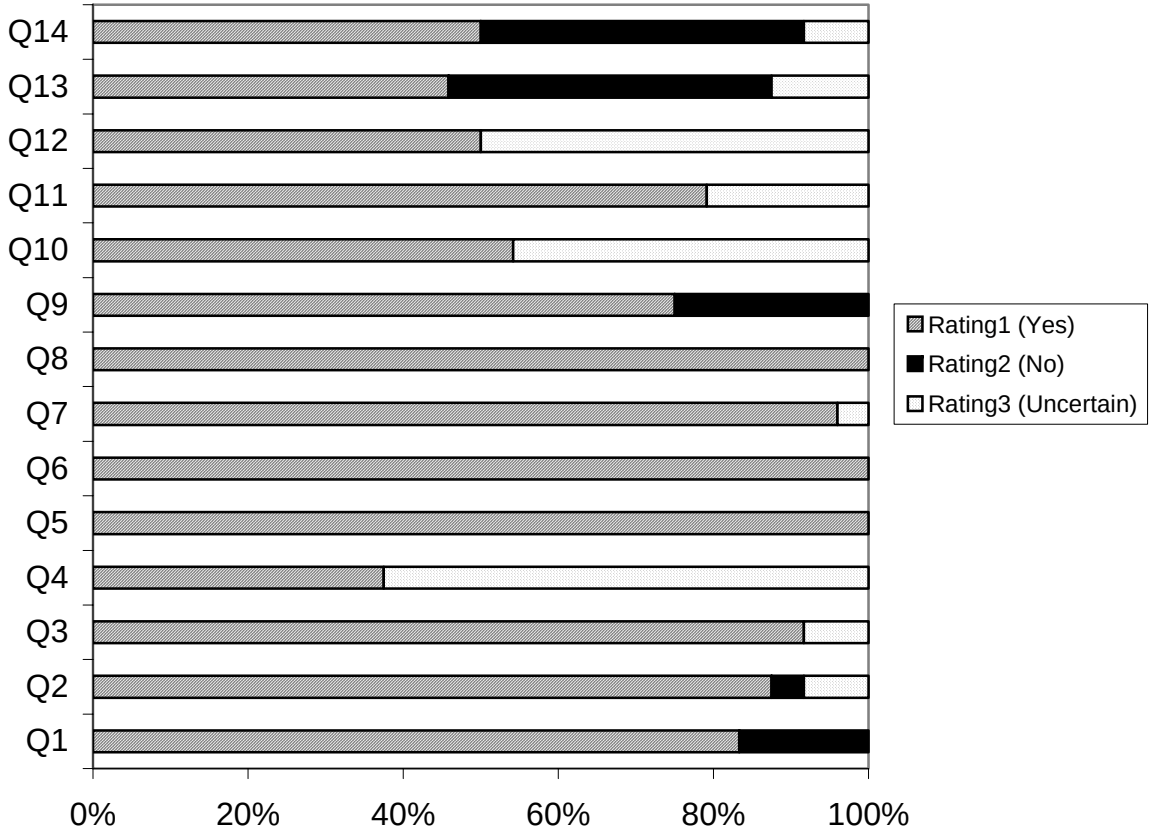
Evidence Figure 2. QUADAS results for question 2aii papers



Evidence Figure 3. QUADAS results for question 2aiii papers



Evidence Figure 4. QUADAS results for all question 2 papers



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Appendix D: Excluded Studies

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Appendix E: Technical Expert Panel

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Structured format for collecting referee comments

We are pleased that you have agreed to review this interim report and thank you in advance for your time. We greatly value your feedback and have provided a series of questions to collect your comments. We have structured these queries into two parts: the first asks for your global impressions of the report and the second part concerns specific components of the systematic review. Lastly, we provide a section for you to write any additional comments that we did not directly probe.

Please note that we are constrained to the format and style of the report as prescribed by AHRQ publication guidelines. However, within this framework, we also ask that you comment on the style and format of the report for purposes of disseminating these findings.

Please complete this form providing as much information as possible including any references or website links. Thank you again for reviewing this report.

Part I – General comments for the AHRQ report

1. Is the Abstract clear and does it provide the pertinent findings?

2. Would you like to see the Executive Summary highlighting different information? Is there information that is excessive or lacking?

3. Is the information in the introduction (Chapter1) sufficient background to prepare the reader for grasping the complexities of the topic and research questions being undertaken in the systematic review?

4. Does the analytic framework convey the essence of how the report was conceptualized?

5. Were the selection criteria appropriate and clearly presented? Do you have any concerns about them and how they may have affected the relevance of the report?

6. Was there conceptual clarity and methodological rigor? (clarity of assumptions and results, treatment of literature, logical reasoning)

7. Do you have any general concerns about the applicability of this report?

8. What are the strengths of this report or those components you valued most?

Part II – Question specific section comments for the AHRQ report

Study Identification

- Is there a thorough search for relevant data using appropriate resources?
- Are there unbiased explicit searching strategies that are appropriately matched to the question?

Study Selection

- Are appropriate inclusion and exclusion criteria used to select articles?
- Are selection criteria applied in a manner that limits bias?
- Are efforts made to identified unpublished data, if this is appropriate?
- Are major changes in selection criteria avoided during the review process?
- Are reasons for excluding studies from the report stated?

Appraisal of Studies

- Is the validity of individual studies addressed in a reliable manner?
- Are important parameters (e.g., setting, study population, study design) that could affect study results systematically addressed?

Data Collection

- Is there a minimal amount of missing information regarding outcomes and other variables considered key to interpretation of results?
- Are efforts made to reduce bias in the data collection process?

Data Synthesis

- Are important parameters, such as study designs, considered in the synthesis?
- Are reasonable decisions made concerning whether and how to combine the data?
- Are results sensitive to changes in the way the analysis was done?
- Is precision of results reported?

Discussion

- Are limitations and inconsistencies of studies stated?
- Are limitations of the review process stated?
- Are review finding integrated within the context of relevant indirect evidence?
- Are implications for research discussed
- Are implications for practice discussed?

Conclusions

- Are conclusions supported by the data reviewed?
- Are plausible competing explanations of observed effects addressed?
- Is evidence appropriately interpreted as inconclusive (no evidence of effect) or as showing a particular strategy did not work (evidence of no effect)?
- Are important considerations for decision makers identified, including values and contextual factors that might influence decisions?
- Is a summary of pertinent findings provided?

Future Recommendations

- Are the future directions described relevant?

Open Comments

- Are there any other comments or suggestions you would like to make ?

This is the end

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Thank you for your expertise in reviewing this report for us.