Effective Health Care Program

Comparative Effectiveness Review
Number 126

Use of Natriuretic Peptide Measurement in the Management of Heart Failure

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Number 126

Use of Natriuretic Peptide Measurement in the Management of Heart Failure

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This report is based on research conducted by the McMaster University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10060-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. 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 email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO

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Use of Natriuretic Peptide Measurement in the Management of Heart Failure

Structured Abstract

Objectives.

- To assess the diagnostic accuracy of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) for detecting heart failure (HF)
- To determine whether BNP and NT-proBNP are independent predictors of mortality and morbidity in HF and whether they add to the predictive value of other markers
- To ascertain whether treatment guided by BNP or NT-proBNP improves outcomes in HF compared with usual care
- To assess the biological variation of BNP and NT-proBNP in HF and non-HF populations

Data sources. Medline®, Embase™, AMED, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL from 1989 to June 2012. Reference lists of included articles, systematic reviews, and gray literature were also searched.

Review methods. Studies were evaluated for eligibility and quality, and data were extracted on study design, demographics, diagnostic test characteristics, predictor factors, interventions, outcomes, and test-performance results.

Results. In emergency settings, BNP (51 studies) and NT-proBNP (39 studies) had high sensitivity and low specificity, and were useful for ruling out but less useful for ruling in HF. Similar results were shown in primary care settings for BNP (12 studies) and NT-proBNP (20 studies). The majority of studies assessing prognosis (183 studies) showed associations between BNP and NT-proBNP and all-cause and cardiovascular mortality, morbidity, and composite outcomes across different time intervals in patients with decompensated and chronic stable HF. Most of these were early-phase predictor-finding studies rather than model-validation or impact studies. Incremental predictive value was assessed in decompensated acute HF (7 studies) and chronic HF (15 studies). Almost all studies showed that calibration and discrimination statistics confirmed the added incremental value of BNP and NT-proBNP. Fewer studies used reclassification and model validation computations to establish incremental value. In the general population (seven studies), an association exists between NT-proBNP and mortality (all-cause, cardiovascular, and sudden cardiac) and morbidity (HF and atrial fibrillation). Overall, therapy guided by BNP/NT-proBNP was shown to reduce all-cause mortality but was graded as low strength of evidence. Seven studies assessed biological variation. The difference in serial results was higher for BNP than NT-proBNP, and the index of individuality for BNP and NT-proBNP was very low.

Conclusions. BNP and NT-proBNP had good diagnostic performance for ruling out HF but were less accurate for ruling in HF. BNP and NT-proBNP had prognostic value in HF and the general population. Therapeutic value was inconclusive. Data on biological variation expressed the differences in results and individuality expected in patients, suggesting that serial measurements need to be interpreted carefully.

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Executive Summary

Background

Heart failure (HF) is a major concern for health care systems because of its chronic nature and resource implications. HF affects approximately 5.7 million Americans, and 670,000 new cases are diagnosed annually.[1] Based on current population estimates,[2] HF is present in 1.8 percent of Americans. The estimated total cost for HF in 2010 was $39.2 billion, or 1 to 2 percent of all health care expenditures.[1] Health care professionals, who face an aging population coupled with the need to be efficient with health care dollars, require sound evidence regarding the diagnosis and management of this disease.

The diagnosis of HF remains a difficult clinical challenge. The diagnosis is based on a constellation of symptoms and signs, supported by objective evidence of impairment of heart function.

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have emerged as promising markers for HF diagnosis, prognosis, and treatment. These peptides are secreted into the bloodstream by cardiac myocytes in response to increased ventricular wall stress, hypertrophy, and volume overload. Elevated levels of these peptides are evident in persons with HF, and it is well established that a low result can exclude HF.[3]

Reviews of the prognostic use of BNP and NT-proBNP have shown that these peptides are independent predictors of mortality and other cardiac outcomes in patients with HF.[3-7] In addition, the reviews suggest that discharge or post-treatment BNP and NT-proBNP are the optimal predictors of prognosis compared with BNP or NT-proBNP measured at other points in time. The reviews also found that BNP and NT-proBNP could add useful information to the standard cardiovascular disease (CVD) risk assessment in certain populations.

Optimization of therapy for patients with HF remains challenging due to the difficulty of diagnosing the condition in the absence of clinically evident signs and symptoms. Measurement of BNP or NT-proBNP has been advocated to guide treatment. This approach is taken because the peptides are independently associated with prognosis[6] and their concentrations decrease with effective therapy.[8] It is unclear whether biomarker-assisted therapy (to achieve a concentration below a target value) or intensified therapy (adjustment of therapy based on a change in biomarker concentration) reduces mortality, rehospitalization, or quality of life (QOL) compared with usual care.

Furthermore, knowledge of the variation of a test measure is important when treatment is based on a difference between serial measurements. We do not currently know how much of a difference in BNP or NT-proBNP concentrations is clinically important. Variation in a test measure is a function of the analytical variation of the assay method (bias and precision) and the inherent biological variation of the molecule tested. The biological variation may also be a function of disease severity, sex, medications, and comorbidity.

A comprehensive systematic review of BNP and NT-proBNP was completed in 2006 by the McMaster University Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ).[3] Due to the vast amount of literature published since the last review, the obsolescence of certain assay types used in earlier studies of BNP and NT-proBNP, and new Key Questions (KQs) that account for the evolution of (and continuing uncertainty within) the field, an entirely new systematic review was required to provide an assessment of the "state of the science" in this field. To summarize the current body of scientific knowledge, this

review examined the diagnostic, prognostic, and therapeutic use of BNP and NT-proBNP and whether the biological variation of BNP and NT-proBNP differs in HF and non-HF populations.

Key Questions

The Key Questions for our review are as follows:

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

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

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

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

Key Question 3: In HF populations, is BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge an independent predictor of morbidity and mortality outcomes?

Key Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge add incremental predictive information to established risk factors for morbidity and mortality outcomes?

Key Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?

Key Question 6: In patients with HF, does BNP-assisted therapy or intensified therapy improve outcomes compared with usual care?

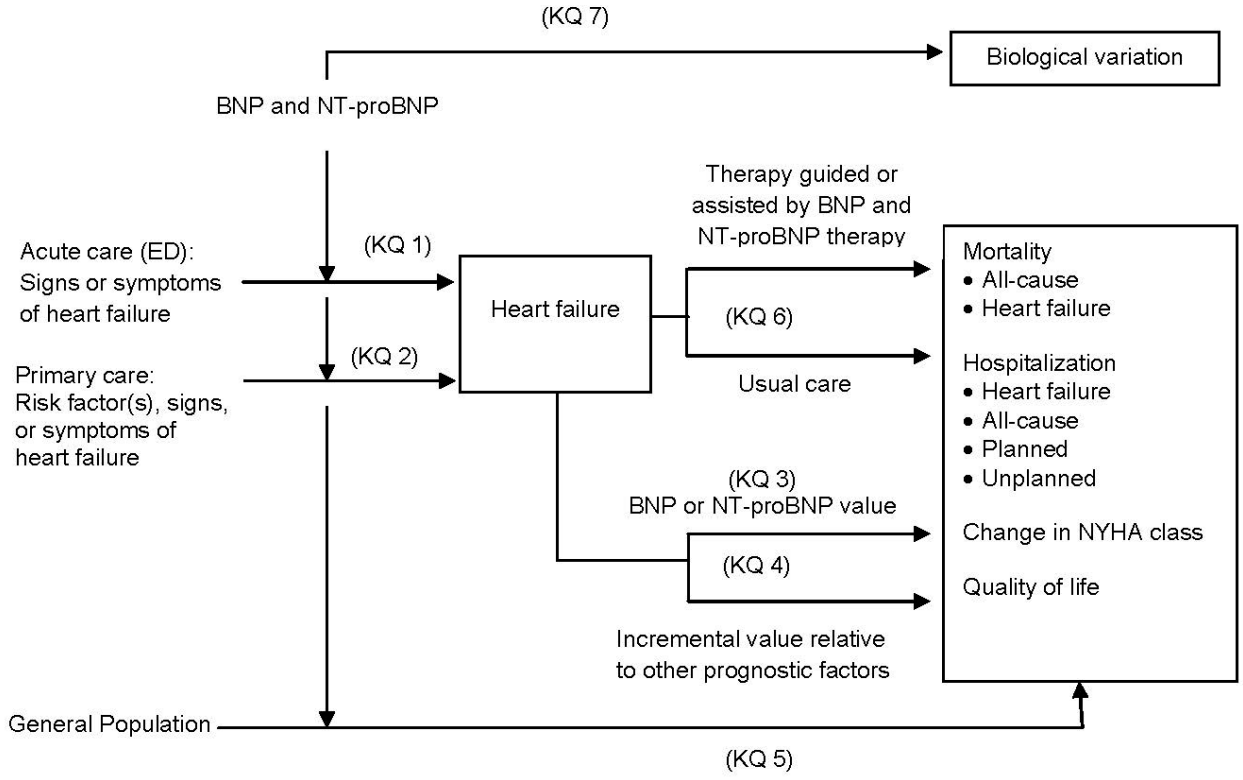
Key Question 7: What is the biological variation of BNP and NT-proBNP in patients with HF and without HF?

Analytic Framework

To guide this systematic review and facilitate the interpretation of the KQs, we developed an analytic framework (Figure A) that depicts the logical progression and interconnection of all seven KQs.

The analytic framework describes the interconnection among the study questions examining diagnosis, prognosis, therapy, and screening. For diagnosis of patients with signs and symptoms compatible with HF, the two settings are acute care (KQ1) and primary care (KQ2). A third setting is the general, undifferentiated population without overt signs or symptoms of HF (KQ5). KQ5 examines the ability of BNP/NT-proBNP to predict mortality and morbidity outcomes in this population. Prognosis of patients with established HF is addressed in KQ3 and KQ4. Prognosis in which the outcome is associated with the concentration of BNP/NT-proBNP is addressed in KQ3, whereas other prognostic measures are dealt with in KQ4. Once a diagnosis of HF has been made, patients are treated. KQ6 examines randomized controlled trials (RCTs) comparing usual care with therapy guided by BNP/NT-proBNP to assess outcome measures. The outcomes to be examined, if reported, include mortality, hospitalization, change in New York Heart Association (NYHA) class, and quality of life. In addition, information on the biological variation of BNP and NT-proBNP was gathered (KQ7).

Figure A. Analytic framework



Note: BNP = B-type natriuretic peptide; ED = emergency department; KQ = Key Question; NT-proBNP = N-terminal proBNP; NYHA = New York Heart Association.

Methods

Input From Stakeholders

The EPC convened a group of experts in the fields of BNP, NT-proBNP, HF, and systematic review methods to form the Technical Expert Panel (TEP). Members of the TEP provided clinical and methodological expertise and input to help interpret the KQs guiding this review, identify important issues, and define parameters for the review of evidence. Discussions among the EPC, the AHRQ Task Order Officer, and the TEP occurred during a series of teleconferences and via email.

The KQs were nominated by a professional society. The KQs were revised for scope and clarity in conjunction with the TEP and the Task Order Officer.

Search Strategy

Six databases (Medline®, Embase™, AMED, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL) were searched and results captured for the period from January 1989 to June 2012. Search strategies were adjusted to conform to the parameters of each database. We also reviewed the reference lists of eligible studies during full-text screening and cross-checked all potentially relevant citations with our citation database. Hand-searching was not done. Gray literature searches included the U.S. Food and Drug Administration (FDA), Health Canada, and European Medicines Agency Web sites; clinical trial registers (clinicaltrials.gov, clinicaltrialsregister.eu, metaRegister of Current Controlled Trials, Clinical Trial Registries, Clinical Study Results, and World Health Organization Clinical Trials); and Conference Papers Index and Scopus (for the previous 2 years only). We limited conference searches to the American Heart Association and the American College of Cardiology conferences.

Study Selection

For KQs 1, 2, and 7, the only excluded study design was the case report. For KQs 3 to 5, cross-sectional and case-control studies were excluded. For KQ6, only RCTs were included. In addition, we excluded letters, editorials, commentaries, and conference proceedings. Systematic reviews and meta-analyses were excluded, although their reference lists were examined for potentially relevant citations. Table A shows study selection criteria.

Data Extraction

Trained data extractors compiled relevant information from individual studies using standardized forms and a reference guide. During the course of writing the report, investigators reviewed the extracted information for accuracy and made corrections as necessary.

Table A. Participant selection criteria

Category	Criteria
Populations	KQs 1–2: Adults presenting to emergency department or urgent care (KQ1) or primary care settings (KQ2) with signs or symptoms consistent with HF. KQs 3–4: Adults with all types of HF. KQ5: Adults in community settings with no disease specified for the study. KQ6: Adults being treated for chronic HF. KQ7: Adults with and without HF.
Interventions and Prognostic Factors	KQs 1–2: FDA-approved assay for BNP or NT-proBNP at admission or discharge or change in BNP/NT-proBNP between admission and discharge using any cutpoint. KQs 3–4: BNP or NT-proBNP measured at admission or discharge or change between admission and discharge; analysis done by appropriate statistical metrics. KQ5: BNP or NT-proBNP assay using any cutpoint. KQ6: Medical therapy based on BNP or NT-proBNP concentration. KQ7: Multiple measurements of BNP or NT-proBNP per subject.
Comparators	KQs 1–2: Any method of diagnosing HF that does not use BNP or NT-proBNP. KQs 3–4: NYHA class of HF, ejection fraction, degree of hyponatremia, decreasing peak exercise oxygen uptake, decreasing hematocrit, widened QRS interval on 12-lead ECG, chronic hypotension, resting tachycardia, renal insufficiency, intolerance to conventional therapy, and refractory volume overload, or risk prediction scores. KQ5: Any predictive scoring system. KQ6: Medical therapy based on usual care for HF patients. KQ7: No comparators.
Outcomes	KQs 1–2: Test performance characteristics (i.e., sensitivity, specificity, positive and negative LR, DOR, and area under ROC curve). KQs 3–6: Mortality, including all cause and HF; morbidity, including hospitalization (HF, all cause, planned, and unplanned); change in NYHA class; and quality of life. Composite outcomes of mortality or morbidity that were not cardiac or HF specific were excluded. KQ7: Calculation of biological variation.
Timing or Followup	Any length of followup.
Setting	KQ1: Emergency or urgent care departments only. KQ2: Primary care settings only. KQs 3–4: Limited to patients admitted to acute care hospitals or recruited from outpatient clinics/ambulatory care settings, hospital settings, or family practice settings. KQ5: Primary care (i.e., community or family practice or equivalent). KQs 6–7: No restriction on inclusion of articles based on setting.

Note: BNP = B-type natriuretic peptide; DOR = diagnostic odds ratio; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; HF = heart failure; KQ = Key Question; LR = likelihood ratio; NT-proBNP = N-terminal proBNP; NYHA = New York Heart Association; ROC=receiver operating characteristic.

Assessment of Risk of Bias

To assess the risk of bias for individual studies, we followed the methods recommended by AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide)[9] and "Methods Guide for Medical Test Reviews."[10] A single rater assessed each study using prescribed tools, clear decision rules, and standardized forms. Piloting of the standardized guide, followed by discussion among the raters, ensured clarity and consistency across raters.

A number of published systems were adapted for use, depending on the study design and the type of analysis. For observational studies, the Newcastle-Ottawa Scale was used;[11] for RCTs, the Jadad scale;[12] for prognosis studies, a modified version of the guidelines proposed by Hayden et al.;[13] and for diagnosis, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2).[14] All modifications and instruments used can be found in the full report.

Data Synthesis

We present study results in four key sections based on diagnosis (KQs 1 and 2), prognosis (KQs 3 to 5), treatment (KQ6), and biological variation (KQ7). All included studies are summarized in narrative form and in summary tables in the full report.

Meta-analysis was carried out only for KQs 1 and 2. Two-by-two contingency tables were created for each study where true positive, false positive, false negative, and true negative could be estimated. Sensitivity and specificity, diagnostic odds ratio, and likelihood ratios with 95% confidence intervals were recalculated for each primary study from the contingency tables. Extracted data were pooled using exact binomial rendition[15] of the bivariate mixed-effects regression model developed by van Houwelingen[16,17] and modified for synthesis of diagnostic test data.[18] The bivariate regression model fits a two-level model, with independent binomial distributions in each study and a bivariate normal model for the logit transforms between studies. Summary sensitivity, specificity, and the corresponding positive likelihood, negative likelihood, and diagnostic odds ratios are derived as functions of the estimated model parameters. This approach corresponds to the empirical Bayesian approach to fitting the hierarchical summary receiver operating characteristic (HSROC) model.[19] Initial analyses considered the level of statistical heterogeneity across the individual studies that were included in the meta-analysis. The Cochran's Q test was used as a measure of statistical heterogeneity in all the meta-analyses and the I^2 as a measure of inconsistency.[20]

Evaluating the Strength of the Evidence

Evaluating the strength of the body of evidence was conducted according to the Methods Guide[9] and "Methods Guide for Medical Test Reviews."[10] We graded the strength of evidence (SOE) for KQs1 and 2 (outcomes of sensitivity and specificity) and KQ6 (death, all cause). We omitted KQs 3 to 5 because criteria to evaluate and score prognostic studies have not been fully developed.[10] We also omitted KQ7 because it asks about biological variation rather than a clinical or diagnostic outcome.

The following strength ratings were used:

- High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate effect and is likely to change the estimate.
- Insufficient: Evidence either is unavailable or does not permit a conclusion.

Results

Results of Literature Search

Results of the review are organized by KQ. The full report includes evidence and summary tables showing findings from individual studies for each KQ.

The search yielded 25,864 records identified from six bibliographic databases. An additional 35 records were identified from three gray literature sources: regulatory agency Web sites, clinical trial databases, and conference sources. After duplicates were removed, a total of 16,893 records were screened at the title-and-abstract level; a total of 3,616 citations moved on to be

screened at full text. Following the application of full-text screening criteria, 310 papers were eligible for all research questions in this review.

A total of 104 papers were allocated for diagnostic accuracy. From these, 76 articles were evaluated for KQ1 and 28 for KQ2. For KQ3, KQ4, and KQ5, 190 unique articles were eligible to address the research questions related to prognosis; of these, 183 were eligible for KQ3, 22 for KQ4, and 7 for KQ5. A total of nine articles were evaluated for treatment guided by BNP or NT-proBNP for KQ6. Seven articles for KQ7 focused on biological variation.

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

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

BNP

Fifty-one publications met the criteria for KQ1 and examined cutpoints for BNP.[21-71] Two of these papers were RCTs,[54,60] 9 were cohort studies,[43,56,61,63,64,66,67,69,71] and the remaining 40 were cross-sectional studies.

Test Performance and Optimal Decision Cutpoints

Papers reporting information on the lowest cutpoint presented by the authors returned a pooled estimate for sensitivity of 95 percent (95% confidence interval [CI], 93 to 97%) and a pooled estimate for specificity of 67 percent (95% CI, 58 to 75%). Twenty-one papers reported on the manufacturers' suggested cutpoint of 100 pg/mL, resulting in a pooled estimate for sensitivity of 95 percent (95% CI, 93 to 96%) and for specificity of 66 percent (95% CI, 56 to 74%).[23,25,29,31-33,35,36,38,39,44,45,47,50-54,59,65,70]

Twenty-eight papers[23,25,27-29,31-33,35,36,39,41,44-54,56,58,65-67] examined an optimal cutpoint, which was defined using various definitions, such as the cutpoint that would maximize accuracy. The pooled estimate for sensitivity was 91 percent (95% CI, 88 to 94%) and for specificity was 80 percent (95% CI, 74 to 85%). Using the optimal cutpoint resulted in a higher overall estimate of the positive likelihood ratio (LR+) of 4.61 (95% CI, 3.49 to 6.09) compared with either the lowest cutpoint (2.85; 95% CI, 2.23 to 3.65) or the manufacturers' suggested cutpoint (2.76; 95% CI, 2.12 to 3.59). The negative likelihood ratio (LR-) was not statistically significantly different ($p > 0.05$).

Choosing the lowest cutpoint, the manufacturers' suggested cutpoint, or the optimal cutpoint had little effect on the diagnostic performance of the test. The test displayed high sensitivity and a high LR-, but low specificity and low LR+.

Determinants Affecting Test Performance

Age: Eight articles[22,23,35,39,46,48,59,66] found increasing age to be associated with increased BNP concentrations, but the effect on the diagnostic performance of the test was not clear in the papers.

Sex: Maisel et al.[22] reported that the difference in BNP concentrations between men and women was not significant. Conversely, Knudsen et al.[23] noted differences in sensitivity and specificity between males and females using 100 pg/mL as the decision point (males: sensitivity 94.3%, specificity 54.9%; females: sensitivity 90.0%, specificity 55.2%).

Ethnicity: Maisel et al.[22] reported that the prevalence of HF in their study population was significantly greater among whites than among African Americans. Similarly, the mean concentration of BNP was significantly greater in the white population with HF than in the African American population with HF (200 vs. 117 pg/mL; p <0.001).

Obesity: Three papers[41,59,60] showed that increasing body mass index (BMI) was inversely associated with BNP concentrations. This finding was consistent whether BMI and BNP were examined in the whole population[59,60] or the population was examined in two groups, namely those with or without HF.[41]

Renal function: Four[42,48,51,67] articles examined estimated glomerular filtration rate (eGFR), and one[59] examined serum creatinine concentration. The BNP concentration was inversely related to renal function. As eGFR decreased or creatinine concentration increased, the BNP concentration increased.

Diabetes: One study[34] reported a nonsignificant difference in areas under the curve (AUCs) calculated for patients with or without diabetes. AUC was 0.878 (95% CI, 0.837 to 0.913) for patients with diabetes and 0.888 (95% CI, 0.860 to 0.912) for patients without diabetes.

NT-proBNP

Thirty-nine articles met the criteria for KQ1 and examined NT-proBNP.[25,38,42,45-48,51,55,61,63,64,66,67,69,72-95] Eleven papers were prospective cohort studies,[61,63,64,66,67,69,85,86,90,94,95] one was a case-control study,[81] and the study design could not be determined in two papers.[82,92] The remaining papers (n = 25) used a cross-sectional design.

Test Performance and Optimal Cutpoints

The 39 papers evaluating NT-proBNP in the emergency department used several cutpoints, ranging from 100[88] to 6,550[42] pg/mL or ng/L. Reported sensitivities ranged from 53 percent[47] to 100 percent[38,47,51,76] (mean = 85.1%; median = 88%); specificities from 5 percent[47] to 100 percent[48] (mean = 70.9%; median = 73.2%); LR+ from 1.05[47] to 115.03;[38] and LR- from 0.02[38,51] to 0.35.[66] AUCs ranged from 0.6[61] to 0.99[79] (mean = 0.88; median = 0.89).

Determinants Affecting Test Performance

Age: The effect of age-optimized cutpoints was unclear. Some articles suggested improved test performance with age-optimized cutpoints and others did not.

Race and sex: Krauser et al.[76] reported that the area under the receiver operating characteristic (ROC) curve was not different for men versus women or for African Americans versus others. There was no difference in the median NT-proBNP concentration between men and women or between African Americans and others.

Obesity: A single paper[74] concluded that BMI-adjusted cutpoints performed well over a wide variety of BMIs. Despite lower sensitivity at the high range of BMI, the predictive values were unchanged.

Renal function: Two papers[48,80] reported an inverse association between renal function and NT-proBNP concentration.

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

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

BNP

Twelve articles met the criteria for this KQ.[96-107] One study used a prospective cohort design,[103] and the remaining studies (n = 11) used a cross-sectional design.

Test Performance and Optimal Decision Cutpoints

Three cutpoints were selected: lowest presented, manufacturers' suggested, and the optimal cutpoint as chosen by the authors. The pooled sensitivity using the optimal cutpoint was 82 percent (95% CI, 69 to 90%), and the pooled specificity was 64 percent (95% CI, 45 to 79%). Summary LR+ and LR- were 2.27 (95% CI, 1.43 to 3.62) and 0.28 (95% CI, 0.16 to 0.49), respectively.

Pooling using the lowest cutpoint produced slightly higher sensitivity and correspondingly lower specificity: 89 percent (95% CI, 77 to 95%) and 54 percent (95% CI, 41 to 66%), respectively. The LR+ and LR- gave similar results: 1.94 (95% CI, 1.47 to 2.57) and 0.20 (95% CI, 0.09 to 0.44), respectively.

The pooled sensitivity of 76 percent (95% CI, 59 to 87%) based on the manufacturers' cutpoint of 100 pg/mL was lower than that for the optimal cutpoint. Corresponding specificity was increased to 71 percent (95% CI, 52 to 85%), compared with 64 percent for the optimal cutpoint. The LR+ and LR- gave results similar to those for the optimal cutpoint: 2.63 (95% CI, 1.59 to 4.36) and 0.34 (95% CI, 0.20 to 0.57), respectively.

Determinants Affecting Test Performance

Age: A single study examined the effect of age on BNP.[101] A higher cutpoint was required in older patients (≥65 years) than in younger patients (<65 years) to detect left ventricular ejection fraction (LVEF) <45 (250 vs. 82 pg/mL) and advanced diastolic dysfunction (DD) (236 vs. 70 pg/mL).

Sex: Test performance did not show statistically significant sex differences in a study by Fuat et al.[97] in which the AUC was 0.79 for men and 0.80 for women. In a study by Park et al.,[101] for patients with LVEF <45, the AUC was 0.89 for men and 0.93 for women; for patients with advanced DD, the AUC was 0.89 for men and 0.91 for women.

BMI: An inverse correlation of BNP with BMI was shown in one study: AUCs for diagnosis of decompensated HF were 0.78 (95% CI, 0.71 to 0.84) for normal-weight patients; 0.72 (95% CI, 0.66 to 0.79) for overweight patients; and 0.62 (95% CI, 0.54 to 0.70) for obese patients.[102] For detecting LVEF <45 in another study,[101] the AUC was 0.93 in patients ≥25 kg/m^2 (cutpoint, 151 pg/mL; sensitivity, 85%; specificity, 85%) and 0.90 in patients <25 kg/m^2 (cutpoint, 154 pg/mL; sensitivity and specificity, 81%). For detecting advanced DD, the AUC was 0.84 in patients ≥25 kg/m^2 (cutpoint, 82 pg/mL; sensitivity and specificity, 80%) and 0.92 in patients <25 kg/m^2 (cutpoint, 140 pg/mL; sensitivity and specificity, 83%).

Renal function: One study assessed the effect of renal function on test performance.[101] Patients were grouped by clearance rates (≥60 mL/min and <60 mL/min). For detecting LVEF <45, AUC estimates were 0.92 (cutpoint, 89 pg/mL; sensitivity and specificity, 82%) for clearance rates ≥60 mL/min and 0.87 (cutpoint, 264 pg/mL; sensitivity and specificity, 78%) for clearance rates <60 mL/min. For detecting advanced DD, AUC estimates were 0.89 (cutpoint, 70 pg/mL; sensitivity, 83%; specificity, 82%) for clearance rates ≥60 mL/min and 0.88 (cutpoint, 247 pg/mL; sensitivity and specificity, 78%) for clearance rates <60 mL/min.

NT-proBNP

Twenty articles met the criteria for KQ2 examining NT-proBNP in primary care settings.[97,99,101,102,106,108-122] Two studies used a prospective cohort design.[116,118] Study design could not be determined in one of the articles.[121] The remaining studies (n = 17) used a cross-sectional design. The 19 studies evaluating NT-proBNP in primary care settings used several cutpoints ranging from 25[118] to 6,180[114] pg/mL or ng/L (mean = 635; median = 379).

Test Performance and Optimal Decision Cutpoints

Three cutpoints were selected: lowest presented, the optimal cutpoint as chosen by the authors, and the manufacturers' recommended cutpoint of 125 pg/mL for patients <75 years of age and 450 pg/mL for patients ≥75 years of age. When the optimal cutpoint chosen by the authors was used, the pooled sensitivity was 0.88 (95% CI, 0.81 to 0.93), and seven of the studies[97,111,113-115,117,119] produced sensitivities greater than 0.90.

Choosing the lowest cutpoint selected by the authors produced increased pooled sensitivity when compared with the optimal cutpoint, with no decrease in pooled specificity. All but three studies[102,118,121] produced sensitivities greater than 0.90.

It was determined that at least four studies were needed in each group to present summary estimates; however, only two studies satisfied our criteria for NT-proBNP according to manufacturers' cutpoint, and thus they were not presented.

Determinants Affecting Test Performance

Age: Two studies investigated the influence of age on the diagnostic ability of NT-proBNP.[101,112] As was seen in the studies of BNP, the optimal cutpoint was higher in older patients. For detecting LVEF <45 in one study,[101] AUCs were 0.88 in patients ≥65 years (cutpoint 1,446 pg/mL; sensitivity 82%; specificity 81%) and 0.91 in patients <65 years (cutpoint, 379 pg/mL; sensitivity and specificity, 84%). One study[101] determined optimal cutpoints of 1,446 pg/mL for those ≥65 years and 379 pg/mL for those <65. A second study[112] determined cutpoints of 652 pg/mL for those >75 years and 357 pg/mL for those ≤75 years.

Sex: Five studies investigated the relationship between sex and NT-proBNP's ability to diagnose HF.[97,101,109,113,117] Using optimal AUC analysis, a range of different cutpoints can be established for men and women. Typically the optimized cutpoint for men was lower than that for women.

BMI: Two studies examined the relationship between NT-proBNP and BMI.[101,102] One study showed an inverse correlation of NT-proBNP with BMI.[102]

Renal function: One study[101] examined the effect of renal function on the ability of NT-proBNP to identify patients with LVEF <45 and advanced DD. The optimized cutpoints were higher with lower creatinine clearance.

Strength of Evidence for BNP and NT-proBNP for All Cutpoints in KQ1 and KQ2

Risk of Bias

Using the QUADAS-2 tool, we rated the risk of bias for both sensitivity and specificity. In the four domains (patient selection, index test, reference standard, and flow and timing), the risk of bias was rated as low.

Directness

KQ1 and KQ2 pertain to diagnostic accuracy and assessment of sensitivity and specificity. These concepts are well understood by clinicians and can be applied in a clinical setting, so we rate this domain as direct.

Precision

For both BNP and NT-proBNP, the CIs around the summary estimates for sensitivity and specificity are not precise. We rate this domain as imprecise.

Consistency

In terms of BNP sensitivity, the directions of the estimates are consistent, and with the exception of a single study,[105] are very similar. In terms of NT-proBNP sensitivity, the directions of the estimates are consistent and the CIs are small. Therefore, we rate this domain as consistent for both BNP and NT-proBNP. However, we rate the specificity as inconsistent because the range of estimates across studies for both BNP and NT-proBNP is large.

The overall SOE estimate for both BNP and NT-proBNP in emergency department and primary care settings is high for sensitivity and moderate for specificity.

Key Question 3: In HF populations, is BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge an independent predictor of morbidity and mortality outcomes?

Patients With Decompensated Heart Failure

Seventy-nine publications (cohorts, case series, and RCTs) evaluated concentrations of BNP (n = 38), NT-proBNP (n = 35), or both (n = 6) as predictors of mortality and morbidity outcomes. Subjects were recruited from emergency or inpatient acute care centers. The majority of studies (n = 55) assessed BNP and NT-proBNP concentrations at admission, with fewer

studies evaluating serial measurements while hospitalized (n = 4) or concentrations at hospital discharge (n = 21) as potential prognostic factors. Additionally, the majority of studies (n = 50) evaluated all-cause mortality and composite outcomes; cardiovascular mortality and morbidity outcomes were measured less frequently. In general, higher concentrations of admission BNP and NT-proBNP were predictive of outcomes of mortality and morbidity, but the range of thresholds for "high" varied markedly across studies. Similarly, for the studies evaluating BNP at discharge, a decrease in BNP concentrations was protective of subsequent mortality and morbidity. Four studies evaluated serial measurements during hospitalization and showed that higher BNP concentrations after admission could also predict mortality. Overall, we judge this body of evidence to be at moderate risk of bias because of the uncertainty with respect to the validity and reliability of the methods used to ascertain the outcome, confounding (inconsistent adjustment for age, sex, BMI, and renal function), and inappropriate statistical analyses (poorly reported).

Generally, studies predicting short-term mortality (up to 31 days) and longer term mortality (24 months or greater) were few in number. Most studies evaluated medium-range time intervals (6 to 12 months), and they consistently showed that BNP or NT-proBNP concentrations are independent predictors of all-cause and cardiovascular mortality, morbidity, and composite outcomes. This was shown across studies for both BNP and NT-proBNP despite the variations in the factors included within the statistical models, including different cutpoints (when used as dichotomous data), other potential prognostic factors included in the statistical models, and time intervals. Conversely, the challenge with these differing study factors was in interpreting the magnitude of the predictive values across studies. Far fewer studies evaluated longer term prognosis (>12 months), and these studies measured admission, discharge, or change from admission concentrations, further limiting the comparisons.

Patients With Chronic Stable Heart Failure

One hundred four publications (cohorts, case series, and RCTs) at moderate risk of bias evaluated concentrations of BNP (n = 15), NT-proBNP (n = 88), or both (n = 1) as predictors of mortality and morbidity in patients with chronic stable HF. In patients with chronic stable HF, there is an association between BNP and the outcome of all-cause mortality. The other mortality outcomes (i.e., cardiac and sudden cardiac death) demonstrated less convincing associations. The importance of BNP as an independent predictor appears to correlate with severity of HF and possibly length of followup. The outcome of hospitalization and the composite outcome of all-cause mortality and cardiovascular morbidity demonstrated a significant independent association with BNP.

Eighty-eight publications evaluated NT-proBNP levels as predictors of mortality and morbidity in patients with chronic stable HF. Overall, the evidence consistently supports the trend that NT-proBNP is an independent predictor of mortality and morbidity outcomes in people with chronic stable HF. The applicability of these results in chronic stable HF patients rests largely in middle-aged or elderly males. The included studies did not explore whether the prognostic effects of NT-proBNP differ by age, sex, or time period. Also, the studies did not suggest a single cutpoint to optimize the prognostic ability of the peptide. In general, the studies were not consistent with respect to measuring the outcome and including our predefined set of variables in the analysis. The largest number of studies and the strongest evidence concerned the outcome of all-cause mortality. Fifty-two publications included all-cause mortality as an outcome, and all of the point estimates measuring association indicated positive associations

between NT-proBNP and all-cause mortality. This conclusion applies across all periods of followup, from 12 months to 44 months. For cardiovascular mortality, the evidence in 17 publications also suggests a positive association with NT-proBNP.

For morbidity outcomes (n = 12), we found some evidence to suggest that higher concentrations of NT-proBNP predict hospitalization. Twenty-six publications evaluated composite outcomes and showed that NT-proBNP is an independent predictor; the results also suggest that higher levels of NT-proBNP predicted greater numbers of composite events.

Patients With Decompensated Heart Failure Having Surgical Procedures

To predict subsequent outcomes, six studies at low risk of bias evaluated BNP levels measured prior to or during cardiac resynchronization therapy (n = 4), cardiac resynchronization defibrillation therapy (n = 1), and noncardiac surgery (n=1) in stable HF patients, as well as in patients undergoing peritoneal dialysis (n = 1) with decompensated HF. All except the peritoneal dialysis study showed that higher BNP levels were associated with subsequent mortality and morbidity.

Three publications evaluated NT-proBNP levels in stable HF patients undergoing cardiac resynchronization therapy (n = 2) and intracoronary infusion of bone marrow–derived mononuclear progenitor cells (n = 1). All studies (for both types of surgeries) showed that higher NT-proBNP levels were associated with subsequent mortality.

Key Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge add incremental predictive information to established risk factors for morbidity and mortality outcomes?

Of 183 studies eligible for KQ3, 39 publications used methods that would allow assessment of the incremental value of adding BNP or NT-proBNP when predicting subsequent outcomes (KQ4). Of these 39 publications, 2 studies[79,123] reported that they undertook statistical computations yet did not present any data for incremental value. Additionally, 15 studies included BNP in the base prognostic model,[71,124-127] NT-proBNP in the base prognostic model,[128-136] or both assays in the base model.[137] Including these assays in the base model does not allow for the assessment of the predictive incremental value of BNP/NT-proBNP. The study findings from the remaining 22 publications that provided the appropriate computations to assess incremental value are presented below.

Patients With Decompensated Heart Failure

Seven publications (six studies) included patients with decompensated HF and evaluated the incremental value of admission BNP[53,138-141] or admission NT-proBNP;[142,143] one study[53] evaluated both BNP and NT-proBNP but reported results only for BNP. Two publications[138,139] pertaining to one study contained overlapping cohorts of consecutive patients recruited from the same center because the study was ongoing and more patients were added to the database; we report findings from both publications even though the cohorts overlap and the publications are considered to be from a single study.

Added Value of BNP to Prognostic Risk Prediction

Data from five studies[53,138-141] suggest that there may be differences in risk prediction by type of mortality outcome (all cause, cardiovascular) in decompensated HF patients. Risk prediction improved incrementally when admission BNP was added to the predictive models that did not contain other markers, despite differences in the models and lengths of followup (which varied from 31 days to 12 months). In some cases, risk prediction improved further when BNP was combined with other markers such as carbohydrate antigen 125 (CA125)[138] or midregional pro-adrenomedullin (MR-proADM).[53]

Added Value of NT-proBNP to Prognostic Risk Prediction

One study[142] of acutely ill patients with HF reported that the inclusion of NT-proBNP alone to a base model failed to show a statistically significant improvement in risk prediction. Conversely, statistically significant improvement was shown when NT-proBNP was combined with other markers in the form of a multimarker risk score based on optimal cutpoints (ROC analysis). Two other studies[79,123] claimed to look at this issue yet did not report any results.

Patients With Stable Heart Failure

Added Value of BNP to Prognostic Risk Prediction

No studies evaluated the incremental predictive value of using BNP as a prognostic risk predictor in stable HF patients.

Added Value of NT-proBNP to Prognostic Risk Prediction

Fifteen publications[144-158] evaluating patients with chronic stable HF considered the prognostic value of NT-proBNP. Overall, NT-proBNP demonstrated incremental predictive value in mortality outcomes, with some evidence suggesting that the incremental value might be more evident in cardiovascular versus all-cause mortality. In one cardiovascular mortality study,[154] the addition of NT-proBNP to the base model resulted in better discrimination for risk prediction than the addition of C-terminal endothelin (CT-proET) (c-statistic = 0.78 vs. 0.77), although the highest value of discrimination was achieved when both NT-proBNP and CT-proET were added to the base model at the same time (c-statistic = 0.79). For all-cause mortality,[159] the base model (clinical variables) with NT-proBNP had a higher discriminatory ability than the base model without NT-proBNP (c-statistic = 0.74 vs. 0.70). The study data also showed that for all-cause mortality, the discriminatory ability for risk prediction was improved by adding copeptin to the model with clinical variables and NT-proBNP (c-statistic = 0.76).

Key Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?

Seven studies[160-166] were eligible for inclusion in this section of the systematic review. A total of 15,656 individuals were included in the seven studies. The smallest study included 274 individuals[161] and the largest 5,447.[165] The length of followup ranged from 3.5[161] to 13.8[160] years. All seven studies measured NT-proBNP. No studies used BNP, and this has been identified as a research gap.

Mortality

All-cause mortality was the outcome in three studies,[161-163] and in all three there was an increasing adjusted hazard ratio (HR) with increasing NT-proBNP measured by tertiles,[161] by increases of 1 standard deviation (SD) unit,[163] and by log(NT-proBNP).[162] The relationship between baseline NT-proBNP and all-cause mortality appeared to be log-linear in nature.

Sudden cardiac death had increasing HRs across the quintiles of NT-proBNP and an adjusted HR = 1.9 (95% CI, 1.7 to 2.1) for ln-NT-proBNP.[165]

Cardiovascular death had a significant adjusted HR for log(NT-proBNP)/SD[164] and log(NT-proBNP).[162] A cutpoint of 100 pg/mL was applied to one population, and results showed an adjusted HR = 1.0 (95% CI, 1.0 to 1.001).[166] However, in a model that was adjusted for known baseline CVD, the adjusted HR became nonsignificant (HR=1.61; 95% CI, 0.79 to 3.28).[162]

Morbidity

Onset of atrial fibrillation (AF) was associated with ln-NT-proBNP in a model including conventional risk factors (adjusted HR = 1.45; 95% CI, 1.28 to 1.65) but not in a model that included midregional pro-atrial natriuretic peptide and c-reactive protein.[160] Onset of incident HF was associated with ln-NT-proBNP in models that included other markers of cardiac risk.[160]

Key Question 6: In patients with HF, does BNP-assisted therapy or intensified therapy improve outcomes compared with usual care?

Nine RCTs examined whether patients whose treatment for HF was guided by BNP or NT-proBNP displayed improved outcomes compared with patients treated for HF with usual care only.[167-175] The term "usual care" encompassed standard of care, clinically guided care, symptom-guided care, or control group. One study used a congestion score strategy compared with BNP-guided therapy.[172] Another study[168] was a three-arm trial with an additional multidisciplinary group, but only the usual-care and NT-proBNP arms are included in this systematic review. There were 7 multicenter studies, including 3 to 45 sites with a minimum of 41 patients up to a maximum of 499 patients. The total number of patients included for all nine studies was 2,104. Four studies measured BNP,[167,172,173,175] and five studies measured NT-proBNP.[168-171,174] The risk of bias for the nine studies was low. Meta-analyses were not performed because of the substantial heterogeneity among the studies, and therefore no quantitative summary estimates could be made.

Primary Endpoint

A composite of endpoints was used in six studies,[168,170,171,173-175] two studies used only one endpoint,[169,172] and one study did not define a primary endpoint.[167] Patients in the BNP/NT-proBNP group had fewer events compared with the usual-care group in three studies.[168,170,173] The other studies showed no difference in the primary endpoint between treatment groups.

Clinic Visits

Clinic visits were reported in only two studies,[168,169] of which one, but not the other, reported more visits for the BNP/NT-proBNP group than the usual-care group.[168]

Hospitalizations

Admissions were considered all cause unless otherwise specified. All studies except one[174] reported on some parameter related to admissions. Most studies reported on cardiovascular

admissions, and three studies[168,170,173] reported fewer admissions in the BNP/NT-proBNP group than the usual-care group. The other studies had no difference in admissions between groups.

Deaths

Of the seven studies that reported on deaths, six reported all-cause mortality,[167-169,171,173,175] four reported death due to a cardiovascular cause,[170,171,173,175] and only two studies reported on death related to HF.[173,175] The SOE was assessed using the single outcome of mortality. Relative risks, confidence intervals, and SOE are presented in Table B. Overall the SOE was rated as low, as two domains (consistency and precision) were not met. Future research is likely to change the magnitude and direction of the effects for the outcome of all-cause mortality.

Table B. Strength of evidence for studies evaluating the benefit of therapy guided by BNP and NT-pro BNP compared with usual care on all-cause mortality in patients with HF

Design	Risk of Bias[a]	Consistency	Directness	Precision	Effect Size, RR (95% CI)	Strength of Evidence
RCT	Low	Inconsistent (5 studies with no effect and 2 studies with a lower RR)	Direct	Imprecise (Unable to assess if the studies were adequately powered and the overall event rates were variable because of length of followup)	Beck–daSilva,[167] 2005: 0.48 (0.05 to 4.85) Berger,[168] 2010: 0.56 (0.35 to 0.89) PRIMA,[169] 2001: 0.79 (0.57 to 1.10) STARS-BNP,[173] 2007: 0.64 (0.26 to 1.58) UPSTEP,[175] 2011: 0.96 (0.61 to 1.50) SIGNAL-HF,[171] 2010: 0.98 (0.36 to 2.72) TIME-CHF,[174] 2009: 0.65 (0.52 to 0.81)	The strength of evidence was rated as low. Therapy guided by BNP/NT-proBNP, when compared with usual care, reduced all-cause mortality. Future research is likely to change the magnitude and direction of the effects for the outcome of all-cause mortality.

[a]Modified Jadad scale.

Note: BNP = B-type natriuretic peptide; ED = emergency department; CI = confidence interval; NT-proBNP = N-terminal proBNP; PRIMA = PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality; RCT = randomized controlled trial; RR = relative risk; SIGNAL-HF = Swedish Intervention study – Guidelines and NT-proBNP AnaLysis in Heart Failure; STARS-BNP = Suivi du Traitement dans l-insuffisAnce caRdiaque Systolique-BNP; TIME-CHF = Trial of Intensified vs standard Medical therapy in Elderly patients with Congestive Heart Failure; UPSTEP = Use of PeptideS in Tailoring hEart failure Project.

Days Alive

Data on days alive, as opposed to death data, were captured in five studies.[169,171-174] Two studies[173,174] showed that patients in the BNP/NT-proBNP group had more days of survival outside the hospital than the usual-care group. The other studies showed no difference between groups.

Quality of Life

Three studies included a QOL questionnaire.[167,171,174] One study[167] used the Kansas City Cardiomyopathy Questionnaire (KCCQ) and showed improvement in score in the BNP/NT-proBNP group compared with the usual-care group. The other two studies used different QOL questionnaires and did not show a difference between groups.

Other Parameters

Studies also reported on acute coronary syndrome,[170] cerebral ischemia,[170] significant ventricular arrhythmia,[170] a combined endpoint of time to cardiovascular death or cardiovascular hospitalization,[171] congestion score,[171] and worsening of HF.[170,176] Only one parameter, worsening HF (new worsening symptoms and signs of HF requiring unplanned intensification of decongestive therapy), was different in the BNP/NT-proBNP group compared with the usual-care group. The study showed fewer events in the BNP/NT-proBNP group.[170]

Medications

Medication use was reported in all nine studies. Of the studies that showed differences in use between the BNP/NT-proBNP group and the usual-care group, most showed increased use in the BNP/NT-proBNP group. These included aldosterone antagonists (AA) in one[170] of three studies,[169,170,175] angiotensin-converting enzyme (ACE-I) in one[172] of four studies,[170-172,175] ACE-I or angiotensin receptor blockers (ARB) in four[168,169,172,174] of five studies,[168,169,171,172,174] ACE-I or ARB and beta-blocker in two[172,177] of three studies,[168,172,177] beta-blocker in two[168,174] of eight studies,[168-175] and spironolactone in one[174] of three studies.[168,172,174]

Medication decreases were found for diuretics (two[168,170] of six studies[168-172,175]) and ARB (one[170] of five studies[168-171,175]) in the BNP/NT-proBNP group compared with the usual care group. No differences between BNP/NT-proBNP and usual-care groups were found for ACE-I and AA,[171] ACE-I plus ARB and AA,[171] digoxin,[168,171] or nitrates.[168,170]

Key Question 7: What is the biological variation of BNP and NT-proBNP in patients with HF and without HF?

Seven studies included data on biological variation for BNP and NT-proBNP.[178-182] All study designs were prospective cohort studies except for one that was a retrospective chart review.[182] Studies varied in length from as short as 1 day to as long as 2 years. Overall, the number of patients or participants sampled was small (mean = 32; range = 5 to 78), as were the samples obtained to calculate biological variation (median = 4; range = 2 to 15). Blood collection parameters and analytical protocols varied among studies and were inconsistently reported.

The analytical coefficient of variation (CV_a) values, or assay imprecision, for BNP were lowest for the Bayer Centaur method (1.8% to 4%) and highest for the Biosite Triage (8.6% to 13.7%), reflecting the higher imprecision for point-of-care devices. Similar CV_a values were obtained for the Roche NT-proBNP method (1.4% to 3.0%). Review of the within-individual variation values (CV_i) for BNP and NT-proBNP in patients with HF or healthy controls showed lower values (by about one-half) for within-hour[180] and within-day[178] values than for values from longer time intervals (1 to 12 weeks). Within-individual variation was similar for BNP (median = 25%) and NT-proBNP (median = 20%).

The relative change value (RCV) is a parameter that constitutes a clinically meaningful change in serial results. The largest RCV values were found for healthy individuals for BNP (123% and 139% for two different methods) and NT-proBNP (92%).[183] The only other study with an RCV value for healthy individuals measured NT-proBNP and reported a much lower value (26%), but this value was log-transformed.[184] For patients with HF, the RCV values were overall higher for BNP (32% to 113%) than for NT-proBNP (16% to 55%). In studies[178,180,181] that analyzed both BNP and NT-proBNP, the RCV was lower for NT-proBNP, mostly as a function of the lower CV_a for the method compared with the BNP methods.

The index of individuality (IOI) is a useful parameter for assessing the degree of individuality for a biomarker and was assessed in four studies.[179,181,183,184] The IOI for NT-proBNP in healthy individuals (0.64 and 0.90) was higher than for patients with HF (0.03 and 0.11). Similarly, the IOI for BNP was higher in healthy individuals (1.1 and 1.8; same patients but different methods) than for patients with HF (0.14). This means there is more individuality for BNP and NT-proBNP in patients with HF than in healthy individuals.

Discussion

Diagnostic Studies (Key Questions 1 and 2)

Key Findings for Emergency Settings

For patients who present to emergency departments or urgent care settings with signs and symptoms suggestive of HF, BNP and NT-proBNP have good diagnostic performance to rule out, but lesser performance to rule in, the diagnosis of HF compared with the reference standard of global assessment of the patient's medical record. Covariates, especially age and renal function, have important effects on the performance of these tests. However, the findings about the effects of age were equivocal, with some studies reporting effects and others not.

Key Findings for Primary Care Settings

This review indicates that BNP and NT-proBNP are useful diagnostic tools to identify patients with HF in primary care settings, with pooled sensitivities ranging from 0.77 to 0.84 for BNP and 0.86 to 0.90 for NT-proBNP, depending on the cutpoint. Both BNP and NT-proBNP have good diagnostic performance in primary care settings for identifying patients who are either at risk of developing HF or have limited symptoms suggestive of HF. Using the manufacturers' suggested cutpoint, BNP can effectively be used to rule out the presence of HF in primary care settings. In the case of NT-proBNP, limited evidence is available to determine if the manufacturers' suggested cutpoint is as effective. Only one study[93] evaluated the cutpoints recommended by the European Society of Cardiology.[177]

A single study looked at the age effect and showed that a higher cutpoint is required for both BNP and NT-proBNP in patients aged 65 years and older to maintain test sensitivity equivalent to that for patients less than 65 years.[101] No sex differences were seen for BNP, and no clear conclusions could be drawn regarding optimal cutpoints for NT-proBNP in males and females. A negative correlation of BMI with BNP or NT-proBNP was reported, with decreasing sensitivities for diagnosing HF. However, no BMI-specific cutpoints were suggested in the included articles. Decreased renal function, measured by creatinine clearance (<60 mL/min), was shown to increase the levels of both BNP and NT-proBNP; however, the effect was more significant with NT-proBNP.[101]

Applicability

The diagnosis of HF in patients presenting to emergency departments is difficult.[185] The differential diagnosis for patients presenting with the chief report of dyspnea is large, including cardiac causes, pulmonary causes, combined cardiac and pulmonary causes, and neither cardiac nor pulmonary causes.[185] This review focused on patients with acute or chronic HF who are admitted to emergency departments or followed in primary care settings, regardless of comorbidity, which helped maximize generalizability.

For BNP, we present data on the common cutpoint of 100 pg/mL proposed by all manufacturers of FDA-approved BNP assays. This should provide users of the test with robust information on the applicability of the test to patients. For NT-proBNP, cutpoints based on age varied among studies. This lack of uniformity for NT-proBNP suggests that clinicians should cautiously apply the findings of this report to their practices in emergency departments and urgent care centers.

In primary care settings, the majority of patients do not present to general practitioners with obvious serious symptoms of HF. Identifying at-risk patients or those with subclinical HF is critical, as undiagnosed HF leads to progression and worse QOL in patients and increased costs to the health care system. BNP, using both the optimal or manufacturers' suggested cutpoint, is effective in identifying patients at risk of HF or identifying patients with little subclinical HF. NT-proBNP is effective at identifying patients at risk of HF using the optimal cutpoint; however, limited evidence exists for using the manufacturers' suggested cutpoint.

Research Gaps

- More studies are needed to determine the effect of age on the diagnostic cutpoints, especially for NT-proBNP. Common cutpoints that can be used in all clinical situations, especially those suggested in recent guidelines, would increase the applicability of this test.
- More studies are needed to determine the effect of declining renal function on the diagnostic performance of both BNP and NT-proBNP, and to establish cutpoints in situations of reduced renal function.
- More studies are needed to determine the effect of sex, ethnicity, and BMI on natriuretic peptide concentrations and ultimately on the cutpoints for diagnosis.
- Studies are needed to examine the role of BNP and NT-proBNP in multimarker panels for the diagnosis of HF.
- A more detailed study of the effects of heterogeneity among the studies would allow a clearer understanding of the effects of various confounders, including comorbidities.

Prognosis Studies: Patients With Acute and Chronic Heart Failure (Key Question 3)

Key Findings

The findings demonstrate that BNP and NT-proBNP are independent predictors for outcomes of mortality and morbidity. All-cause mortality and composite outcomes across different time intervals (from 14 days to 7 years in decompensated HF patients and from 12 to 44 months in chronic stable patients) were most often evaluated; cardiovascular mortality and morbidity were less frequently evaluated and showed some inconsistency in demonstrating an association with these peptides. In general, higher levels of BNP/NT-proBNP were associated with greater risk, but the thresholds used to categorize groups varied widely. In studies of decompensated HF patients, a decrease in BNP/NT-proBNP levels relative to admission levels was also predictive of decreased rates of mortality and morbidity.

The studies were rated as having moderate risk of bias overall. However, it was observed that the majority of studies had high risk of bias in two main domains: control of confounding and adequate measurement of the outcome. Many of the studies failed to assess prediction of outcomes using multivariable models that included adjustments for age, sex, BMI, and renal

function, the minimum set that we established based on expert consultation and our previous review. Despite this concern, the overall conclusion that BNP and NT-proBNP are independent predictors of mortality and morbidity outcomes in persons with decompensated and stable HF remains, given the consistent association across different time periods and HF populations. It should be noted that the majority of studies employed lower hierarchical statistical approaches, reflecting early-phase prognostic study development; few studies undertook validation or impact investigations.

Applicability

With respect to applicability, most papers pertained to populations aged 60 years or older. However, we could not find specific evidence to suggest that the predictive value of BNP or NT-proBNP varies by the age, sex, or race of the study population. Although many studies controlled for sex in multivariable regression models, few investigated sex as a potential effect modifier. Thus, we cannot comment on whether the results differ in males and females. Comparing across studies that considered various cutpoints, higher cutpoints appear to be associated with greater risk. However, the studies considered a wide variety of cutpoints. Also, proportions of change (relative to baseline) varied widely in the studies, thus rendering any clear thresholds for practical clinical guidance problematic.

From a clinical perspective it is challenging to apply the test result, as there are neither established cutpoints nor tools for interpreting logBNP or logNT-proBNP to help physicians apply the information to their patients. However, the association of higher levels of BNP or NT-proBNP with poor outcomes over a variety of time periods is consistent. Current clinical guidelines do not provide information on how to use BNP and NT-proBNP in prognosis but suggest that they add prognostic information.

Research Gaps

- Future studies should consider including more women and various races. Sex and age should be investigated as effect modifiers.
- Consensus should be obtained on some key predetermined cutpoints or change relative to baseline and on clinically meaningful intervals for followup that are relevant to decompensated patients and chronic stable patients.
- Researchers should agree on and use a standard group of covariates to account for potential confounding in nonrandomized studies. In particular, future studies should include either BMI or another measure of body fat (such as waist circumference or waist-to-hip ratio) and a measure of renal function in multivariable regression models.
- Outcome assessment should also be standardized, both in terms of the types of outcomes investigated and the ways in which these outcomes are defined and measured.
- We recommend consideration of a phased approach to establishing the predictive value of BNP or NT-proBNP. Attempts to validate predictive models (internal or external) are an important priority for future research.
- There is a need for more impact studies assessing the clinical utility of using the predictive models.
- For populations with acute HF, more studies are needed to evaluate the potential differences in predictive ability between admission and discharge levels of BNP and NT-proBNP.

Prognosis Studies: Adding Predictive Information to Other Prognostic Methods in Patients With Heart Failure (Key Question 4)

Key Findings

For patients with decompensated HF, only mortality outcomes were evaluated with respect to incremental prognostic value; in chronic stable HF patients, mortality, morbidity, and composite outcomes were assessed. Overall, despite the differences in base predictive models, cutpoints, and lengths of followup, BNP and NT-proBNP were both shown to add incremental predictive value in acutely ill HF patients for all-cause mortality; however, the highest incremental predictive value was achieved when BNP or NT-proBNP was combined with other markers such as CA125 or MR-proADM. Fewer studies evaluated cardiovascular mortality, but they also demonstrated the independent predictive value of BNP.

When considering composite outcomes, NT-proBNP was shown to be an independent predictor; there are too few studies evaluating morbidity to assess incremental prognostic value. Only one study attempted internal validation and none employed external validation. Five publications undertook reclassification statistics, and results show inconsistency regarding the incremental prognostic value of NT-proBNP.

Applicability

Studies addressing KQ4 consisted predominately of middle-aged and elderly male subjects with HF. Time intervals were heterogeneous for studies of both decompensated HF (from 31 days to 6.8 years) and chronic stable HF (from 12 to 37 months), making comparisons across studies problematic. There were also differences in statistical base models, cutpoints, and lengths of followup, thereby suggesting that the studies are applicable to these specific factors.

Research Gaps

- There is a need to move to higher level hierarchical approaches (internal and external validation) when selecting statistical evaluations (i.e., reclassification methods), as well as designing impact studies.
- There is a need to evaluate outcomes of morbidity and composite outcomes in decompensated HF subjects with respect to the incremental value of BNP and NT-proBNP.
- There is a need to evaluate BNP in stable chronic populations with respect to incremental predictive value.
- Future research recommendations for KQ3 (see above) are also applicable for KQ4.

Prognosis Studies: General Populations (Key Question 5)

Key Findings

The adjusted HR demonstrates the log-linear relationship between baseline NT-proBNP and cardiovascular death as well as all-cause mortality, taking into consideration age, sex, BMI, and renal function. Our findings demonstrate clearly that there is an association between NT-proBNP and the outcomes of morbidity (HF and AF), as well as mortality (all cause, cardiovascular, and sudden cardiac).

For outcomes that are associated with cardiac disease (incident HF and AF), there appears to be a log-linear relationship between NT-proBNP and the outcome, taking into consideration age, sex, BMI, and renal function. In addition, NT-proBNP seems to perform well, even when adjusted for other conventional risk markers and biomarkers.

Applicability

While the association is clear, the directness or applicability of these findings to patient care is not demonstrated well in the included papers. Two papers considered the application of NT-proBNP to other traditional risk factors and used the c-statistic to assess the additional discrimination for risk prediction.[160,163] To translate this into clinical practice will require the development of specific risk calculators that take into consideration confounders and any other established risk markers.

Research Gaps

Future research should develop specific risk calculators that take into consideration confounders and any other established risk markers. Such models will require testing in population cohorts before the use of NT-proBNP or BNP can be validated for use as a prognostic marker in community settings.

BNP-Assisted Therapy (Key Question 6)

Key Findings

Few RCTs have been undertaken to assess whether BNP-guided therapy has benefits over usual care. Studies varied in patient selection; baseline characteristics of patients; therapy (type, schedule, goals); BNP/NT-proBNP target; outcome types; and how the findings were reported. The conclusions from these studies are varied, in part because of the differences in study design and outcomes. Meta-analyses were not performed because of the substantial heterogeneity among the studies, and therefore no quantitative summary estimates could be made. Differences among studies provide greater understanding of how BNP/NT-proBNP therapy can be used, despite whether trials succeeded or failed.

Four of five studies reported at least one outcome that was better in the group with therapy guided by BNP/NT-proBNP than in the usual-care group.[168,170,173,174] Five studies reported negative results, three[167,171,172] of which had short followups (3–9 months) that would have limited the number of long-term outcomes.

One limitation to this systematic review was the exclusion of two trials, the 2000 trial assessing therapy guided by NT-proBNP[186] and a more recent study in 2010 done by the same research group.[187] They were not included because the NT-proBNP assay used is not commercially available. These data would have strengthened the results of this systematic review but not altered the conclusions.

Applicability

Understanding the usefulness of BNP or NT-proBNP measurement in the assessment of HF status will allow better management of HF patients, essentially serving as a barometer. Currently, the data from the studies that have evaluated BNP or NT-proBNP for this purpose are inconclusive.

Research Gaps

Future trials should consider the following design features:

- Therapy optimized at baseline according to clinical guidelines.
- BNP or NT-proBNP target near the median value for patients with stable HF.
- Consideration of use of the relative change value when gauging the value of a change in therapy.
- Followup of 2 years or more.
- Inclusion of all relevant endpoints: cardiovascular mortality, total mortality, days alive and not hospitalized for HF, number of HF hospitalizations, number of HF events not requiring hospitalization, surrogate measures of renal function (e.g., creatinine) and ischemia (e.g., troponin), number of patients who have achieved target BNP/NT-proBNP concentration, and number of patients who have achieved recommended medication doses. Also, inclusion as part of medication information of the number of patients who are taking additional medications or doses above the recommended amounts. Inclusion of QOL questionnaires for additional value.
- Sample size calculations to demonstrate adequate study power for the outcomes selected.

Biological Variation (Key Question 7)

Key Findings

This systematic review of biological variation was specific to patients with stable HF or healthy controls. In the two studies in which healthy individuals were evaluated, the RCVs were higher than those in studies of patients with stable HF. Within-individual variation was similar for BNP (median = 25%) and NT-proBNP (median = 20%), but lower in short measurement intervals (hours, days) than longer measurement intervals (weeks, year). Although the circulating half-life of BNP is much shorter (21 minutes) than that for NT-proBNP (60–120 minutes), this did not seem to affect the within-individual variation (CV_i) values much.[188] No meta-analysis could be done to compute summary estimates for CV_i or RCV, as confidence limits were not provided for variance data in any study.

Most studies included in this systematic review considered at least some known preanalytical factors and tried to minimize or address them. However, the determinants of within-person biological variation have not been well explored; more is known about between-person variation, such as sex, age, exercise, and comorbidity.[189] The biological variations are likely due to subclinical changes in hemodynamics, hormonal regulation, and clearance, and perhaps even differences in the type of circulating forms of BNP.[188]

The IOI for BNP and NT-proBNP was between 0.03 and 0.14, which is lower than any of the common biochemistry analytes.[190] A low IOI (<0.48) is considered to reflect strong individuality, which in turn indicates that an individual patient should be assessed with respect to his or her individual hormonal level.

Applicability

The applicability of the RCV values calculated from stable HF patients is to assess instability in HF patients. Although the inclusion criteria of patients with stable HF varied among studies, this did not seem to influence the RCV values by a large degree. The timeframe of collection for the biological variation data seemed to influence the RCV. The within-hour and within-day values were much lower, yet there was no discernible difference beyond this time period (up to 2

years). Interestingly, the RCV values for BNP were about double those for NT-proBNP, suggesting that NT-proBNP would be more sensitive than BNP for detecting a significant change. The implication is that NT-proBNP may be better than BNP for serial monitoring.

Research Gaps

Additional studies are needed to provide supporting evidence of the biological variation parameters. These studies should be designed to capture sources of biological variation determinants by multivariable regression analysis and would therefore require larger sample sizes than have been used thus far. Preanalytical and analytical variation should be minimized by collection of samples in the early morning, increasing the frequency of collection, and duplicating determinations to increase the accuracy of the measure. Calculations should include CIs to show reliability and allow meta-analyses to be done.

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Introduction

Heart failure (HF) is a major concern for health care systems because of its chronic nature and resource implications. HF affects approximately 5.7 million Americans and about 670,000 new cases are diagnosed annually.[7] Based on current population estimates,[8] HF is present in 1.8 percent of Americans. The estimated total cost for HF in 2010 was $39.2 billion, or 1 to 2 percent of all healthcare expenditures.[7] Health care professionals require sound evidence to provide direction for the diagnosis and management of this disease, as they face an aging population along with the need to be efficient with health care dollars.

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have emerged as promising markers for HF diagnosis, prognosis, and treatment. These peptides are secreted into the bloodstream by cardiac myocytes in response to increased ventricular wall stress, hypertrophy, and volume overload.

BNP is a 32 amino acid polypeptide whose release is modulated by calcium ions.[9] BNP binds to and activates natriuretic peptide receptors A and B. NT-proBNP is a 76 amino acid N-terminal fragment of BNP and is secreted along with BNP.[9]

The physiologic actions of BNP are similar to A-type natriuretic peptide (ANP) and include decreases in systemic vascular resistance and central venous pressure as well as increases in natriuresis. Thus, the net effect of BNP and ANP is a decrease in blood volume which lowers systemic blood pressure and afterload, yielding an increase in cardiac output, partly due to a higher ejection fraction. Since BNP and NT-proBNP levels are increased in persons with HF, measurement of these two peptides have consequently come to be included in clinical practice guidelines for HF.[10] It is interesting to note that the various guidelines weight the evidence related to natriuretic peptides differently.[10-12] This suggests that the evidence related to the natriuretic peptides is difficult to evaluate. Currently the guidelines recommend the use of natriuretic peptides to help in the diagnosis of HF at the time of presentation because of their ability to rule out HF (Acute HF, Strong recommendation, moderate quality of evidence; chronic HF, Strong recommendation, High quality of evidence[11] and class IIa Level C[12]). Both these guidelines include a comment with the diagnostic information that suggests prognostic information is obtained from the natriuretic peptide test. The European Society of Cardiology (ESC) guideline[13] mentions serial testing of natriuretic peptides but does not weight the evidence and the Canadian Cardiovascular Society guidelines[11] suggest the addition of an additional drug if natriuretic peptides remain elevated, suggesting that serial monitoring may be performed.

HF is a syndrome characterized by combinations of symptoms, signs and diagnostic test changes.[14] It is further sub-categorized into a number of categories that include terms such as “acute”, “decompensated”, “exacerbation”, “systolic”, “diastolic”, “right”, “left”, “congestive” and “chronic”.[11,15-17] The challenge facing any synthesis of evidence in a complex syndrome such as HF is in defining what the individual authors and studies interpret and use as HF. However, it remains true that clinicians in practice continue to use the syndrome of HF as a diagnostic term[11,12,15,18] and that this condition results in substantial use of the health care system. The challenge in evaluating a diagnostic test is the comparison against a reference “Gold Standard”. The only available standard in HF is clinical judgment and this is an imperfect reference standard. Thus the evaluation of natriuretic peptides needs to be considered in the context of a condition with a variable definition.[19] Due to these factors, synthesis of data should try and contextualize the clinical setting to allow the practicing physician the opportunity to identify the set of data that is applicable to the patients that are being evaluated.

A comprehensive systematic review of BNP and NT-proBNP was completed in 2006 by the McMaster Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ).[20] This review included studies published up to January 2005.

Due to the vast amount of literature published after January 2005, the obsolescence of certain assay types used in earlier studies of BNP and NT-pro-BNP, as well as new Key Questions (KQ) that account for the evolution of the field, an entirely new systematic review is required to provide an assessment of the "state of the science" in this field.

To summarize the current body of scientific knowledge, this review examines the diagnostic and prognostic use of BNP and NT-proBNP in several aspects of HF. The review will consider BNP and NT-proBNP test performance, cutpoints, and factors that affect test performance in emergency, urgent care, and primary care settings. As well, the review will investigate whether BNP and NT-proBNP are independent predictors of morbidity and mortality in HF, or whether they add information to other methods used to predict morbidity and mortality. The review will examine whether therapies involving BNP and NT-proBNP improve outcomes in HF patients and whether the biologic variation of BNP and NT-proBNP differs in HF and non-HF populations.

Diagnosis, Prognosis, and Treatment Strategies

Diagnosis of Heart Failure

Congestive HF is a common condition, especially among the elderly, and one of the most common reasons for admission to hospital. The diagnosis of HF remains a difficult clinical challenge. The diagnosis is based on a constellation of symptoms (e.g., breathlessness, fatigue, and ankle swelling) and signs (e.g., tachycardia, tachypnea, rales, increased jugular venous pressure, hepatomegaly, and edema), supported by objective evidence of structural abnormality of the heart shown by abnormalities in the echocardiogram or chest X-ray. Reviews of the role of the natriuretic peptides BNP and NT-proBNP suggest that they have value in ruling out the presence of HF due to the high sensitivity of the test. However, low specificity limits the test's usefulness for ruling in HF.[20,21] In addition there are challenges in assessing the diagnostic utility of a test when there is no valid reference standard.[19]

Clinical guidelines,[11,12] including the 2009 update to the American College of Cardiology/American Heart Association (ACC/AHA) 2005 guideline for the diagnosis and management of HF in adults,[10] indicate that measuring natriuretic peptides may be a useful addition to the standard set of diagnostic tools used to evaluate suspected HF. These guidelines caution users about poor specificity and the need to account for potential confounders, such as age, ethnicity, and comorbidities (including renal disease and obesity).

Since the publication of the AHRQ review in 2006,[20] several primary publications have addressed the diagnostic test accuracy of the natriuretic peptides for patients with HF presenting to the emergency department and to primary care physicians.[22-28] Both the emergent population (those with symptoms acute enough to warrant presentation to the emergency department or urgent care facilities) and the primary care population (those with risk factors, signs, and symptoms evaluated by a primary care physician) are areas of research that would benefit from a systematic review of the evidence. Decision cutpoints have been proposed in several publications (most recently in the National Institute for Health and Clinical Excellence (NICE) Clinical Guideline No. 108, 2010[29]), but they have not been optimized for specific populations. Also, the effect of comorbidities on the decision cutpoints has not been systematically reviewed in terms

of diagnosis. The value of these tests will be further refined by examining which decision cutpoints maximize the diagnostic criterion of interest and how they perform in specific populations, including patients with comorbidities.

Prognosis of Heart Failure

Prognostic use of BNP and NT-proBNP has been studied in a number of primary studies and has been the subject of at least four systematic reviews.[30-33] The most recent of these systematic reviews includes primary studies up to July 2009.[30]Although these systematic reviews differed in the eligible studies evaluated, they reported consistent evidence that BNP and NT-proBNP were independent predictors of mortality and other cardiac outcomes in patients with HF.[30-33] In addition, they suggested that a discharge or post-treatment BNP and NT-proBNP is a better predictor of prognosis.[30-33] The reviews also found that BNP and NT-proBNP could add useful information to the standard cardiovascular disease (CVD) risk assessment in certain populations. In fact, the updated NICE guideline[29] for CHF notes that higher BNP and NT-proBNP levels are associated with poorer prognosis in HF. NICE recommends high priority research in the area of determining prognostic stratification (page 208) and lists important outcomes in this respect. The most recent update to the Canadian guideline includes reference to the use of natriuretic peptides in a prognostic score.[11] The European guideline includes a table of prognostic factors that includes the natriuretic peptides.[12] Neither of these guidelines separate out the prognostic use of BNP and NT-proBNP from the diagnostic use.

Two systematic reviews, published in 2005[31] and 2006,[20] have evaluated the evidence that BNP and NT-proBNP are predictive of mortality and other cardiac events in patients with HF. Doust et al.[31] evaluated studies in patients with HF and also in persons with no overt disease. Based on this review, BNP was shown to be consistently associated with an increased relative risk (RR) of death, even among asymptomatic subjects. The second systematic review[20] employed broader eligibility criteria and included almost double the number of eligible studies. This review showed similar results to the review by Doust et al. and indicated that baseline BNP or NT-proBNP levels were independent predictors of mortality across various cutpoints.

The prognostic value of these tests requires further evaluation in the different clinical settings (acute care and physician office or out-patient clinic) and type of HF (decompensated and chronic) in which the tests are proposed for use as a prognostic factor.

Therapy

Optimization of therapy for patients with HF remains challenging due to the difficulty in perceiving signs and symptoms associated with HF unless they are overt. Current practice guidelines are based on target doses used in clinical trials, but are not individualized for patients. Up-titrations of these medications may take into consideration factors such as age, disease severity, and other comorbidities, but do not include any biological parameter of HF. That is, a biomarker that reflects the functioning of the heart, similar to other biomarkers used in disease therapy such as thyroid stimulating hormone for hypothyroidism or hemoglobin A1c for diabetes monitoring. The measurements of BNP and NT-proBNP have been advocated as biomarkers to guide treatment because the peptides are independently associated with prognosis[32] and their concentrations decrease with effective therapy.[34] It is unclear whether biomarker-assisted therapy to achieve a concentration below a target value, or intensified therapy (the adjustment of therapy based on a change in biomarker concentration) reduces mortality, rehospitalization, or increases quality of life, compared with usual care.

When the AHRQ report on BNP was produced in 2006, the large interventional trials to address this question had just begun, so minimal data were available. Since then, nine randomized controlled trials (RCTs) have been completed and several more RCTs are currently underway. The design of the RCTs are such that one arm receives usual care for HF and the other arm receives management based on a target BNP or NT-proBNP goal. In the most recent systematic review,[35] eight RCTs were reviewed and BNP-guided therapy was found to be beneficial: the RR for all-cause mortality was lower in the guided therapy group compared with the usual care group (RR=0.76; 95% CI, 0.63 to 0.91; p=0.03). However, this review has been critiqued for having an absence of information on the included studies and a discussion that does not thoroughly explain the findings.[36] Pooling of different studies with different populations and different management algorithms limits the robustness of the effect estimate.

Furthermore, knowledge of the variation of a test measure is important when treatment is based on a difference between serial measurements. It is not currently known how much of a difference in BNP or NT-proBNP concentrations is clinically important. Variation in a test measure is a function of the analytical variation of the assay method (bias and precision) and the inherent biologic variation of the molecule tested. The biologic variation may also be a function of disease severity, sex, medications, and comorbidity.

Several studies have collected data in an attempt to understand the magnitude of the variation of BNP and NT-proBNP.[37-39] These studies have looked at the within-day, day-to-day, and week-to-week variations of BNP and NT-proBNP in healthy individuals and in patients with stable chronic HF. The biologic variation for individuals (CV_I) was found to increase with time between measurements for both BNP and NT-proBNP. However, there is inconsistency among studies, method types, and statistical analysis methods.

Key Questions

The EPC convened a group of experts in the fields of BNP, NT-proBNP, HF, and systematic review methods to form the Technical Expert Panel (TEP). Members of the TEP provided clinical and methodological expertise and input to help interpret the KQs guiding this review, identify important issues, and define parameters for the review of evidence. Discussions among the EPC, Task Order Officer (TOO), and the TEP occurred during a series of teleconferences and via email.

The KQs listed in the Introduction were provided by the American Association for Clinical Chemistry (AACC). We revised the KQs for scope and clarity in conjunction with the AACC, TEP, and TOO.

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

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

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

a. What is the test performance of BNP and NT-proBNP for HF?

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

Key Question 3: In HF populations, is BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge, an independent predictor of morbidity and mortality outcomes?

Key Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge, add incremental predictive information to established risk factors for morbidity and mortality outcomes?

Key Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?

Key Question 6: In patients with HF, does BNP-assisted therapy or intensified therapy improve outcomes compared with usual care?

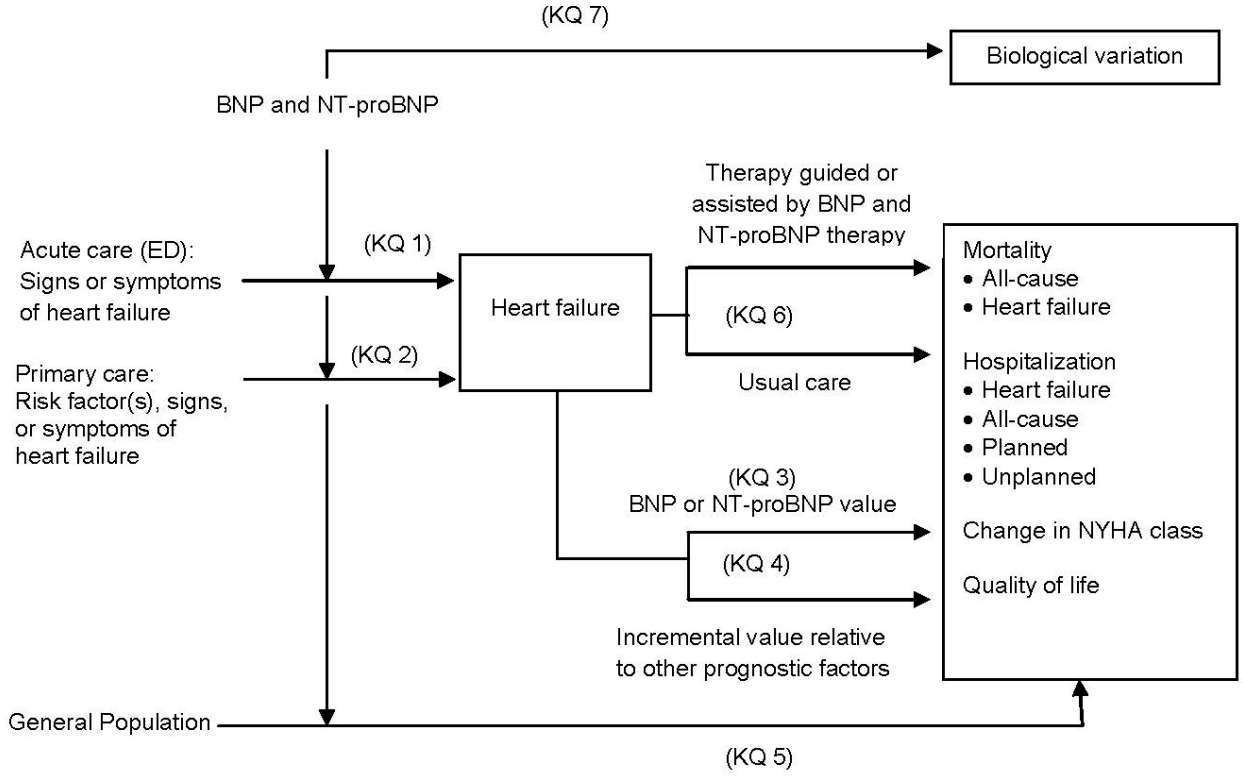
Key Question 7: What is the biological variation of BNP and NT-proBNP in patients with HF and without HF?

Analytic Framework

To guide this systematic review and facilitate the interpretation of the KQs, an analytic framework (Figure 1) that depicts the logical progression and interconnection of all seven KQs was developed.

The analytic framework describes the interconnection between the study questions examining diagnosis, prognosis, therapy and screening. For diagnosis of patients with signs and symptoms compatible with HF, the two settings are acute care (KQ1) and primary care (KQ2). A third setting is the general, undifferentiated, population without overt signs or symptoms of HF (KQ5). KQ5 examines the ability of BNP/NT-proBNP to predict mortality and morbidity outcomes in this population. Prognosis of patients with established HF is addressed in KQ3 and 4. Prognosis, where the outcome is associated with the concentration of BNP/NT-proBNP is addressed in KQ3, whereas other prognostic measures are dealt with in KQ4. Once a diagnosis of HF has been made, patients are treated. KQ6 will examine RCTs comparing usual care with BNP/NT-proBNP guided therapy to assess outcome measures. The outcomes to be examined, if reported, include mortality, hospitalization, change in New York Heart Association (NYHA) class and quality of life. In addition, information on the biological variation of BNP and NT-proBNP will be gathered (KQ7).

Figure 1. Analytic framework



Note: BNP = B-type natriuretic peptide; ED = emergency department; KQ = Key Question; NT-proBNP = N-terminal proBNP; NYHA = New York Heart Association.

Methods

The present review examines evidence for the use of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) in the diagnosis and prognosis of heart failure (HF) and in guiding therapy for persons with HF. A systematic review of the published scientific literature was conducted. Established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[40] and the Methods Guide for Medical Test Reviews[41] were employed. The protocol for this review is available online at AHRQ's Effective Health Care Program Web site (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=899).

The Task Order Officer (TOO) was responsible for overseeing all aspects of this project. The TOO facilitated a common understanding among all parties involved in the project, resolved ambiguities, and fielded all Evidence-based Practice Center (EPC) queries regarding the scope and processes of the project. The TOO and other staff at AHRQ reviewed the report for consistency and clarity and to ensure that it conformed to AHRQ standards.

Literature Search Strategy

Search Strategy

A broad literature search strategy was implemented to reflect the scope of this review (i.e., BNPs and their use with HF diagnosis, monitoring, treatment, and outcome). The search strategy (see Appendix A) was based on our earlier review,[20] which was sufficiently broad for the current topic. Specifically, the search used terms for BNPs and was refined by date, language, and study subjects.

Search strategies used combinations of controlled vocabulary (medical subject headings and keywords) and text words. The results were captured from January 1989 to June 2012. The search was restricted to human studies (specifically removing results that included only animal data) and to English-language publications.

The search involved six databases: Medline, Embase, AMED, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL. Search strategies were adjusted to conform to the parameters of each database.

The reference lists of eligible studies at full text screening were reviewed and crosschecked with the citation database. Any references not found within the database were retrieved and screened at full text. Hand searching was not done.

Three sources for grey literature were searched: regulatory agency Web sites, clinical trial databases, and conference sources. The regulatory information included the U.S. Food and Drug Administration (FDA), Health Canada, and European Medicines Agency. Clinical trial databases included clinicaltrials.gov, clinicaltrialsregister.eu, metaRegister of Current Controlled Trials, Clinical Trial Registries, Clinical Study Results, and World Health Organization Clinical Trials. Conference papers were searched in Conference Papers Index and Scopus for the previous 2 years only. Conference searches were limited to the American Heart Association and the American College of Cardiology conferences.

Citations meeting the search criteria were downloaded into Reference Manager Version 12 and then imported into systematic review software (DistillerSR 2011, Ottawa, Ontario). Once in DistillerSR, citations were screened using specified eligibility criteria.

Study Selection and Eligibility Criteria

With input from the Technical Expert Panel (TEP) and the TOO, selection criteria were developed for identifying studies for each Key Question (KQ). The criteria were based on the Participants, Interventions, Comparisons, Outcomes, Time, and Setting (PICOTS) framework and are shown below. For KQ1, 2, and 7, the only excluded study design was case reports. For KQ3 to 5, case reports, cross-sectional, and case-control studies were excluded. Retrospective studies as well as randomized controlled trials (RCT) and other prospective studies were included, provided these studies were based on medical or database records that permitted the construction of historical cohort, before/after, or time series data. For KQ6, only RCTs were included. For all KQ, only studies that measured BNP/NT-proBNP with methods approved by the FDA were included (see Appendix B). In addition, we excluded letters, editorials, commentaries, and conference proceeding abstracts. Reference lists of systematic reviews and meta-analyses were examined for potentially relevant citations. See Appendix C for study selection and criteria forms.

Inclusion and Exclusion Criteria

Population

All KQs: Adults >18 years of age.

KQ1: Patients presenting to the emergency department or urgent care settings with signs or symptoms consistent with HF. **Exclusion:** Studies where all subjects are ≤18 years of age, subjects that arrive at the emergency department or urgent care area with already diagnosed acute HF or known exacerbation of stable chronic HF, and studies that include only subjects with specific conditions that may impact BNP results, such as heart transplantation, obesity, hypertrophic cardiomyopathy, or valvular lesions.

KQ2: Patients presenting to a primary care physician with signs or symptoms consistent with HF. Primary care was defined according to the American Academy of Family Physicians' definition.[42] **Exclusion:** Studies where all subjects are ≤18 years of age, subjects with known acute HF or known exacerbation of stable chronic HF, and studies that include only subjects with specific conditions that may impact BNP results, such as heart transplantation, obesity, hypertrophic cardiomyopathy, or valvular lesions.

KQ3, KQ4: Patients with all types of HF (with or without any comorbidity). The type of HF categorized at data extraction (e.g., acute, chronic, or chronic with acute exacerbation). **Exclusion:** Adults at risk of coronary artery disease (CAD) or with CAD, and other adults at risk of HF without documented HF (e.g., diabetes and renal failure).

KQ5: Adults in a community setting with no disease specified for the study (a nonselected or general population). **Exclusion:** Any study where a specific disease has been used to include or exclude subjects (e.g., acute coronary syndrome, CAD, diabetes, and renal failure).

KQ6: Patients being treated for chronic HF. **Exclusion**: Admitted patients with known HF or patients with acute HF.

KQ7: Adults with and without HF.

Interventions and Prognostic Factors

KQ1 and 2: FDA-approved assay for BNP or NT-proBNP at admission or discharge or change in BNP/NT-proBNP between admission and discharge. No restriction on the BNP or NT-proBNP decision cutpoint. **Exclusion:** Use of non-FDA-approved assay or non-BNP or NT-proBNP assay (i.e., pre-proBNP or atrial natriuretic peptide (ANP) and other versions of ANP).

KQ3: BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge. No restriction on cutpoint. **Exclusions**: Studies that provided only univariate analyses to assess prognostic risk and predict outcome.

KQ4: BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge. No restriction on cutpoint. Any other prognostic factors compared with BNP or NT-proBNP using the appropriate statistical metrics.

To assess the degree to which BNP and NT-proBNP add predictive and prognostic information to established risk factors for mortality and morbidity outcomes, studies that used at least one of the following statistical approaches were included: likelihood-based measures, indices of calibration, discrimination statistics, and measures of risk reclassification. The selection of these statistical approaches was based on suggested methods[43-49] to evaluate and quantify the incremental predictive information of novel biomarkers. The likelihood-based measures, such as likelihood ratio (LR) and LR chi-square (global chi-square and incremental chi-square) statistics, are global measures of model fit.[50,51] These measures are a sensitive index of information when new markers are included in prognostic models that have already been adjusted for various established risk factors.[46,48,50,51] The indices of calibration, such as the Hosmer-Lemeshow statistic (goodness-of-fit test),[52] measure the accuracy of risk prediction of a biomarker by comparing the observed and predicted frequency of events (risk).[46,50,51] The discrimination statistics, such as c-index or c-statistics,[43,46-48,50,51] are based on the area under the curve (AUC) of a receiver operating characteristic (ROC) curve.[46,50,51] The c-statistic measures the probability that an individual with an event at a specific time has a higher risk score than an individual with no event during the same time period. Studies were included that used the time-dependent AUC approach (c-index or c-statistics) and excluded studies that used simple extensions of the AUC, which ignore time to event and treat censored patients or dropouts as non-events.[47,51] The c-index or c-statistic is used as a standard measure to quantify the predictive discrimination of a biomarker.[50] The measures of risk reclassification, such as Net Reclassification Improvement/Index (NRI)[46,49,51] and Integrated Discrimination Improvement (IDI),[49]determine how many subjects would be reclassified in clinical risk groups and whether the new risk group is more accurate for the reclassified subjects (level of discrimination).[43,46,47,49,51] Studies that met inclusion criteria but did not report meaningful results are also presented; that is, (1) studies indicated that the authors undertook computations evaluating model discrimination, calibration, or reclassification statistics, but did not report results; (2) they reported pairwise comparisons of c-statistics or overall c-statistic, where the base model includes BNP or NT-proBNP, and as such the incremental value cannot be assessed; or, (3) they reported univariate c-statistic analyses. **Exclusion:** Studies that used simple extensions of AUC without accounting for time or events, to assess the relative or incremental contribution

of BNP/NT-proBNP and other prognostic factors. Studies that used only the log rank test to assess the incremental value of prognostic factors.

KQ5: No restriction on cutpoint. **Exclusion:** Non-BNP or NT-proBNP assay.

KQ6: Medical therapy based on BNP or NT-proBNP concentration.

KQ7: Multiple measurements of BNP or NT-proBNP per subject.

In the case of one study,[53] which was relevant for KQ7 only, the authors reported insufficient information to ascertain whether they used an FDA-approved assay. Normally, this would lead to exclusion of the paper. However, one investigator believed this paper was of such importance to the review topic that the authors should be contacted for clarification of the assay method. The corresponding author was contacted and this paper was ultimately included in the review. No authors of any other paper were contacted for clarification of assay method. A sensitivity analysis was not conducted to assess the impact upon the results of including versus excluding this paper.[53]

Comparators

KQ1 and KQ2: Any method of diagnosing HF that does not use BNP or NT-proBNP. Since no gold standard diagnostic criteria exist in HF, sensitivity and specificity of BNP or NT-proBNP were calculated using whatever comparator methods or prediction scores were used in the included studies.

KQ3 and KQ4: New York Heart Association **(**NYHA) functional classification of stages of HF,[54] ejection fraction, degree of hyponatremia, decreasing peak exercise oxygen uptake, decreasing hematocrit, widened QRS interval on 12-lead electrocardiogram, chronic hypotension, resting tachycardia, renal insufficiency, intolerance to conventional therapy, and refractory volume overload[10] or risk prediction scores (e.g., Seattle HF Model[55]). **Exclusion:** No restrictions.

KQ5: Any predictive scoring system (e.g., Framingham[56]). **Exclusion:** No restrictions.

KQ6: Medical therapy based on usual care for HF patients.

KQ7: No comparators.

Outcomes

KQ1: Article reported test performance characteristics (i.e., sensitivity, specificity, positive and negative LRs, diagnostic odds ratio (DOR), and area under the ROC curve).

Article studied the effect of various decision cutpoints and the effect of various determinants (e.g., age, sex, and comorbidities) on the test performance characteristics. Article reported adverse events (AE) associated with administration of the test or being exposed to the results. AE could be specific to patients or generalizable to the health care system. **Exclusion:** No restriction.

KQ2: Article reported test performance characteristics (i.e., sensitivity, specificity, positive and negative LR, DOR, and area under the ROC curve).

Article studied the effect of various decision cutpoints and the effect of various determinants (e.g., age, sex, and comorbidities) on the test performance characteristics. Article examined AE associated with administration of the test or being exposed to the results. Adverse events could be specific to patients or generalizable to the health care system. **Exclusion:** No restriction.

KQ3 to KQ6: Mortality including all-cause and HF; morbidity including hospitalization (including HF, all-cause, planned, and unplanned); change in NYHA class; and quality of life. A broad definition of 'hospitalization' was employed, which included any episode of HF that required admission to a hospital bed beyond the emergency department for any length of time. This included hospitalization for an initial diagnosis, readmission, stabilization, and investigation. **Exclusion:** KQ3 toKQ6: No restriction

KQ7: Calculation of biological variation.

Timing of Followup

KQ1 to KQ7: No restriction on inclusion of articles based on length of followup.

Setting

KQ1: Emergency or urgent care departments only.

KQ2: Primary care settings only.

KQ3 toKQ4: Patients must have been admitted to acute care hospitals or have been recruited from outpatient clinics/ambulatory care settings, hospital settings, or family practice settings.

KQ5: Patients were studied in primary care (i.e., community, family practice. or equivalent). **Exclusion:** Any setting that was not primary care (e.g., specialized outpatient clinics, emergency department, or patients admitted to hospital).

KQ6: No restriction on inclusion of articles based on setting.

KQ7: No restriction on inclusion of articles based on setting.

Data Extraction

Trained data extractors, using standardized forms and a reference guide (see Appendix D), extracted relevant information from included studies. A calibration exercise was conducted using a random sample of included studies to test the forms. During the course of writing the report, investigators reviewed the information for accuracy and made corrections as necessary.

Extracted data for all studies included general study characteristics, details of the patient population, and comorbidities. Blood sample type was also extracted for BNP measurement (plasma or serum), assay source (name), type of peptide assessed (BNP, NT-proBNP, or both), and storage temperature of BNP (if applicable). Outcomes extracted were the type of instrument or scale, cutpoints, primary or secondary outcome status, type of effect measure (endpoint or change score, measures of variance), and definition of treatment response.

For KQ1 and 2 related to diagnosis, the location of care (emergency/urgent care, primary care), information regarding the reference standard, and test performance characteristics (either primary data to allow us to calculate these characteristics, or the summary data for sensitivity, specificity, positive and negative LR, DOR, and ROC curves) at various decision points and for various subgroups (e.g., age, sex, and comorbidities) were extracted. Adverse events were extracted if identified.

For KQ3, 4, and 5 related to prognosis, data were extracted for: HF score (NHYA or AHA/ACC); acute (and acute on chronic) or chronic HF; ejection fraction; other prognostic markers used as comparators (i.e., degree of hyponatremia, decreasing peak exercise oxygen uptake, decreasing hematocrit, widened QRS on 12-lead electrocardiogram, chronic hypotension, resting tachycardia, renal insufficiency, intolerance to conventional therapy, and refractory volume overload); study design (i.e., association with outcome; effect of BNP measurement on outcome; and effect of BNP within a composite score on outcome); predefined confounders (i.e., age, NYHA, AHA/ACC, left ventricular ejection fraction (LVEF)); timing of BNP testing; BNP decision points used (cutpoints); derivation of BNP cutpoints; prevalence; length of followup; outcome (as per PICOTS); and, multivariable analyses (multivariable Cox regression analysis; multiple logistic regression analysis; multiple linear regression analysis; c-statistic; reclassification measures (IDI, NRI)).

For KQ6, data extracted included a description of treatment arms (i.e., usual care, guided therapy, and other); length of followup; blinding strategy; primary endpoint(s); secondary endpoint(s); HF etiology; percentage of patients achieving target dose of medications in each study arm; statistical methods; adjustment factors; BNP or NT-proBNP concentrations at baseline and other time points, including change values; and, relative risk (RR) for all groups reported in the studies.

Data extracted for KQ7 included the number of sequential measurements per subject; time between blood collections (e.g., hour, day, week, month, and year); study length; sample collection parameters (e.g., tube type, handling, processing, and storage); statistical methods to calculate coefficient of variation (CV), correlation, multivariate regression; CV, analytical (CVa); CV, individual (CVi); CV, between individual (CVg); relative change value; and, index of individuality and factors associated with biological variation of BNP or NT-proBNP.

In the case of studies in which outcomes were reported in chart or graphical form only (e.g., sensitivity or specificity in an ROC curve or survival in a Kaplan-Meier curve), outcome data were not extracted due to the uncertainty involved in estimating numerical data from pictures in published study reports.

Assessment of Risk of Bias

Methods to assess and interpret individual study risk of bias followed approaches recommended by AHRQ.[40,41] Criteria to assess risk of bias were ascertained from established tools (Newcastle-Ottawa scale (NOS), QUADAS-2, Hayden Criteria, Jadad), clear decision rules, and standardized forms (see Appendix E and F). The investigators trained a pool of experienced raters on the application of these tools. Piloting of the standardized guide and discussion ensured clarity and consistency across raters. The raters were trained using a sample of studies to ensure a consistent approach to the quality assessment. During this pilot testing phase, at least two raters assessed the quality of each sample study. Studies were evaluated by one rater, and then checked by a second. Any inconsistencies were resolved to reach consensus.

Assessment of Risk of Bias: Diagnosis Studies

QUADAS-2[57] was used to assess the risk of bias in this systematic review. As recommended by the QUADAS-2 developers, the investigators tailored the QUADAS-2 to this review by discussing whether some of the tool's signaling questions should be removed from consideration. These questions are intended to help researchers judge the risk of bias in each of the four domains on the QUADAS-2. The review of signaling questions was undertaken prior to the assessment of the risk of bias.

The modified signaling questions and a standardized guide of decision rules was developed to assist in the consistency of evaluating studies for risk of bias (see Appendix E).

Assessment of Risk of Bias: Prognosis Studies

The risk of bias of prognosis studies was assessed using a modified version of the guidelines proposed by Hayden et al.[58] This set of guidelines lists six potential areas of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, measuring and accounting for confounding, and appropriateness of statistical analysis. Within each bias area are two to three domains, or items encompassed by the bias (Appendix E). To enhance the appropriateness of these guidelines for this systematic review, several modifications to the guidelines were made prior to commencing the assessment of risk of bias. These modifications included the addition of a criterion for study design and modifications to the application of the bias some domains within the prognostic factor measurement area. As well, the number of response options were reduced from four to three by eliminating the "partly" response and retaining only the "yes" (low risk of bias), "no" (high risk of bias), and "unclear" responses.[59]

Raters used the simplified response options to first assess each of the signaling questions, followed by a global assessment of each of the seven potential areas of bias. Each bias was globally rated based on the lowest rating for any one of the signaling questions. For example, for study participation, if two of the signaling questions were rated "yes" and one was rated "no," then the global bias rating for study participation would be rated as "no." The modified interpretation of the Hayden index questions and a standardized guide of decision rules was developed to assist in the consistency of evaluating studies for risk of bias in prognosis studies (see Appendix E). The Hayden index form is found in Appendix F.

Assessment of Risk of Bias for Randomized Controlled Trials

For RCTs, the Jadad scale[60] was used to assess the risk of bias and questions were added on allocation concealment, justification of sample size, use of intention-to-treat analysis, and reporting of outliers. The response categories for the original and supplemental questions on the Jadad scales were maintained; the response options were used: "yes" (low risk of bias), "no" (high risk of bias), and "unclear" (medium risk of bias).

Data Synthesis and Presentation

Study results were presented in four key sections based on diagnosis (KQ1 and KQ2), prognosis (KQ3 to KQ5), treatment (KQ6), and biological variation (KQ7). All included studies were summarized in narrative form and in summary tables that contained key information on population characteristics, BNP test features, study outcomes, sample sizes, settings, funding sources, and comparator treatments (e.g., type, dose, duration, and provider).

The primary study paper was considered for statistical analysis in the case of multiple publications of the same study cohort. Results for BNP and NT-proBNP measurements were reported using pg/mL units. For example, conversions were made to pg/mL using the following: 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 KQ1 and KQ2. Quality scores were not used for weighting data in any of the analyses. For each primary study included in KQ1a and KQ2a, the following measures of test results were calculated on accuracy: sensitivities, specificities, LRs (positive LR^+ and negative LR^-), and DOR. The data were recorded in the form of a 2x2 table if the actual data (true positive (TP), false positive (FP), false negative (FN), and true negative (TN)) were reported, or where enough information was given to allow the calculation of these numbers. Sensitivity and specificity, DOR, and LR with 95% CIs, are recalculated for each primary study from the contingency tables.

All of the measures mentioned in the last paragraph were calculated across different cutpoints (manufacturer cutpoints, optimum cutpoints, and maximized sensitivity) and by study setting (emergency department and primary care) for BNP and NT-proBNP separately. Published papers used four different types of assay for measuring BNP, so analyses were performed by assay type. However, only a single assay was used for measuring NT-proBNP, so combined results are presented. Extracted data were pooled using exact binomial rendition[61] of the bivariate mixed-effects regression model developed by van Houwelingen[62,63] and modified for synthesis of diagnostic test data.[64] It fits a two-level model, with independent binomial distributions in each study and a bivariate normal model for the logit transforms between studies. Summary sensitivity, specificity, and the corresponding positive likelihood, negative likelihood and DORs are derived as functions of the estimated model parameters. The Deeks' method assesses the publication bias by performing linear regression of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry in diagnostic meta-analyses and a non-zero slope coefficient is suggestive of significant small study bias.[65] For KQ1a and KQ2a, Deeks tests were used to investigate (both graphically and statistically) whether publication bias or other small study effects may have adversely affected the results.

The initial analyses considered the level of statistical heterogeneity across the individual studies that were included in the meta-analysis. The Cochrane's Q test and I^2 statistics were used to assess the statistical heterogeneity among studies included in meta-analyses.[66] Moderate-to-high statistical heterogeneity was observed in many of the meta-analyses and results were reported using the random effects model. Subgroup analyses and stratification were carried out to further explore the causes of heterogeneity. Multivariable meta-regression analysis was also employed to investigate which study characteristics might have influenced heterogeneity. Publication year, assay type, and either one of the cutpoints (lowest, optimum, or manufacturer) were considered in the meta-regression model. All statistical analyses were carried out using Stata/SE 12.0 for Windows (Stata Corporation) and Meta Package.[67]

The study results were summarized in a summary ROC (SROC) curve, which shows the possible correlation between the sensitivity and specificity of diagnostic tests. Areas under the SROC curves were used as a measure of the diagnostic performance of the tests.[68] DOR was calculated and pooled using the generalized linear mixed (GLM) model approach to bivariate meta-analysis of sensitivity and specificity suggested by Chu and Cole.[61] This approach corresponds to the empirical Bayes approach to fitting the hierarchical summary receiver operating curve (HSROC) model.[69]

Evaluating the Strength of Evidence

Grading the strength of the body of evidence was conducted as per the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews[40] and the Methods Guide for Medical Test Reviews.[41] The strength of evidence (SOE) in KQ1, 2, and 6 was graded. For diagnostic studies the outcomes of sensitivity and specificity were addressed and all-cause mortality for KQ6. Key Questions 3 to 5 were omitted because criteria to evaluate and score prognostic studies have not been fully developed.[41] KQ7 was also omitted because it asks about biological variation rather than a clinical or diagnostic outcome.

For outcomes in KQ1, 2, and 6, the SOE was graded in four domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, unknown, or not applicable), directness (direct or indirect), and precision of the evidence (precise or imprecise).[40,41]

The overall SOE for each outcome in KQ1, 2, and 6 was rated as high, moderate, low, or insufficient.[40] The definitions for the strength ratings are listed below:

- High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate effect and is likely to change the estimate.
- Insufficient: Evidence either is unavailable or does not permit a conclusion.

Applicability

The key attributes of applicability of the key research questions were determined a priori with respect to the population, intervention, comparator, and outcome in the context of a wider spectrum of patients that would likely benefit from these interventions in "real world" conditions.

Population characteristics to which these findings are applicable include:

- Men and woman older than 18 years of age
- People with a suspected HF admitted to emergent care or primary care settings
- People with decompensated or stable HF

Population characteristics to whom the findings of this review are not applicable include:

- For KQ1 and KQ2: Adults of either sex who have a primary diagnosis of HF.

Intervention characteristics that these findings are applicable to include:

- Studies that used BNP and NT-proBNP assays that are currently approved by the FDA.

Intervention characteristics to whom these findings do not apply include:

- Studies that used BNP and NT-proBNP assays that are not currently approved by the FDA.

Comparator for which these findings are applicable include:

- Studies that used any type of intervention to assess for HF or people who were treated for HF by any particular method.

Reporting the Review

The Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines[70] were followed to report the introduction and methods of this review. Although PRISMA is designed to guide the reporting of systematic reviews that examine the benefits and harms of health care interventions rather than reviews of diagnostic and prognostic studies,[71] PRISMA was used as the basis for reporting the results and discussion for all of the KQ.

Peer Review and Public Commentary

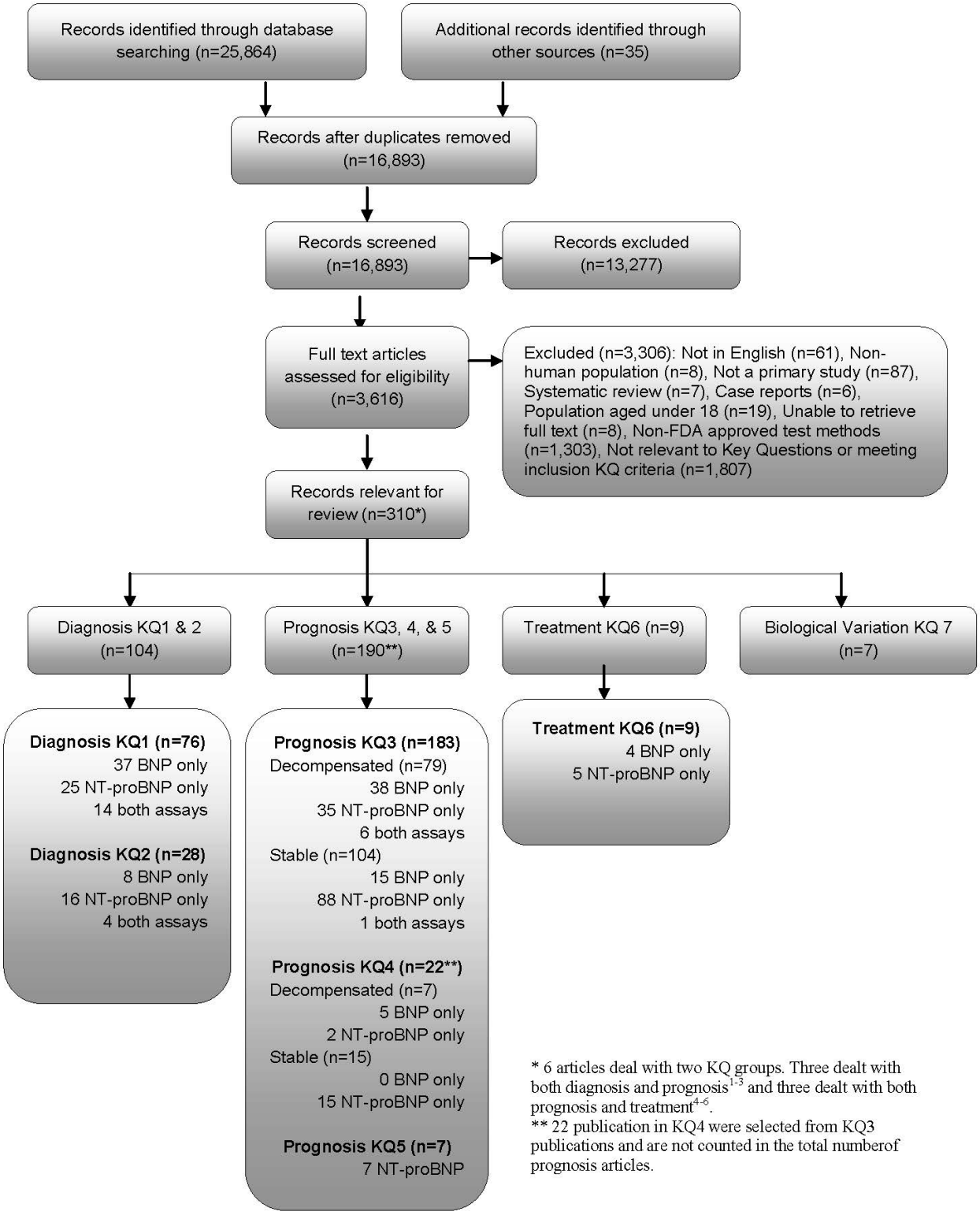
Clinical experts, experts in epidemiology, medical specialties, researchers, and individuals representing stakeholder and user communities were invited to provide external peer review. The AHRQ TOO and an associate editor also provided comments prior to submission for peer review. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. All reviewer comments were addressed, involving revising the text as appropriate, and documenting everything in a disposition of comments report that was made available on the AHRQ Web site 3 months after the posting of the final report.

Results

The search yielded 25,864 records identified from six bibliographic databases (Figure 2). An additional 35 records were identified from three grey literature sources: regulatory agency Web sites, clinical trial databases, and conference sources. After duplicates were removed, a total of 16,893 records were screened at title and abstract level; a total of 3,616 citations moved on to be screened at full text. Following the application of full text screening criteria, there were 310 eligible papers for all research questions in this review. See Appendix G for list of all excluded articles.

A total of 104 papers were allocated for diagnostic accuracy, and from these 76 articles were evaluated for Key Question (KQ) 1, and 28 for KQ2. For KQ3, KQ4, and KQ5, 190 articles were eligible to address the research questions related to prognosis; from these 183 were eligible for KQ3, 22 for KQ4, and seven publications for KQ5. A total of nine articles were evaluated for treatment guided by BNP or NT-proBNP for KQ6, and seven articles for KQ7 focusing on biological variation.

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



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

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

Sample and Design Characteristics of Papers Assessing BNP

There were 51 publications that met the criteria for KQ1 and examined cutpoints for BNP. Thirty-seven examined BNP only[3,72-107] and 14 examined both BNP and NT-proBNP.[108-121] See Appendix H KQ1 Evidence Set.

Study Design

Prospective study designs included two randomized controlled trials (RCT)[97,102] and nine cohort studies.[92,98,106,116-121] The remaining papers (n=40) used a cross-sectional design. The selected articles were published between 2001 and 2011 and were conducted in a wide range of regions: nine in North America,[72,82,83,90,101,105,107,117,120] twenty-two in Europe[74,79,85,87,88,94,96,100,102-104,106,109-115,118,119,121] two in Asia,[86,95] one in South America,[78] two in Australia,[89,97] and one in New Zealand.[108] Thirteen papers were conducted in multinational sites[3,73,75-77,80,81,84,91-93,98,99] and one was unclear as to region of conduct.[116]

Population Characteristics

Most articles, with the exception of ten,[74,84,87,90,91,96,109,115,119,120] provided diagnostic information on the overall study sample. Some papers provided diagnostic information on populations grouped according to age,[73,74,85,89,101,111,113,119] sex,[73,74] and ethnicity.[73]

Some papers presented diagnostic information according to body mass index (BMI) status,[91,101,102] diabetes status,[84] previous history of heart failure (HF),[72,89,96] permanent/paroxysmal atrial fibrillation (AF),[92] renal function/estimated glomerular filtration rate (eGFR),[101,109,113,114,120] history of hypertension or blood pressure elevation on admission,[99] and left ventricular ejection fraction (LVEF).[116] Three papers included information on HF populations.[76,100,102]

In all papers, study patients presented to emergency departments with shortness of breath and were 18 years of age and older. Seventeen articles had a patient population with mean or median ages from 60 to 69 years old[72,73,75-77,79-81,83,84,91,93,99,104,118,121,122] and 14[74,78,87,89,95-97,101,102,106-109,114] had populations with mean or median age ranges between 70 and 79. Four studies had a mean or median patient population over 80 years of age[85,94,105,112] and ten did not report on age of study population.[3,82,86,88,90,98,116,117,119,120] Six articles reported ages in the following ranges: 65 to 100,[111] 43 to 90,[113] 67 to 82,[123] 58 to 82,[110] 68 to 82,[100] and 30 to 95 years.[103]

The percentage of males enrolled in each study ranged from 5.6 percent[84] to 100 percent[72] (mean=66.2%; median=66.2%). Sample size populations (including subpopulations) ranged from 9[89] to 1,614[3] (mean=404, median=251). The prevalence of HF in the study populations ranged from 8.3 percent[100] to 84 percent[96] (mean=45.1%; median=46.6%).

Component Articles

Of the 51 selected papers, 11 used data from the Breathing Not Properly Multinational Study,[73,75-77,80,81,84,91-93,99] three used data from the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study,[96,102,106] one from the Biomarkers in Acute Heart Failure (BACH) study,[3] and one from the BNP in Shortness of Breath study.[97] One article used data from the Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment (HEARD-IT) study,[98] and one was from the epidemiological study of acute dyspnea in elderly patients (EPIDASA) study.[85] One set of authors published results on the same data sets[114,119] and the remaining articles (n=31) were independent papers, publishing results on unique data sets.

Assays Tests

Seven articles used the Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA)),[95,97,98,100,106,110,115] five used the TRIAGE-B-Type Natriuretic Peptide (BNP) test for the Beckman Coulter Immunoassay Systems,[3,103,116,118,121] two used the I-STAT BNP test,[101,107] two used the ADVIA-Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay,[98,113] and two used the ADVIA-Centaur® B-Type Natriuretic Peptide (BNP) Assay.[88,98] The remaining papers (n=35) used the TRIAGE-B-Type Natriuretic Peptide (BNP) test.

Diagnosis of Heart Failure in Papers

The majority of articles (n=45) based the diagnostic reference standard on clinical judgment.[3,72-81,83-85,87,89-99,101-104,106-109,111-121] Of these 45 articles, most (n=34) had a reference standard agreed upon by at least two physicians (mostly cardiologists), ten based the final diagnosis on the opinion of a single cardiologist or other type of clinician,[72,78,89,96,102,107,109,118-120] and one article did not indicate this information.[121] The adjudication physicians each arrived at a diagnosis of HF based on their interpretation of all available clinical data; this often included echocardiography results. One article[106] included BNP in the data used for adjudication. Of the 45 papers using clinical judgment to make the final diagnosis, the Framingham criteria were used in 15, and the National Health and Nutrition Examination Survey (NHANES) was used in 10.

Of the remaining articles (n=6), three based the final diagnosis of HF both on clinical judgment and results of echocardiography,[82,88,100] one based it on echocardiography results alone,[86] one reported that the definitive diagnosis was based on the Framingham criteria,[110] and one reported that the HF status was based on discharge diagnosis.[105]

BNP: Test Performance and Optimal Cutpoints in Emergency Department

Diagnostic Properties in BNP

The 51 papers evaluating BNP in the emergency department used several cutpoints ranging from 12.5[86] to 983.5[86] pg/mL or ng/L (mean=213.1; median=162). One study measured BNP in pmol/L and had cutpoints ranging from 20 to 100.[108] These were converted to pg/mL for analysis. Reported sensitivities ranged from 36 percent[92] to 100 percent[74,78,86,89,113] (mean=82.4 percent; median=86 percent), specificities from 14 percent[76] to 99 percent[96] (mean=75.4 percent; median=79.5%), and areas under the curve (AUC) of 0.08[92] to 0.99[78,82] (mean=0.84; median=0.89). Of the 51 papers looking at BNP, 14 also looked at NT-proBNP.[88,108-120] Appendix H Tables H-1 and H-2 present summary tables of these studies.

The majority of papers reported on the Triage BNP Point-of-Care test. Two papers reported on the Triage BNP test licensed to Beckman Coulter for use on their laboratory instruments.[3,103] Four papers reported using the Abbott AxSYM,[97,100,101,110] and one reported using the ADVIA-Centaur system.[88] Gorissen et al.[113] reported on two systems (ADVIA-Centaur and Triage).

Data were extracted, 2x2 tables prepared, and forest plots of sensitivities, specificities, positive and negative likelihood ratios (LRs), diagnostic odds ratios (DORs), and summary receiver operator characteristic (ROC) curves are presented (see Appendix H Figures H-1 to H-12). Three cutpoints were selected: lowest presented, manufacturers' suggested, and the optimal cutpoint as chosen by the authors.

If the lowest cutpoint presented by the authors is chosen, all papers except four[111,113,119,120] return sensitivities greater than 90 percent (summary estimate 95 percent, (95% confidence interval (CI) 93 to 97 percent)). Negative LRs (LR^-) were all less than 0.20 for this group. Overall, specificity was lower and much more variable, ranging from 27 to 88 percent (summary estimate 67 percent (95% CI, 58 to 75 percent)).

Among papers that reported a sensitivity less than 90 percent, Ray et al.[111] and Chevenier-Gobeaux et al.[119] enrolled patients older than 65 years. Both papers used higher cutpoints than most other papers (Ray: 250 pg/mL; Chevenier-Gobeaux: 270 pg/mL 65-84 years, and 290 pg/mL >85 years). deFilippi et al.[120] enrolled a population with a high prevalence (47 percent) of subjects with eGFR <60 mL/min/1.73 m^2. Gorrison et al.[113] reported using the ADVIA-Centaur and Triage assay systems. They also selected a high cutpoint (225 pg/mL) and report a sensitivity of 65 percent and 73 percent, below all other papers.

Using package inserts, 501(k) submission forms, and product brochures, we determined the manufacturers' recommended cutpoints. In all cases the manufacturer suggested a cutpoint of 100 pg/mL to rule out the diagnosis of HF. Twenty-one papers reported for this cutpoint. Sensitivities ranged from 86 to 100 percent (summary estimate 95 percent (95% CI, 93 to 96%)), and specificities ranged from 31 to 97 percent (summary estimate 66 percent (95% CI, 56 to 74 percent)).[3,74,79,81-83,85,86,88,89,93,95-97,101,104,107,108,110,112,114]

Twenty-eight papers[3,74,77-79,81-83,85,86,89,91,93-98,100,104,108,110-114,119,120] examined an optimal cutpoint. The majority (n=19) of the studies determined a cutpoint that maximized accuracy, either using an ROC curve or by examining several arbitrary cutpoints[74,77-79,81-83,85,86,94,96,97,108,110-113,119,120] Three studies maximized sensitivity,[89,93,104] three others used the manufacturers' suggested cutpoint or other accepted threshold[3,91,114] and one study used multiple logistic regression,[95] one set the sensitivity at 90 percent and determined specificity,[100] and one set the sensitivity at 96 percent in all subgroups and determined specificity.[98] Sensitivities ranged from 65 percent to 100 percent (summary estimate 91 percent (95% CI, 88 to 94 percent)), specificities ranged from 34 percent to 97 percent (summary estimate 80 percent (95% CI, 74 to 85 percent)). Using the optimal cutpoint resulted in a higher overall estimate of the positive LR (LR^+ (4.61, 95% CI, 3.49 to 6.09) compared to either the lowest cutpoint (2.85 (95% CI, 2.23 to 3.65)), or the manufacturer cutpoint (2.76 (95% CI, 2.12 to 3.59)). The LR^- was not significantly different ($p>0.05$).

Choosing the lowest, manufacturer, or the optimal cutpoint had little effect on the diagnostic performance of the test. The test displayed high sensitivity and a high LR^-, but a low specificity and LR^+.

BNP: Determinants of Test Performance in Emergency Department

The effect of various determinants upon the diagnostic performance of BNP for the diagnosis of HF were examined.

Age

Eight articles[73,74,85,89,101,111,113,119] examined the relationship between age and BNP. In all cases, increasing age was associated with an increase in BNP concentration, but the correlation of age with the diagnostic performance of the test was not clear in the papers.

Six papers examined the effect of age on the AUC (Table 1).[73,74,85,89,113,119]

Table 1. Effect of age on AUC for BNP

Author, Year	Assay	Age	AUC	95% CI
Maisel,[73] 2004	Triage	18 to 69	0.915	0.869 to 0.934
		70 to 105	0.844	0.813 to 0.875
Knudsen,[74] 2004	Triage	41 to 75	0.88	0.80 to 0.97
		76 to 96	0.82	0.73 to 0.92
		≥76	0.82	0.73 to 0.92
		≤76	0.88	0.80 to 0.97
Ray,[85] 2004	Triage	≥65	0.87	0.793 to 0.955
Chung,[89] 2006	Triage	<79	0.88	0.80 to 0.97
		≥79	0.85	0.76 to 0.94
		80 + 5	0.85	0.76 to 0.94
		70 + 9	0.88	0.80 to 0.97
Gorissen,[113] 2007	Triage	<65	0.750	
		65 to 75	0.795	
		>75	0.765	
	Centaur	<65	0.705	
		65 to 75	0.773	
		>75	0.767	
Chenevier-Gobeaux,[119] 2008	Triage	<85	0.835	0.778 to 0.882
		≥85	0.797	0.738 to 0.860

Abbreviations: AUC = area under the curve; BNP=B-type natriuretic peptide; CI = confidence interval; KQ = Key Question

Four papers[73,101,111,119] examined different decision cutpoints based upon age, each using different reasoning and criteria (Table 2). Maisel et al.[73] suggested cutpoints no greater than 100 pg/mL for both age groups, above and below 70 years of age. These decision points maximized sensitivity, with specificity being the second concern. Their reasoning was that a false negative result was less desirable than a false positive in terms of cost to the patient.

Rogers et al.[101] using the manufacturers' suggested cutpoint of 100 pg/mL, established the sensitivity of the entire cohort at 91 percent. To achieve 91 percent sensitivity in those 75 years of age and older, the decision point was set at 184 pg/mL. The specificity at this point was 54 percent.

Chenevier-Gobeaux[119] examined the very elderly, 85 years of age and older, compared with those aged 65 to 84. For the younger group, the optimal cutpoint was 270 pg/mL (sensitivity 73%, specificity 83%), whereas for the very elderly the optimal cutpoint was 290 pg/mL (sensitivity 80%, specificity 69%).

For those aged 65 and older, Ray et al.[111] established an optimal cutpoint of 250 pg/mL (sensitivity 73%, specificity 91%). In an earlier paper,[85] these authors also established an optimal

cutpoint of 250 pg/mL (sensitivity 78%, specificity 90%). It is not clear if these publications used independent study populations.

Gorissen et al.[113] examined two different BNP assays and divided their population into three age groups. For the Triage assay, the optimal cutpoint for those less than 65 years was 91 pg/mL (sensitivity 55%, specificity 100%), for those 65 to 75 years of age it was 260 pg/mL (sensitivity 83%, specificity 82%), and for those greater than 75 years the optimal cutpoint was 309 mg/mL (sensitivity 71%, specificity 68%). Similarly, for the Siemens Centaur assay the cutpoints were 91 mg/mL (sensitivity 55%, specificity 100%), 188 pg/mL (sensitivity 83%, specificity 73%), and 247 pg/mL (sensitivity 77%, specificity 68%) respectively.

Table 2. Effect of age on diagnostic performance of BNP

Author Year	Assay	Age	Decision Point pg/mL	Sensitivity %	Specificity %
Maisel,[73] 2004	Triage	18 to 69	100	86.3	81.6
			200	76.9	90.9
			300	68.8	93.8
			400	59.5	94.7
		70 to 105	100	93.6	53.3
			200	84.8	72.0
			300	75.3	77.0
			400	65.1	83.1
Ray,[111] 2005	Triage	>65	250	73	91
Rogers,[101] 2009	iSTAT	>75	100	94	41
			184	91	66
Chenevier-Gobeaux,[119] 2008	Triage	65 to 84	270	73	83
		>85	290	80	69

Abbreviations: BNP=B-type natriuretic peptide; pg/mL = picograms per milliliter

All authors reported that the optimal BNP threshold for diagnosis of HF increases with age, but there is no consensus on how to set the threshold.

Sex

Two papers examined sex and BNP[73,74] (Table 3). Maisel et al.[73] reported that the difference in BNP concentrations between men and women was not significant. Knudson et al.[74] noted differences in sensitivity between males and females using 100 pg/mL as the decision point (males: sensitivity 94.3%, specificity 54.9%; females: sensitivity 90.0%, specificity 55.2%).

Table 3. Effect of sex on AUC for BNP

Author, Year	Sex	AUC	95% CI
Maisel,[73] 2004	Male	0.918	0.900 to 0.937
	Female	0.870	0.844 to 0.897
Knudsen,[74] 2004	Male	0.90	0.82 to 0.97
	Female	0.86	0.78 to 0.93

Abbreviations: AUC = area under the curve; CI = confidence interval

Ethnicity

One study examined the effect of ethnicity on the diagnostic properties of BNP. Maisel et al.[73] reported that the prevalence of HF in their population was significantly greater among whites than among African Americans. Similarly, the concentration of BNP in the white

population was significantly greater than in the African American population (200 vs. 117 pg/mL, p<0.001). The AUC is shown in Table 4.

Table 4. Effect of ethnicity on AUC for BNP

Author, Year	Ethnicity	AUC	95% CI
Maisel,[73] 2004	White	0.888	0.865 to 0.912
	Black	0.903	0.881 to 0.926

Abbreviations: AUC = area under the curve; BNP=B-type natriuretic peptide; CI = confidence interval

Obesity/Body Mass Index

Three papers[91,101,102] examined the effect of obesity on the diagnostic properties of BNP. All three showed that increasing BMI was associated with reduced BNP concentrations. This was true if BMI and BNP were examined in the whole population,[101,102] or if the population was examined in two groups: those with and without HF.[91]

Daniels et al.[91] examined the diagnostic properties using a fixed decision point of 100 pg/mL. The sensitivity decreased, but the specificity increased as the BMI increased. In this study the decision points to achieve 90 percent sensitivity was 170 pg/mL for BMI less than 25 kg/m^2, 110 pg/mL for BMI 25 to 35 kg/m^2, and 54 pg/mL for BMI greater than 35 kg/m^2. Specificity was greater than 70 percent in all three subgroups. Rogers et al.[101] also adjusted the decision point of the BMI greater than 35 kg/m^2 group to achieve the same sensitivity (91%) as the entire cohort (100 pg/mL). This decision point (25 pg/mL) resulted in a reduced specificity. Noveanu et al.[102] examined the diagnostic properties at two decision points, 100 and 500 pg/mL. Table 5 displays the diagnostic properties of these papers.

Table 5. Effect of body mass index on diagnostic performance of BNP

Author, Year	BNP Cutpoint (pg/mL)	BMI (kg/m^2)	Sensitivity %	Specificity %	AUC	95% CI
Daniels,[91] 2006	100	<25	93.5	64.5	0.90	0.88 to 0.93
		≥25 &<35	92.0	76.3	0.91	0.89 to 0.94
		>35	77.1	84.1	0.88	0.84 to 0.93
Rogers,[101] 2009	100	≥35	64	61		
	25		91	25		
Noveanu,[102] 2009	100	<30	96	56	0.884	0.80 to 0.96
		>30	91	68	0.885	0.84 to 0.92
	500	<30	73	89		
		>30	56	96		

Abbreviations: AUC = area under the curve; BMI = body mass index; BNP=B-type natriuretic peptide; pg/mL = picograms per milliliter; CI = confidence interval

Renal Function

Five papers[101,109,113,114,120] examined the relationship between renal function and the diagnostic properties of BNP. Four[109,113,114,120] examined eGFR (Table 6) and one[101] examined serum creatinine concentration. Three papers[109,114,120] optimized the decision point based on eGFR, two[109,114] maximized sensitivity, and one[120] maximized accuracy.

The BNP concentration was inversely related to renal function: as the eGFR decreased or creatinine concentration increased, the BNP concentration increased.

Table 6. Effect of renal function on diagnostic performance of BNP

Author, Year	BNP Cutpoint (pg/mL)	eGFR (ml/min/1.73m^2)	Sensitivity %	Specificity %	AUC	95% CI
Chenevier-Gobeaux,[109] 2005	90	89 to 60	88	76	0.841	
	480	59 to 30	81	74	0.798	
	515	29 to 15	89	82	0.890	
Gorissen,[113] 2007	Triage 202	>60	63	81		
	Triage 309	≤60	74	64		
	Centaur 127	>60	85	73		
	Centaur 229	≤60	70	64		
Chenevier-Gobeaux,[114] 2010	100	all subjects	99	41	0.82	0.79 to 0.88
	210	≥58.6	86	71	0.85	0.77 to 0.91
	280	44.3 to 58.5	88	72	0.86	0.78 to 0.91
	550	≤44.2	85	65	0.76	0.67 to 0.83
deFilippi,[120] 2007	100	≥60	89.9	36.8	0.75	0.70 to 0.79
	200	<60	82	53	0.68	0.63 to 0.74

Abbreviations: AUC = area under the curve; BNP=B-type natriuretic peptide; CI = confidence interval; eGFR = estimated glomerular filtration rate; mL/min/m2 = milliliter per minute per meters squared; pg/mL = picograms per milliliter

Using the recommended cutpoint of 100 pg/mL, Rogers et al.[101] reported a sensitivity of 100 percent and a specificity of 30 percent for those subjects with serum creatinine ≥2 mg/dL. They then adjusted the decision point for those subjects with serum creatinine ≥2 mg/dL to equal the sensitivity of the entire cohort using the recommended decision point of 100 pg/mL (sensitivity 91%, specificity 54%). This resulted in a cutpoint of 449 pg/mL (specificity 78%).

While these authors recognized that sex, ethnicity, obesity, and renal function have significant effects upon concentration of BNP and potentially on the diagnostic performance of BNP in the diagnosis of HF in the emergency department, all also recognized the difficulty in establishing multiple decision points.

Diabetes

One study[84] examined the effect of diabetes mellitus on the use of BNP for the diagnosis of HF. This study reported a nonsignificant difference in the AUC of 0.888 (95% CI, 0.860 to 0.912) for nondiabetics versus 0.878 (95% CI, 0.837 to 0.913) for diabetics.

Sample and Design Characteristics of Papers Assessing NT-proBNP

Thirty-nine articles met the criteria for KQ1 and examined NT-proBNP. Twenty-five examined NT-proBNP only[1,2,26,88,122,124-143] and 14 examined both BNP and NT-proBNP.[108-121] (Appendix H Table H-3).

Study Design

Eleven papers were prospective cohort studies,[116-122,135,136,139,143] one was case-control[131] and in two papers, the study design could not be determined.[132,141] The remaining papers (n=25) used a cross-sectional design. The selected articles were published between 2003 and 2011. Thirteen were conducted in North America,[1,117,120,125,127,128,130,132-134,136,138,139] 18 in Europe,[26,88,109-115,118,119,121,124,129,131,135,142,143] one in New Zealand,[108] two in Asia,[122,137] and one in Australia.[141] Two papers were conducted in multinational sites[2,126] and two were unclear as to region of conduct.[116,140]

Population Characteristics

Most papers, with the exception of ten,[109,119,120,126,127,130,137,139,140,142] provided diagnostic information on the overall study sample presenting to the emergency department with dyspnea. Some papers provided diagnostic information on populations grouped according to age,[2,113,119,122,129,133] sex,[127] and ethnicity.[127] Some presented diagnostic information according to BMI status,[126] renal function,[113,130] chronic obstructive pulmonary disease status (COPD)/HF history,[128] clinical certainty/uncertainty,[139] normal/abnormal chest radiograph,[134] with/without diabetes mellitus,[140] and NT-proBNP versus usual care.[125] Papers examined groups by eGFR readings,[109,113,114,120] LVEF readings,[116] and red cell distribution width.[137]

In all papers, patients presented to emergency department with shortness of breath and were 18 years of age and over. Twelve papers had a patient population with mean or median ages from 60 to 69 years[2,26,118,120-122,127,128,134,137,139,142] and 19 had mean or median ages between 70 and 79 years.[1,88,108-110,113-115,124-126,130-133,136,138,141,143] Five had mean populations aged 80 and over[111,112,119,129,135] and one had a population with a mean age under 60 years.[117] Two papers did not report age.[116,140]

The percentage of males enrolled in each study ranged from 39.0 percent[114] to 93.2 percent[110] (mean=53.3%; median=51.0%). Sample size populations ranged from 68[141] to 1,256[2] (mean=377, median=378). The prevalence of HF in the study populations ranged from 8.3 percent[144] to 63.5 percent[128] (mean=37.9%, median=34.9%).

Component Papers

Of the 39 selected papers, ten were from the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study,[1,2,127,128,130,132-134,139,140] two were from the Mannheim NT-proBNP Study (MANPRO),[26,142] one was from the International Collaborative of NT-proBNP (ICON) data set,[126] one was from the BACH study,[125] one was from the Improved Management of Patients with Congestive Heart Failure (IMPROVE CHF) trial,[136] and one came from the epidemiological study of acute respiratory failure in elderly patients (EPIDASA) study.[111] The remaining (n=23) were independent papers, publishing results on unique data sets.

Assays Tests

The majority of papers (n=35) used the ELECSYS® proBNP Immunoassay. Of the remaining papers, three used the DIMENSION-EXLTm N-terminal Pro-Brain Natriuretic Peptide (NTP) Flex® Reagent Cartridge (RF623)[26,142,145] and, in the case of one study, the assay used was not stated.[143]

Diagnosis of Heart Failure in Papers

The majority of papers (n=35) based the diagnostic reference standard on clinical judgment. Most of these (n=31) had a reference standard agreed upon by at least two physicians (mostly cardiologists) and five based the final diagnosis on the opinion of a single cardiologist or other type of clinician.[1,26,110,118,141] One study did not indicate the number or qualifications of the adjudicators.[122] The adjudication physicians each arrived at a diagnosis of HF based on their interpretation of all available clinical data; this often included echocardiography results. Of the papers judging final diagnosis using clinical judgment, (n=34) three used the Framingham,[110,136,143] two used the Boston Criteria,[135,143] one used the European Society of Cardiology guideline,[142] and one used the NHANES.[136]

Of the remaining papers (n=2), one based the final diagnosis of HF both on clinical judgment and echocardiography results[137] and one based it solely on the European Society of Cardiology guidelines.[131]

NT-proBNP: Test Performance and Optimal Cutpoints in Emergency Department

Diagnostic Properties in NT-proBNP

The 39 papers evaluating NT-proBNP in the emergency department used several cutpoints ranging from 100[26] to 6,550[109] pg/mL or ng/L. Reported sensitivities ranged from 53 percent[112] to 100 percent[88,112,114,127] (mean=85.1%; median=88%), specificities from 5 percent[112] to 100 percent,[113] (mean=70.9% ; median=73.2%), LR^+ from 1.05[112] to 115.03,[88] LR^- from 0.02[88,114] to 0.35,[119] and AUC of 0.6[116] to 0.99[2] (mean=0.88; median=0.89). Most of the papers (n=32) looked at NT-proBNP alone, with the exception of 15 that examined both BNP and NT-proBNP.[88,108-121] Appendix H Table H-4 presents summary data for those papers that examined NT-proBNP.

Of the 19 papers with diagnostic performance data,[2,26,88,108,110-115,119,122,124,129,131,135,138,141,143] 17 reported on data from the Roche NT-proBNP assay system. One[26] used the Dimension EXL system, and one[143] used the Roche Cardiac Reader point-of-care test.

Data were extracted, 2x2 tables prepared, and forest plots of sensitivities, specificities, LR^+ and LR^-, DOR, and summary ROC curves are presented (Appendix H Figures H-13 to H-24). Two cutpoints were selected: lowest presented, and the optimal cutpoint, as chosen by the authors to examine in greater detail.

The diagnostic performance was examined using the lowest cutpoint presented by each author in order to maximize the test sensitivity.

Nineteen papers used an optimal cutpoint in their analysis.[2,26,88,108,110-115,119,122,124,129,131,135,138,141,143] Eleven papers used a cutpoint to maximize accuracy, either using an ROC curve or with several arbitrary cutpoints. These points ranged from 825 to 2,000 pg/mL. Two studies[122,129] used two decision points; one at 300 or 1,200 pg/mL, respectively, to maximize sensitivity, and one at 900 or 4,500 pg/mL, respectively, to maximize specificity. Two papers chose 300 pg/mL, one[26] to maximize sensitivity, and one[114] chose this value as the "accepted" threshold. One study[143] used the Roche Cardiac Reader point-of-care assay and chose the cutpoint of 1,000 pg/mL but did not provide a reason.

NT-proBNP: Determinants of Test Performance in Emergency Department

The effect of various determinants upon the diagnostic performance of NT-proBNP for the diagnosis of HF for the 39 papers assessing NT-proBNP was examined.

Age

Januzzi et al.[2] determined two cutpoints to separate the population into three age groups. For those less than 50 years of age, 450 pg/mL was determined as the best cutpoint to rule out HF (maximum sensitivity). For those 50 to 74 years of age, they chose 900 pg/mL as the best combination of sensitivity and specificity to maximize test accuracy, and for those 75 years of age or older, 1,800 pg/mL provided the maximum specificity in order to rule in HF. Two other papers[138,141] adopted this protocol as the optimal cutpoints. Using this approach did not appear to result in significantly improved diagnostic performance compared with the overall estimate. Table 7 shows the diagnostic performance of these papers compared to the overall estimate of the entire group of NT-proBNP papers.

Table 7. Effect of age optimized cutpoints on diagnostic performance of NT-proBNP

Author, Year	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Natural log DOR (95% CI)
Januzzi,[2] 2006	0.90 (0.88 to 0.92)	0.84 (0.81 to 0.87)	5.63 (4.63 to 6.84)	0.12 (0.10 to 0.15)	3.86 (3.52 to 4.19)
Liteplo,[138] 2009	0.85 (0.71 to 0.93)	0.63 (0.50 to 0.75)	4.29 (1.58 to 3.33)	0.24 (0.11 to 0.51)	2.27 (1.24 to 329)
Robaei,[141] 2011	0.81 (0.63 to 0.92)	0.66 (0.51 to 0.79)	2.38 (1.50 to 3.79)	0.29 (0.13 to 0.65)	2.11 (0.95 to 3.27)
Overall Estimate	0.88 (0.84 to 0.91)	0.73 (0.64 to 0.82)	3.53 (2.41 to 519)	0.18 (0.13 to 0.29)	3.10 (2.67 to 3.53)

Abbreviations: DOR = diagnostic odds ratio; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; NT-proBNP=N-terminal pro-B-type natriuretic peptide

Compared to the lowest cutpoint, the optimal cutpoint displayed a higher overall estimate of specificity and LR^+, but was not significantly different in other performance indicators. These data are presented in Table 8.

One study[122] used two cutpoints (900 pg/mL >50 years and 450 pg/mL <50 years) for rule in, and a single cutpoint (300 pg/mL) for rule out.

Table 8. Effect of cutpoint on diagnostic performance of NT-proBNP

	Lowest Cutpoint (95% CI)	Optimal Cutpoint (95% CI)
Sensitivity %	0.92 (0.90 to 0.95)	0.88 (0.84 to 0.91)
Specificity %	0.56 (0.43 to 0.67)	0.73 (0.64 to 0.82)
LR-	0.13 (0.08 to 0.21)	0.18 (0.13 to 0.23)
LR+	2.29 (1.72 to 3.07)	3.53 (2.41 to 5.19)
Natural log DOR	3.04 (2.53 to 3.54)	3.10 (2.67 to 3.53)
AUC	0.890 (0.850 to 0.930)	0.814 (0.86 to 0.92)

Abbreviations: AUC = area under the curve; DOR = diagnostic odds ratio; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; NT-proBNP=N-terminal pro-B-type natriuretic peptide

Six papers[2,113,119,122,129,133] reported on the effect of age on the performance of NT-proBNP in the diagnosis of HF.

Berdagué et al.[129] examined subjects 70 years of age and older, and proposed the use of two decision points for this population: a lower decision point of 1,200 pg/mL to maximize sensitivity (97%) and an upper point of 4,500 pg/mL to maximize specificity (86%). Patients with values in the intermediate "gray" zone required further investigation. A single decision point of 2,000 pg/mL resulted in a test accuracy of 80 percent, deemed unacceptable by the authors of this report.

Januzzi et al.[133] examined decision points based on age to optimize rule in, the single cutpoint proposed by the manufacturer, as well as independently generated decision points to evaluate rule out capabilities of the test (Table 9). Januzzi et al.[2] used data from the ICON study, an international collaboration that includes data from the PRIDE study,[133] which reported separate, selected decision cutpoints that emphasized sensitivity for younger patients and specificity for older ones. They proposed three decision points for age groups under 50, 50 to 75, and older than 75 years to rule in the diagnosis and a single point to rule out. Shaikh et al.[122] optimized rule-in cutpoints based on age <50 and >50, but used a single rule-out cutpoint regardless of age. Gorrison et al.[113] also suggested that the decision points be increased as the age of the patient increases. Chevenier-Gobeaux et al.[119] examined the very elderly (≥85 years of age) and proposed distinct decision points (2,800 pg/mL vs. 1,700 pg/mL) for those over and under 85 years of age (Table 9).

Table 9. Effect of age on diagnostic performance of NT-proBNP

Author, Year	Age	Decision point pg/mL	Sensitivity %	Specificity %	AUC	95% CI
Berdague,[129] 2006	≥70	1,200	97	55	0.860	NR
		2,000	87	72	NR	NR
		4,500	64	86	NR	NR
Januzzi,[133] 2005	Overall	900	90	85	0.94	NR
	<50	450	93	95	NR	NR
	≥50	900	91	80	NR	NR
	Overall rule out	300	99	68	NR	NR
Januzzi,[2] 2006	Overall	Age optimized	90	84	NR	NR
	<50	450	97	93	0.99	NR
	50-75	900	90	82	0.93	NR
	≥75	1,800	85	73	0.86	NR
	Overall rule out	300	99	60	NR	NR
Gorissen,[113] 2007	Overall	1,550	80	65	0.774	NR
	<65	591	55	100	0.614	NR
	65-75	1,922	75	73	0.750	NR
	≥75	1,737	71	84	0.831	NR
Chenevier-Gobeaux,[119] 2008	<85	NR	NR	NR	0.786	0.737 to 0.835
	≥85	NR	NR	NR	0.787	0.726 to 0.848
	≥85 Rule out	1,750	85	59	NR	NR
	≥85 Optimal	2,800	74	70	NR	NR
	≥85 Rule in	6,000	53	NR	NR	NR

Table 9. Effect of age on diagnostic performance of NT-proBNP (continued)

Author, Year	Age	Decision point pg/mL	Sensitivity %	Specificity %	AUC	95% CI
Shaikh,[122] 2011	<50 Rule in	450	100	33	NR	NR
	>50 Rule in	900	96	86	NR	NR
	Overall rule out	300	100	42	NR	NR

Abbreviations: AUC = area under the curve; CI = confidence interval; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NR = not reported; pg/mL = picograms per milliliter

Sex and Ethnicity

Krauser et al.[127] examined the influence of ethnicity and sex on the diagnostic properties of NT-proBNP. They reported that the AUC was not different for men versus women or for African Americans versus non-African Americans. There was no difference in the median NT-proBNP concentration between men and women. Similarly, there was no difference in the median concentration between African Americans and non-African Americans.

Obesity/Body Mass Index

A single paper[126] examined the effect of obesity and BMI on NT-proBNP performance (Table 10). Using age-specific decision points previously identified, this substudy of the ICON study divided the population into three BMI groups and then calculated the LR^+ for each group. Using the overall rule out decision point, they calculated LR^-.

They commented that the age-adjusted decision points performed well over a wide variety of BMI. Despite lower sensitivity at the high range of BMI, the predictive values were unchanged.

Table 10. Effect of body mass index on diagnostic performance of NT-proBNP

Author, Year	BMI	LR+	LR-	AUC	95% CI
Bayes-Genis,[126] 2007	<25	5.34	0.02	0.94	0.91 to 0.96
	25 to 29.9	13.32	0.03	0.95	0.93 to 0.96
	≥30	7.54	0.08	0.94	0.92 to 0.94

Abbreviations: AUC = area under the curve; BMI = body mass index; CI = confidence interval; NT-proBNP=N-terminal pro-B-type natriuretic peptide; LR- = negative likelihood ratio; LR+ = positive likelihood ratio

Renal Function

Two papers[113,130] examined the relationship between renal function, expressed as eGFR, and NT-proBNP for the diagnosis of HF (Table 11). Both papers noted an inverse relationship between renal function and NT-proBNP concentration. The relationship was less robust among those with HF than those without. Anwaruddin et al.[130] in a substudy of the PRIDE cohort, used the age-adjusted decision points from the main study to determine diagnostic parameters. Gorrison et al.[113] used the ROC curve to establish the optimal decision points.

Table 11. Effect of renal function on diagnostic performance of NT-proBNP

Author, Year	eGFR mL/min/1.73 m^2	Decision point pg/mL	Sensitivity %	Specificity %	NPV	AUC
Anwaruddin,[130] 2006	≥60	Age adjusted	85	88	NR	0.95
	<60	Age Adjusted	97	68	NR	0.88
	≥60	300	NR	NR	100	NR
	<60	300	NR	NR	94	NR
Gorissen,[113] 2007	>60	1,118	85	73	NR	0.781
	≤60	2,592	70	64	NR	0.702

Abbreviations: AUC = area under the curve; eGFR = estimated glomerular filtration rate; mL/min/m2 = milliliter per minute per meters squared; NPV = negative predictive value; NT-proBNP=N-terminal pro-B-type natriuretic peptide; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; pg/mL = picograms per milliliter

Assessment of Quality for Papers With Emergency Department Settings

BNP

The QUADAS-2[146] was used to assess quality in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias (low, high, unclear) and concerns regarding applicability (low, high, unclear), with associated signaling questions to help with bias and applicability judgments (Figures 3 and 4, and Appendix H Table H-5).

The potential for bias in the domain of **patient selection** was assessed on the basis of the enrollment of the study sample (consecutive, random, or convenience), the avoidance of case-control design, and the avoidance of inappropriate patient exclusions. For this domain, 25 percent of papers (n=13) were rated as low risk for bias and 20 percent (n=10) were rated as high risk. The remaining papers (n=28; 55%) were rated as unclear as to risk of bias. Papers were assessed as to patient population applicability to those targeted by the review question in terms of severity of the target condition, demographic features, presence of differential diagnosis or comorbid conditions, and setting of the study. Overall, 33 percent (n=17) of papers were assessed as high risk of bias for concerns about applicability on this domain and 57 percent (n=29) were rated as low on concern. The remaining 10 percent (n=5) were deemed unclear on the domain of applicability for patient selection.

The potential for bias in the domain of the **index test** was assessed according to whether results were interpreted without knowledge of the results of the reference standard and whether a prespecified threshold was used for BNP cutpoints. Seventy-one percent (n=36) of papers were rated as high risk, 20 percent were rated as low risk (n=10), and 9 percent were rated as unclear (n=5) on this domain. Papers were assessed on concerns of applicability on the basis of whether the index test methods varied from those specified in the review questions. Concerns about applicability on this domain were assessed as low for 76 percent (n=39) of papers, as high for 22 percent (n=11), and as unclear for 2 percent (n=1).

The potential for bias in the domain of the **reference standard** (i.e., the criteria used to confirm a diagnosis of HF) was judged on the basis of whether the reference standard was likely to correctly classify the target condition and whether the results were interpreted with knowledge of the BNP marker results. Papers were rated as low risk for 94 percent (n=48), as high risk for 4 percent (n=2), and as unclear for 2 percent (n=1). Concerns about applicability were assessed as to whether the target condition, as defined by the reference standard, differed from the target condition specified in the review question. Seventy-eight percent (n=40) of papers were assessed as low and 22 percent (n=11) were assessed as high on this domain.

The potential for bias in the domain of **flow and timing** was assessed on the basis of inappropriate intervals between index test and reference standard, standardized administration of reference standard among patients, and equal inclusion of patients in the analysis. Papers were assessed as low risk of bias for 69 percent (n=35), as high for 20 percent (n=10), and as unclear for 12 percent (n=6) of papers.

NT-proBNP

For papers of diagnostic tests of NT-proBNP (KQ1), QUADAS-2[146] was used to assess quality in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias (low, high, unclear) and concerns regarding applicability (low, high, unclear), with associated signaling questions to help with bias and applicability judgments (see Figures 5 and 6, and Appendix H Table H-6).

The potential for bias in the domain of **patient selection** was assessed on the basis of enrollment of study sample (consecutive, random, or convenience), the avoidance of a case-control design, and the avoidance of inappropriate patient exclusions. For this domain, 28 percent of papers (n=11) were rated as low risk for bias and 46 percent (n=18) were rated as high risk. The remaining papers (n=10; 26%) were rated as unclear as to risk of bias. Papers were assessed as to patient population applicability to those targeted by the review question in terms of severity of the target condition, demographic features, presence of differential diagnosis or comorbid conditions, and setting of the study. Overall, 33 percent (n=13) of papers were assessed as high for concerns about applicability on this domain, 64 percent (n=25) were rated as low, and five percent (n=2) were rated as unclear on concern.

The potential for bias in the domain of the **index test** was assessed according to whether results were interpreted without knowledge of the results of the reference standard and whether a prespecified threshold was used for NT-proBNP cutpoints. Slightly more than half of papers (n=22, 57%) were rated as high risk on this domain, 28 percent were rated as low (n=11), and 15 percent were rated as unclear (n=6). Papers were assessed on concerns of applicability on the basis of whether the index test methods varied from those specified in the review questions. Concerns about applicability on this domain were assessed as low for 72 percent (n=28) of papers, as high for 26 percent (n=10), and as unclear for two percent (n=1).

The potential for bias in the domain of the **reference standard** (i.e., the criteria used to confirm a diagnosis of HF) was judged on the basis of whether the reference standard was likely to correctly classify the target condition and whether the results were interpreted with knowledge of the NT-proBNP results. Sixty-two percent of papers (n=24) were rated as low risk, 23 percent (n=9) were rated as high, and 15 percent (n=6) were rated as unclear. Concerns about applicability were assessed as to whether the target condition, as defined by the reference standard, differed from the target condition specified in the review question. Seventy-two percent (n=28) of papers were assessed as low on this domain, 26 percent (n=10) were assessed as high, and 2 percent were rated as unclear (n=1).

The potential for bias in the domain of **flow and timing** was assessed on the basis of inappropriate intervals between index test and reference standard, standardized administration of reference standard among patients, and equal inclusion of patients in the analysis. The majority of papers (n=37, 95%) were assessed as low risk of bias on the domain of flow and timing, while 5 percent (n=2) were rated as unclear.

Strength of Evidence for Papers With Emergency Department Settings

To grade the strength of evidence (SOE) in this diagnosis section we chose to assess two primary outcomes: sensitivity and specificity. These are concepts that are well understood by clinical users of diagnostic tests. Other diagnostic performance indicators (positive (PPV) and negative (NPV) predictive values, LR^+ and LR^-, accuracy, and DOR) can be calculated from sensitivity and specificity if the prevalence of disease is known. As such, the conclusions regarding SOE for these performance indicators are unlikely to be different from those drawn for sensitivity and specificity.

For all papers that presented sensitivity and specificity data (BNP n=28;[3,74,78,79,81-83,85,86,88,89,93-97,100,101,103,104,108,110-113,119,120,147] NT-proBNP n=18[2,26,88,108,110-115,119,124,129,131,135,138,141,143]), we examined SOE using a variety of cutpoints. For BNP, we selected the lowest provided, manufacturers' suggested, and optimal as chosen by the author. For NT-proBNP we chose lowest and optimal. The papers in the manufacturers' suggested and optimal cutpoint groupings are subsets of the lowest cutpoint grouping.

BNP

The SOE estimates were the same for all three cutpoints evaluated. The complete table can be viewed in Appendix H Tables H-7a, H-7b, and H-7c.

Risk of Bias

Using the QUADAS-2 tool, the risk of bias in these studies for both sensitivity and specificity was rated (Figures 3 and 4). The tests for publication bias exposed no significant bias in the following conditions in our meta-analysis of BNP diagnostic use in the emergency department: (1) optimum cutpoint; (2) lowest cutpoint; and (3) manufacturer cutpoint (Appendix H Table H-8 and Figure H-25). However, in the four domains of patient selection, index test(s), reference standard, and flow and timing, the concern regarding bias was rated as low.

Figure 3. Proportion (%) of diagnostic studies using BNP with low, high, or unclear concerns regarding risk of bias in emergency department

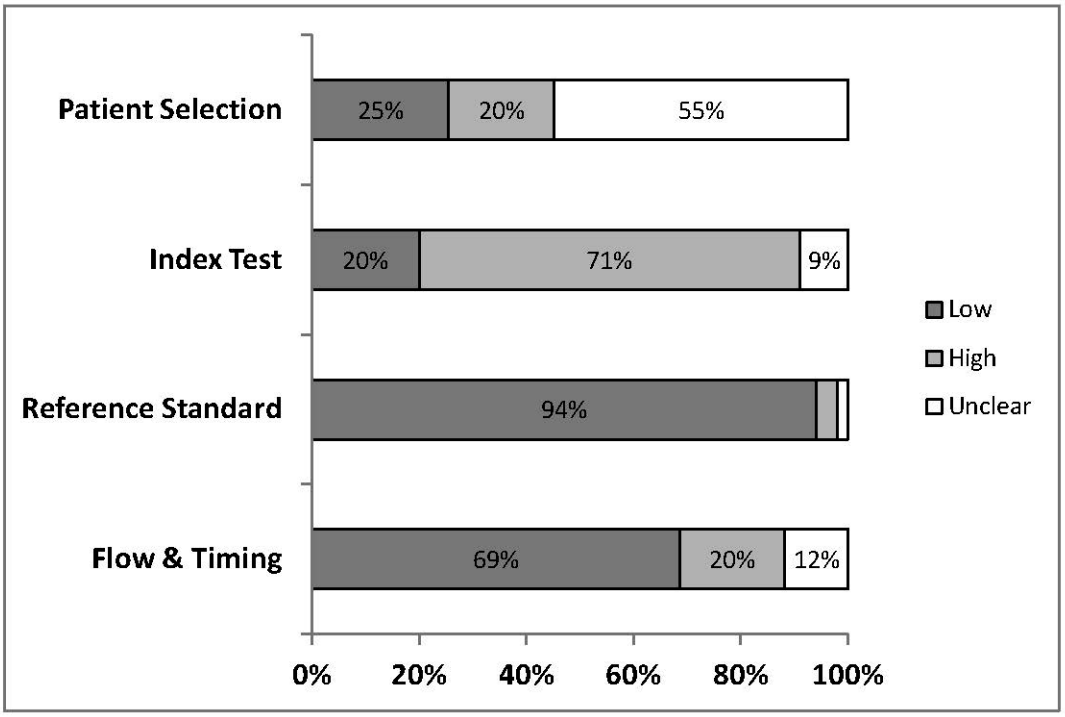
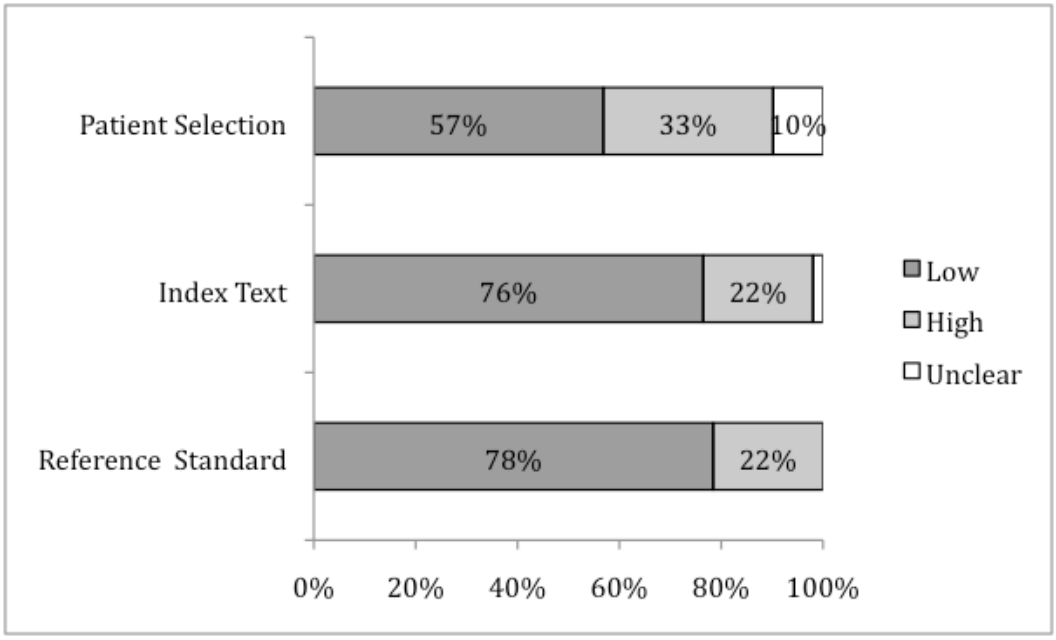


Figure 4. Proportion (%) of diagnostic studies using BNP with low, high, or unclear concerns regarding applicability in emergency department



Directness

Both sensitivity and specificity are concepts that are well understood by clinicians and can inform them with regard to clinical practice. The related parameters of NPV, PPV, LR^+, LR^-, and DOR can also inform clinicians. We rate this domain as direct.

Precision

The CIs around the summary estimates of sensitivity and specificity are small (lowest: 0.93 to 0.96; manufacturers' suggested: 0.93 to 0.96; optimal: 0.88 to 0.92). The CIs around specificity are larger (lowest: 0.57 to 0.72; manufacturers' suggested: 0.57 to 0.71; optimal: 0.72 to 0.83). Because the statistical heterogeneity for all summary estimates is large, we rate this domain as imprecise (Table 12).

Consistency

With respect to sensitivity, the range of estimates across papers is small. We rate this domain as consistent. With respect to specificity, the range of estimates across papers is larger, from 0.64 to 0.77. We rate this domain as inconsistent for specificity (see Table 12).

NT-proBNP

The SOE estimates were the same for both cutpoints evaluated. The outcome of sensitivity was rated as high for both cutpoints (optimal, lowest). The outcome of specificity wars rated as moderate for both cutpoints due to inconsistency in the value of specificity among studies. Nevertheless, the summary SOE was rated as high. The complete table can be viewed in Appendix H Tables H-9a and H-9b.

Risk of Bias

Using the QUADAS-2 tool, we rated the risk of bias in this study for both sensitivity and specificity (Figures 5 and 6). The tests for publication bias exposed no significant bias in the following conditions in our meta-analysis of NT-proBNP diagnostic use in the emergency department: (1) optimum cutpoint, (2) lowest cutpoint, and (3) manufacturer cutpoint (Appendix H Table H-8 and Figure H-25). In the four domains of patient selection, index test(s), reference standard, and flow and timing, the concern regarding bias was rated as low.

Figure 5. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding risk of bias in emergency department

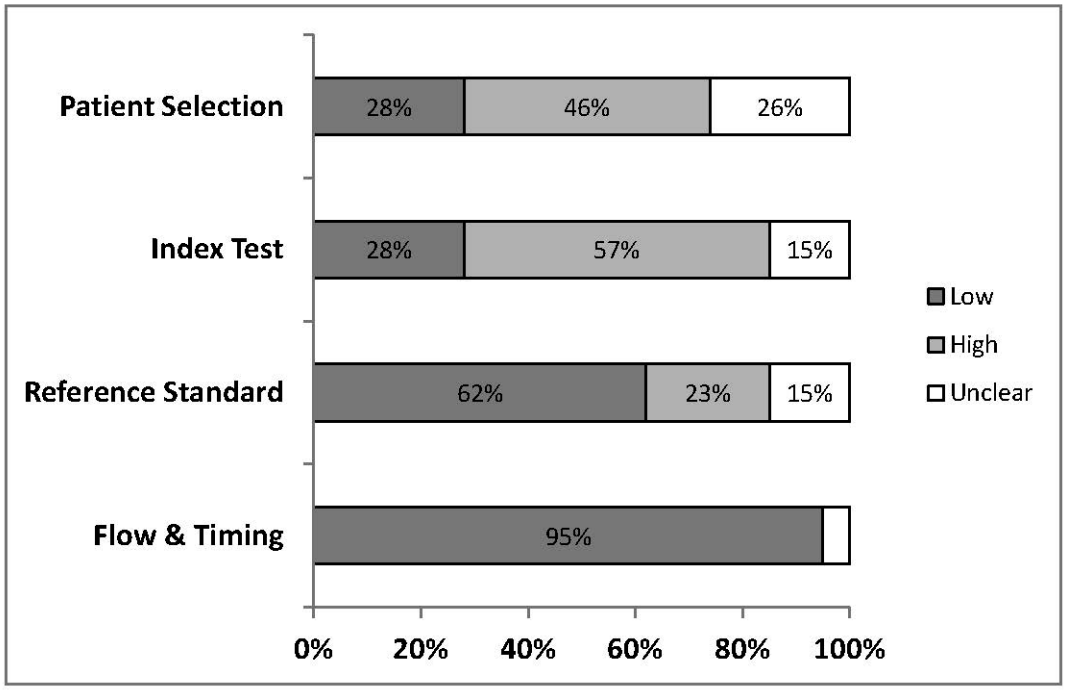
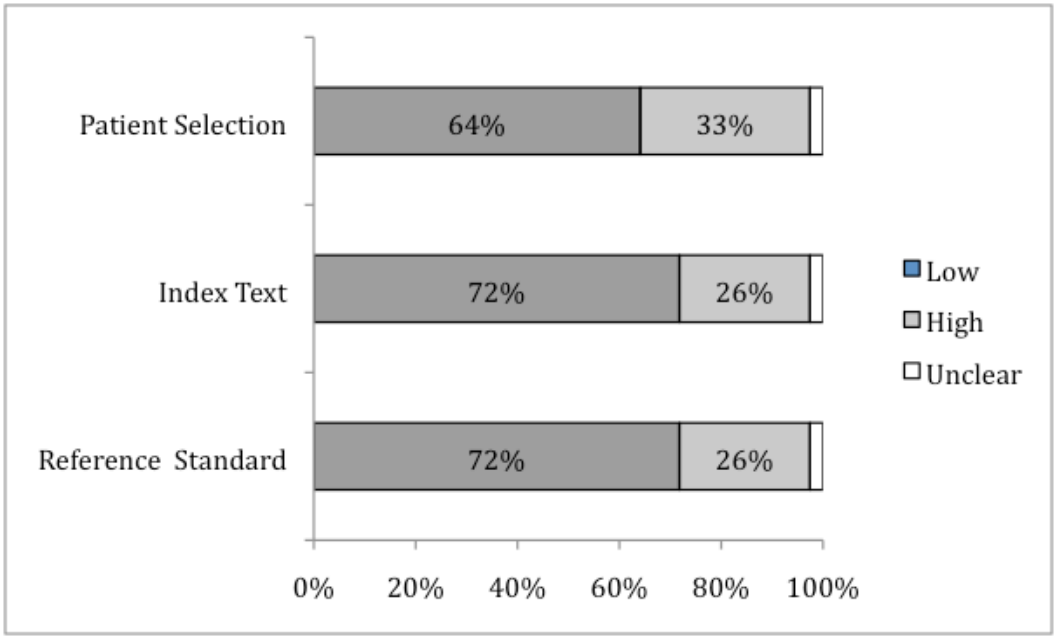


Figure 6. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding applicability in emergency department



Directness

Both sensitivity and specificity are concepts that are well understood by clinicians and can inform them with regard to clinical practice. The related parameters of NPV, PPV, LR^+, LR^-, and DOR can also inform clinicians. This domain was rated as direct.

Precision

The CIs around the summary estimates of sensitivity and specificity are small (lowest: 0.90 to 0.95; optimal: 0.84 to 0.91). The CIs around specificity are larger (lowest: 0.43 to 0.69; optimal: 0.64 to 0.82). Because we included papers that recruited unrestricted populations (patients presenting with signs and symptoms of HF with or without comorbidities), the statistical heterogeneity is large. As such, this domain was rated as imprecise (see Table 12).

Consistency

With respect to sensitivity, the direction of estimates is consistent, and the range of estimates across papers is small. We rate this domain as consistent. With respect to specificity, the direction of estimates is consistent, but the range of estimates across papers is large, from 0.64 to 0.77. This domain was rated as inconsistent for specificity (see Table 12).

Table 12. Statistical summary of test performance characteristics based on the manufacturer, optimum, and lowest cutpoints in the emergency department

Test	Cutpoint	Assay type	N study	Sensitivity			Specificity			LR+			LR-			log DOR			AUC	
				Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI
ED-BNP	Manu-facturer	A	1	0.86	0.76, 0.93	-	0.98	0.85, 1.00	-	39.1	3.59, 426	-	0.14	0.07, 0.30	-	5.61	3.03, 8.19	-	-	-
		B	3	0.95	0.93, 0.97	25.8	0.61	0.49, 0.72	87.3	2.43	1.75, 3.37	89.9	0.09	0.04, 0.17	72.6	3.36	2.38, 4.34	82.5	-	-
		C	1	0.96	0.94, 0.97	-	0.62	0.59, 0.65	-	2.51	2.32, 2.71	-	0.07	0.05, 0.10	-	3.56	3.14, 3.98	-	-	-
		D	17	0.95	0.93, 0.97	84.9	0.62	0.53, 0.70	96.9	2.71	2.16, 3.40	95.9	0.09	0.07, 0.13	72.1	3.56	3.10, 4.03	81.6	0.92	0.90, 0.95
		All*	22	0.95	0.93, 0.96	81.3	0.63	0.57, 0.70	96.7	2.64	2.23, 3.12	94.7	0.09	0.07, 0.12	72.1	3.55	3.18, 3.92	79.4	0.92	0.90, 0.94
	Optimum	A	2	0.81	0.51, 1.00	92.9	0.92	0.85, 1.00	22.2	9.34	2.12, 41.2	61.1	0.15	0.01, 1.59	91.4	4.23	0.80, 7.66	86.6	-	-
		B	4	0.88	0.80, 0.96	91.4	0.78	0.72, 0.85	77.1	3.9	3.22, 4.71	40.6	0.14	0.07, 0.27	89.5	3.41	2.86, 3.97	67.9	0.91	0.88, 0.95
		C	1	0.96	0.94, 0.97	-	0.62	0.59, 0.65	-	2.51	2.32, 2.71	-	0.07	0.05, 0.11	-	3.56	3.14, 3.98	-	-	-
		D	22	0.9	0.87, 0.93	91	0.77	0.71, 0.83	96.1	4.45	3.30, 6.02	96.5	0.14	0.11, 0.18	84.3	3.67	3.27, 4.08	84.8	0.93	0.91, 0.95
		All	29	0.9	0.88, 0.92	90.4	0.78	0.72, 0.83	96.3	4.3	3.45, 5.35	95.5	0.14	0.11, 0.17	86.8	3.6	3.28, 3.92	82.1	0.92	0.91, 0.94
	Lowest	A	2	0.81	0.51, 1.00	92.9	0.92	0.85, 1.00	22.2	9.34	2.12, 41.2	61.1	0.15	0.01, 1.59	91.4	4.23	0.80, 7.66	86.6	-	-
		B	4	0.94	0.92, 0.97	55.4	0.64	0.55, 0.73	85	2.6	1.96, 3.46	87.2	0.1	0.06, 0.17	69.5	3.32	2.63, 4.01	74.5	0.91	0.87, 0.95
		C	2	0.96	0.94, 0.98	1.1	0.62	0.59, 0.65	0	2.5	2.32, 2.69	0	0.07	0.05, 0.10	0	3.57	3.16, 3.99	0	-	-
		D	23	0.94	0.92, 0.96	91.7	0.62	0.52, 0.71	98.2	2.67	2.17, 3.29	97.2	0.09	0.06, 0.14	88.7	3.5	3.06, 3.94	81.1	0.92	0.89, 0.94
		All	31	0.94	0.92, 0.96	90.7	0.64	0.56, 0.71	97.8	2.71	2.28, 3.21	96.8	0.1	0.07, 0.14	88.6	3.47	3.12, 3.81	79.3	0.92	0.90, 0.94
ED-NT-proBNP	Manu-facturer	E	4	0.9	0.87, 0.94	46.8	0.65	0.44, 0.86	95.8	2.72	1.27, 5.82	97.1	0.16	0.11, 0.25	55.1	2.79	1.79, 3.79	85.3	0.87	0.79, 0.95
	Optimum	E	19	0.88	0.84, 0.92	90.7	0.73	0.65, 0.82	96.5	3.59	2.46, 5.23	97.5	0.17	0.13, 0.22	81.3	3.16	2.73, 3.59	80.7	0.90	0.87, 0.93
	Lowest	E	19	0.93	0.91, 0.95	90.4	0.55	0.42, 0.68	98.3	2.26	1.71, 2.99	98.5	0.12	0.08, 0.20	87.6	3.08	2.56, 3.58	78.4	0.89	0.86, 0.93

NOTE: AUC was calculated for the group with 4 or more studies

ASSAY: A-ADVIA -Centaur® BNP Assay, B-Abbott AxSYM® B-Type, C-TRIAGE -B-Type Beckman, D-TRIAGE -B-Type Test, E-ELECSYS -proBNP Immunoassay *Sanz 2006 counted twice for using ADVIA and TRIAGE B-type assay

Abbreviations: AUC = area under the curve; CI = confidence interval; DOR = diagnostic odds ratio; ED = emergency department; Est = estimate; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; n=sample size; PC= primary care

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

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

Sample and Design Characteristics of Studies Assessing BNP

There were 12 articles that met the criteria for KQ2 that examined BNP in primary care settings. Eight examined BNP only[148-155] and four examined both BNP and NT-proBNP.[156-159] See Appendix I. KQ2 Evidence Set.

Study Design

One study used a prospective cohort design[151] and the remaining studies (n=11) used a cross-sectional design. The selected articles were published between 2005 and 2011 and were conducted in a wide range of regions: two in North America,[152,159] eight in Europe,[148,150,151,153-157] one in Asia,[158] and one paper in which country of origin could not be determined.[149]

Population Characteristics

Most studies, with the exception of three,[150,158,159] provided diagnostic information on an overall study sample with dyspnea in a primary care setting. One study provided diagnostic information on populations grouped according to age and sex.[158] Several studies presented diagnostic information according to BMI status,[158,159] renal function,[158] LVEF levels,[158] and left ventricular systolic dysfunction (LVSD) status.[150,155]

In all studies, study patients presented to a primary care facility with shortness of breath and were over 18 years of age. Most studies (n=8) had a patient population with mean or median ages from 70 to 79 years old. Three studies had patient populations with means or medians between 60 and 69 years old[155,158,159] and one[160] had a population under 60 years of age.

The percentage of males enrolled in each study ranged from 25 percent[153] to 100 percent[158] (mean=51.2%; median=50%). Sample size populations ranged from 53[152] to 1,032[158] (mean=346.8; median=357). The prevalence of HF in the study populations ranged from seven percent[158] to 67 percent[148] (mean=41.5 %; median=38.5%).

Component Studies

The majority of papers (n=9) were independent studies, publishing results on unique data sets. One article used data from the study for the evaluation of the clinical applicability of BNP in the diagnosis and management of patients with suspected HF in primary care (PANAMA),[153] one reported results from the Utrecht Heart Failure Organization - Initial Assessment (UHFO-IA) study[154] and one study recruited patients from the Screening to Prevent Heart Failure (STOP-HF) study.[155]

Assays

Ten studies used the TRIAGE-B-Type Natriuretic Peptide (BNP) test,[148-153,155-157,159] one used the ADVIA-Centaur® B-Type Natriuretic Peptide (BNP) Assay,[158] and one used the Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA).[154]

Diagnosis of Heart Failure

Most studies (n=8) based the diagnostic reference standard solely on clinical judgment.[148-151,154,157-159] Most of these had a reference standard agreed upon by at least two physicians (mostly cardiologists), with the exception of two papers, which based the final diagnosis on the opinion of a single cardiologist or other type of clinician.[157,159] The adjudication physicians each arrived at a diagnosis of HF based on their interpretation of all available clinical data; this often included echocardiography results. Four of the studies[148,149,151,153] judging final diagnosis using clinical judgment stated that the Framingham criteria were used to assist in judgment.

Of the remaining studies, two based final diagnosis of HF on echocardiography results alone,[152] and one simply reported that the diagnosis was "based on the Framingham criteria."[153] One study did not report the reference standard used.[155]

BNP: Test Performance and Optimal Cutpoints in Primary Care

Diagnostic Properties in BNP

The 12 studies evaluating BNP in primary care settings used several cutpoints ranging from 30[148,157] to 500[148] (mean=158; median=100) pg/mL or ng/L, and reported sensitivities from 25 percent[153] to 97 percent[148] (mean=82.1%; median=83.9%), specificities from 23 percent[151] to 92 percent[148] (mean=73.8%; median=80.4%), and AUCs of 0.62[159] to 0.93[158] (mean=0.86; median=0.88). Six studies examined BNP only[154-159] and six focused on both BNP and NT-proBNP.[148-153] See Appendix I Tables I-1 and I-2.

When the appropriate data were available for extraction or calculation, 2x2 tables were prepared and forest plots of sensitivities, specificities, positive and negative LRs, logDOR, and summary ROC curves are presented (Appendix I Figures I-1 to I-9). Three cutpoints were selected: lowest presented, manufacturers' suggested, and the optimal cutpoint as chosen by the authors.

The pooled sensitivity using the optimum cutpoint was 0.82 (95% CI, 0.69 to 0.90). All but a single study by Barrios et al.[153] which had a sensitivity of 0.25, had specificities greater than 0.80. The low sensitivity of the Barrios study may be due to a predominantly elderly population and high prevalence of diastolic HF. Pooled specificities were, as expected, not as high and gave an overall specificity of 0.64 (95% CI, 0.45 to 0.79). Summary LR^+ and LR^- and the logDOR were 2.27 (95% CI, 1.43 to 3.62), 0.28 (95% CI, 0.16 to 0.49), and 2.06 (95% CI, 1.27 to 2.84), respectively. Pooling using the lowest cutpoint produced a slightly higher sensitivity of 0.89 (95% CI, 0.77 to 0.95) and a corresponding lower specificity of 0.54 (95% CI, 0.41 to 0.66). The LR^+ and LR^- and logDOR gave similar results: 1.94 (95% CI, 1.47 to 2.57), 0.20 (95% CI, 0.09 to 0.44), and 2.27 (95% CI, 1.32 to 3.22), respectively.

Studies were pooled based on the manufacturers' suggested cutpoint because this is likely the most commonly used cutpoint in clinical use. Studies were included if the cutpoint used was within 5 pg/mL of 100. Eight studies were included in the pooled statistics, as they all used the Triage BNP assay. Other manufacturers were not included. The overall sensitivity of 0.76 (95% CI, 0.59 to 0.87) based on the manufacturers' cutpoint was slightly lower than that for the

optimal cutpoint. Corresponding specificity was increased slightly to 0.71 (95% CI, 0.52 to 0.85). The LR^+ and LR^- and logDOR gave results similar to the optimal cutpoint, 2.63 (95% CI, 1.59 to 4.36), 0.34 (95% CI, 0.20 to 0.57), and 2.08 (95% CI, 1.24 to 2.92), respectively.

Summary ROC curves were also developed. As with the summary plots, the ROC curves were developed based on the optimum, lowest, and manufacturers' cutpoints and are presented in Appendix I Figures I-10 to I-12. The AUCs were 0.81 (95% CI, 0.77 to 0.84) for the optimum cutpoint, 0.76 (95% CI, 0.72 to 0.80) for the lowest cutpoint, and 0.80 (95% CI, 0.76 to 0.83) for the manufacturers' suggested cutpoint.

BNP: Determinants of Test Performance in Primary Care

The effect of various determinants upon the diagnostic performance of BNP for the diagnosis of HF was examined.

Age

A single study examined the association of age with BNP. Park et al.[158] compared the performance of BNP for patients above and below 65 years of age for the identification of LVEF or advanced diastolic dysfunction (DD). For patients 65 years of age and greater, using a cutpoint of 250 pg/mL, the AUC was 0.903 (sensitivity=83.9, specificity=83.7). For identification of advanced DD and a cutpoint of 236 pg/mL, the AUC was 0.900 (sensitivity=83.9, specificity=84.1). For patients less than 65 years old with LVEF less than 45, cutpoint of 82 pg/mL was used, which gave an AUC of 0.916 (sensitivity=84.1, specificity=84.2). A cut-off of 70 pg/mL was used to identify advanced DD with an AUC of 0.912 (sensitivity=83.3, specificity=83.3).

Sex

Two studies investigated the relationship between sex and BNP.[156,158] Fuat et al.[156] compared the AUC of males and females and did not find a significant difference (males 0.79, females 0.80). Park et al.[158] compared the ability of BNP to identify male and female patients with LVEF less than 45 and advanced DD. The results of Park et al. are presented in Table 13.

Table 13. Effect of sex on AUC for BNP (Park et al., 2010[158])

Sex	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity %	Specificity %
Males	LVEF <45	0.892	111	81.1	78.9
	Advanced DD	0.890	99	80.0	80.4
Females	LVEF <45	0.929	209	85.1	85.0
	Advanced DD	0.907	166	84.8	84.6

Abbreviations: AUC = area under the curve; BNP=B-type natriuretic peptide; DD = diastolic dysfunction; LVEF = left ventricular ejection fraction; pg/mL = picograms per milliliter

Body Mass Index

Two studies examined the relationship between BNP and BMI.[158,159] Christenson et al.[159] grouped patients as normal (BMI <25 kg/m^2), overweight (BMI 25 to 30 kg/m^2), or obese (BMI >30 kg/m^2), and demonstrated an inverse correlation of BNP with BMI. The AUC for diagnosis of decompensated HF in the three groups (<25kg/m^2, 25-30kg/m^2, and >30 kg/m^2) were 0.78 (95% CI, 0.71 to 0.084), 0.62 (95% CI, 0.54 to 0.70), and 0.72 (95% CI, 0.66 to 0.79), respectively. Using a cutpoint of 100 pg/mL, sensitivity and specificity of BNP were 89 percent

and 38 percent for normal weight patients, 85 percent and 38 percent for overweight patients, and 81 percent and 49 percent for obese patients, respectively.

Park et al.[158] also investigated the relation of BNP with BMI for the identification of patients with LVEF less than 45 and advanced DD. A similar inverse correlation trend was seen, more so with the advanced DD patients. Results are presented in Table 14.

Table 14. Effect of body mass index on diagnostic performance of BNP

BMI	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity %	Specificity %
≥25kg/m^2	LVEF <45	0.933	151	85.0	85.0
	Advanced DD	0.841	82	80.0	80.1
<25kg/m^2	LVEF <45	0.897	154	81.3	81.3
	Advanced DD	0.916	140	83.0	83.1

Abbreviations: AUC = area under the curve; BMI = body mass index; BNP=B-type natriuretic peptide; DD = diastolic dysfunction; kg/m2 = kilograms per meter squared; LVEF = left ventricular ejection fraction; pg/mL = picograms per milliliter

Renal Function

Park et al.[158] studied the effect of renal function on the ability of BNP to identify patients with LVEF less than 45 and advanced DD. Renal function was estimated by creatinine clearance calculated by the Cockroft-Gault equation. Patients were grouped as clearance less than 60 mL/min or greater than 60 mL/min. As can be seen, as renal function decreases the cutpoint must increase to maintain a similar sensitivity and specificity. The effect of decreased LVEF or advanced DD was overwhelmed by the effect of renal function, and had little effect on the optimal cutpoint. Results are presented in Table 15.

Table 15. Effect of renal function on diagnostic performance of BNP

eGFR	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity %	Specificity %
≥60mL/min	LVEF <45	0.915	89	82.2	82.2
	Advanced DD	0.894	70	83.3	81.5
<60mL/min	LVEF <45	0.866	264	78.2	78.0
	Advanced DD	0.876	247	78.4	78.2

Abbreviations: AUC = area under the curve; BNP=B-type natriuretic peptide; DD = diastolic dysfunction; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; mL/min=milliliter per minute; pg/mL = picograms per milliliter

Sample and Design Characteristics of Studies Assessing NT-proBNP

There were 20 articles that met the criteria for KQ2 examining NT-proBNP in primary care settings. Sixteen examined NT-proBNP only[154,161-175] and four examined both BNP and NT-proBNP.[156-159] (Appendix I Table I-3).

Study Design

Two studies used a prospective cohort design.[169,171] Study design could not be determined in one of the articles.[174] The remaining studies (n=17) used a cross-sectional design. The selected articles were published between 2003 and 2011 and were conducted in a wide range of regions: one in North America,[159] 18 in Europe,[154,156,157,161-175] and one in Asia.[158]

Population Characteristics

Most studies, with the exception of five,[154,158,162,163,165] provided diagnostic information on the overall study sample presenting with dyspnea in a primary care setting. Some studies

provided diagnostic information on populations grouped according to age[158,165,170] and sex.[156,158,162,166,170] Some studies presented diagnostic information according to BMI status,[158,159] diabetes status,[161] previous history of HF,[161] LVEF,[163] renal failure,[158] and hemoglobin (Hb) measures.[158] One study presented groups according to their suspected HF/valvular disease (LVSD),[167] and one study grouped subjects according to diagnosis of major structural heart disease in patients with AF) compared with those with sinus rhythm (SR).[165]

In all studies, study patients presented to a primary care facility with shortness of breath and were over 18 years of age. Seven studies had a patient population with mean or median ages from 60 to 69 years old.[158,159,161-163,168,172] Eleven had populations with mean or median ages between 70 and 79 years.[154,156,157,164-166,170,171,173-175] Two examined populations 80 years of age and over.[167,169]

The percentage of males enrolled in each study ranged from 32.1 percent[170] to 100 percent[158] (mean=42.8%; median=46%). Sample size populations ranged from 14[163] to 1,321[165] (mean=239; median=140). The prevalence of HF in the study populations ranged from 4 percent[168] to 75 percent[173] (mean=31.2%; median=33.1%).

Component Studies

Most of the papers (n=17) were independent studies, publishing results on unique data sets. One study used data from the Echocardiographic Heart of England screening study (ECHOES),[161] one reported results from the Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure (DIAST-CHF),[174] and one used results from the UHFO-IA.[154]

Assays

All studies (n=20) used the ELECSYS® proBNP Immunoassay to measure NT-proBNP.

Diagnosis of Heart Failure

The majority of studies (n=11) based the diagnostic reference standard solely on clinical judgment. Less than half of these had a reference standard agreed upon by at least two physicians[154,158] (mostly cardiologists), with eight studies basing the final diagnosis on the opinion of a single physician.[157,159,167,168,170-173] The adjudication physicians each arrived at a diagnosis of HF based on their interpretation of all available clinical data; this often included echocardiography results. One of the studies used the Framingham criteria to aid in clinical judgment.[174]

Of the remaining studies, four based the final diagnosis of HF both on clinical judgment and results of echocardiography,[156,161,162,164,166] one based it on echocardiography results alone,[163,165] and one simply reported that the definitive diagnosis was "based on the Framingham criteria."[169] One study used an outcome panel that evaluated all available information, excluding the NT-proBNP results.[175]

NT-proBNP: Test Performance and Optimal Cutpoints in Primary Care

Diagnostic Properties

The 20 studies evaluating NT-proBNP in primary care settings used several cutpoints ranging from 25[171] to 6180[167] (mean=635; median=379) pg/mL or ng/L. Three studies[161,162,164] measured

NT-proBNP in pmol/L. Reported sensitivities ranged from 44 percent[167] to 100 percent[164-166,169] (mean=80.6%; median=84.4 %), specificities from 3 percent[165] to 97 percent,[163,168] (mean=58.5% ; median=60.6%), and AUC of 0.70[161] to 0.98[166] (mean=0.86; median=0.88). The majority of the studies focused on NT-proBNP alone (n=14), and the remainder focused on both BNP and NT-proBNP.[154,156-159] Appendix I Table I-4 presents data to answer KQ2.

When the appropriate data was available for extraction or calculation, 2x2 tables were prepared and forest plots of sensitivities, specificities, positive and negative LRs, DOR, and summary ROC curves are presented (Appendix I Figures I-13 to I-18).Three cutpoints were selected: lowest presented, the optimal cutpoint as chosen by the authors to examine in greater detail, and the manufacturers' recommended cutpoint of 125 pg/mL for patients younger than 75 years of age and 450 pg/mL for those patients 75 years of age or older. At least four studies were needed in each group to present summary estimates; however, for NT-proBNP according to manufacturers' cutpoint, only two studies satisfied our criteria and, thus, will not be presented.

When the optimal cutpoint chosen by the authors was used, the pooled sensitivity was 0.88 (95% CI, 0.81 to 0.93) and seven of the studies[156,164,166-168,170,172] produced sensitivities greater than 0.90. A single study by Stahrenberg et al.[174] had a significantly lower sensitivity of 0.55 (95% CI, 0.44 to 0.65) due to a relatively high cutpoint of 22 pg/mL; however, they did produce a relatively good specificity 0.61 (95% CI, 0.47 to 0.74). The pooled specificity (0.58) was, as expected, not as high as the pooled sensitivity, as the authors tend to optimize sensitivity.

Using the lowest cutpoint chosen by the authors produced increased pooled sensitivity (0.90) when compared to the optimal cutpoint (0.88), with no decrease in pooled specificity (0.50). All but three studies[159,171,174] produced sensitivities greater than 0.90.

As with the summary plots, the ROC curves were developed based on the optimum and lowest cutpoints. The AUC were 0.86 (95% CI, 0.82 to 0.88) for the optimum cutpoint, and 0.82 (95% CI, 0.79 to 0.85) for the lowest cutpoint (Appendix I Figures I-19 to I-20).

NT-proBNP: Determinants of Test Performance in Primary Care

We examined the effect of various determinants on the diagnostic performance of NT-proBNP for the diagnosis of HF.

Age

Two studies investigated the influence of age on the diagnostic ability of NT-proBNP.[158,165] In both cases the optimal cutpoint for identification of major structural heart disease (defined as LVEF <40, left ventricular DD, or right ventricular dilation) was higher in older patients. Shelton et al.[165] compared patients above and below the age of 75 years. They also compared the difference between patients in SR and those in AF. Park et al.[158] compared the performance of BNP for patients above and below 65 years of age for the identification of LVEF or advanced DD. Table 16 provides a summary of this data.

Table 16. Effect of age on diagnostic performance of NT-proBNP

Author, Year	Age	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Park,[158] 2010	≥65 years	LVEF <45	0.875	1,446	82.1	81.0
		Advanced DD	0.894	1,356	83.9	82.6
	<65 years	LVEF <45	0.912	379	84.1	84
		Advanced DD	0.893	276	83.3	82.4
Shelton,[165] 2006	SR ≤75 years	MSHD	NR	357	73.4 (47.3 to 79.3)	78.6 (51.3 to 84.2)
	SR >75 years	MSHD	NR	652	69.1 (43.0 to 79.0)	78.6 (47.7 to 87.8)
	AF ≤75 years	MSHD	NR	1,758	69.8 (58.3 to 92.7)	90.2 (63.2 to 96.9)
	AF >75 years	MSHD	NR	1,764	68.9 (38.7 to 87.8)	60.6 (43.9 to 97.2)

Abbreviations: AF = atrial fibrilation; AUC = area under the curve; CI = confidence interval; DD = diastolic dysfunction; LVEF = left ventricular ejection fraction; MSHD = major structural heart disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NR = not reported; pg/mL = picograms per milliliter; SR = sinus rhythm

Sex

Five studies investigated the relationship between sex and the ability of NT-proBNP to diagnose HF.[156,158,162,166,170] Using a regression model, Mikkelsen et al.[166] identified sex as a significant influence on NT-proBNP. The AUC for the diagnosis of HF in females was 0.97 (95% CI, 0.95 to 1.00) and 0.91 (95% CI, 0.83 to 0.98) for males. Due to the sex differences, the optimal cutpoints were different between males and females: 85 pg/mL and 110 pg/mL, respectively.

Nielsen et al.[162] examined the ability of NT-proBNP to identify HF in men and women 50 years of age and above, as the prevalence of HF in those less than 50 years of age was very low. ROC curves for men gave an AUC of 0.93 (95% CI, 0.89 to 0.97) for men and an AUC of 0.90 (95% CI, 0.84 to 0.97) for women. Using a NPV of 97 percent, they suggest a cutpoint of 11 pmol/L for men and 17 pmol/L for women.

Fuat et al.[156] compared the ability of NT-proBNP to rule out the presence of HF in men and women. They maximized sensitivity without producing an unacceptable loss of specificity. The AUC for men was 0.79, and using a cutpoint of 100 pg/mL produced a NPV of 0.89 (95% CI, 0.74 to 1.00). Women had a slightly higher AUC of 0.82, and using a cutpoint of 150 pg/mL produced a NPV of 0.94 (95% CI, 0.88 to 1.00).

Linear regression analysis performed by Olofsson and Bowman[170] showed no significant difference in diagnosis of HF between males and females, while multiple linear regression showed that age and male sex was significantly associated with higher levels of NT-proBNP.

Park et al.[158] compared the ability of NT-proBNP to identify male and female patients with LVEF less than 45 and advanced DD. Data for multiple cutpoints and results of papers that used sensitivity and specificity as an outcome are shown in Table 17. Fuat et al.[156] maximized sensitivity, then specificity, and reported an outcome of NPV. This study is therefore not presented in Table 17.

Table 17. Effect of sex on diagnostic performance of NT-proBNP

Author, Year	Sex	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Mikkelsen,[166] 2006	Male	HF	0.91	85 pg/mL	95 (83 to 99	71 (55 to 84)
	Female	HF	0.97	110 pg/mL	98 (87 to 100)	88 (71 to 97)
Nielsen,[162] 2004	Male	HF	0.93	9 pmol/L	100	60
		HF		11 pmol/L	86	67
		HF		18 pmol/L	89	79
	Female	HF	0.90	8 pmol/L	100	27
		HF		17 pmol/L	94	69
		HF		26 pmol/L	91	84
Olofsson,[170] 2010	Male	HF		100 ng/L	100	33
		HF		200 ng/L	90	56
		HF		300 ng/L	80	78
		HF		400 ng/L	80	89
		HF		500 ng/L	70	89
	Female	HF		100 ng/L	86	28
		HF		200 ng/L	79	64
		HF		300 ng/L	64	76
		HF		400 ng/L	57	88
		HF		500 ng/L	57	92
Park,[158] 2010	Male	LVEF <45	0.867	510	81.1	80.8
		Advanced DD	0.879	431	82.5	81.3
	Female	LVEF <45	0.925	1,678	87.2	87.3
		Advanced DD	0.878	860	84.8	84.6

Abbreviations: AUC = area under the curve; CI = confidence interval; DD = diastolic dysfunction; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pg/mL = picograms per milliliter

Body Mass Index

Two studies examined the relationship between NT-proBNP and BMI.[158,159] In a relatively large study of 685 patients, Christenson et al.[159] grouped patients as normal (BMI <25 kg/m^2), overweight (BMI 25 to 30 kg/m^2), or obese (BMI >30 kg/m^2), and demonstrated an inverse correlation of NT-proBNP with BMI. The AUCs for a diagnosis of decompensated HF in the three groups (normal, overweight, and obese) were 0.77 (95% CI, 0.70 to 0.084), 0.64 (95% CI, 0.56 to 0.72), and 0.71 (95% CI, 0.65 to 0.77), respectively. Using the International Collaborative of NT-proBNP study cutpoints[2] of 450 pg/mL for under 50 years of age, 900 pg/mL for ages 50 to 75, and 1,800 pg/mL for ages over 75, sensitivity and specificity of BNP were 88 percent and 50 percent for normal weight patients, 68 percent and 51 percent for overweight patients, and 69 percent and 64 percent for obese patients, respectively.

Park et al.[158] also investigated the relation of NT-proBNP with BMI for the identification of patients with LVEF less than 45 and advanced DD. Results are presented in Table 18.

Table 18. Effect of body mass index on diagnostic performance of NT-proBNP

BMI	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity %	Specificity %
≥25kg/m^2	LVEF <45	0.947	771	85.0	86.8
	Advanced DD	0.852	309	80.0	80.1
<25kg/m^2	LVEF <45	0.869	830	81.3	80.7
	Advanced DD	0.885	682	81.1	81.1

Abbreviations: AUC = area under the curve; BMI = body mass index; DD = diastolic dysfunction; kg/m2 = kilograms per meter squared; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pg/mL = picograms per milliliter

Renal Function

Park et al.[158] also studied the effect of renal function on the ability of NT-proBNP to identify patients with LVEF less than 45 and advanced DD. Renal function was estimated by creatinine clearance calculated by the Cockroft-Gault equation. Patients were grouped as clearance less than 60 mL/min or clearance of 60 mL/min or over. Using multivariate regression analysis, clearance less than 60 ml/min was shown to be an independent determinant of NT-proBNP. The AUC, sensitivity, and specificity results are presented in Table 19.

Table 19. Effect of renal function on diagnostic performance of NT-proBNP

Creatinine clearance	Endpoint	AUC	Cutpoint (pg/mL)	Sensitivity %	Specificity %
≥60mL/min	LVEF <45	0.915	418	84.4	84.4
	Advanced DD	0.889	276	83.3	82.1
<60mL/min	LVEF <45	0.832	1,981	78.2	78.0
	Advanced DD	0.836	1,733	78.4	76.4

Abbreviations: AUC = area under the curve; DD = diastolic dysfunction; LVEF = left ventricular ejection fraction; mL/min = milliters per minute; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pg/mL = picograms per milliliter

Assessment of Quality for Studies With Primary Care Settings

BNP

For studies of diagnostic tests (KQ2), we used the QUADAS-2 to assess quality in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias (low, high, unclear) and concerns regarding applicability (low, high, unclear), with associated signaling questions to help with bias and applicability judgments (Figures 7 and 8, and Appendix I Table I-5).

The potential for bias in the domain of **patient selection** was assessed on the basis of the enrollment of the study sample (consecutive, random, or convenience), the avoidance of a case-control design, and the avoidance of inappropriate patient exclusions. For this domain, 42 percent of studies (n=5) were rated as low risk for bias and 58 percent (n=7) were rated as unclear as to risk of bias. Studies were assessed as to patient population applicability to those targeted by the review question in terms of severity of the target condition, demographic features, presence of differential diagnosis or comorbid conditions, and setting of the study. Overall, 83 percent (n=10) of studies were assessed as high, 8 percent (n=1) as low, and 8 percent (n=1) as unclear for concern regarding applicability on this domain.

The potential for bias in the domain of the **index test** was assessed according to whether results were interpreted without knowledge of the results of the reference standard and whether a prespecified threshold was used for BNP cutpoints. Twenty-five percent (n=3) of studies were rated as low risk on this domain, 33 percent (n=4) were rated as high, and 42 percent (n=5) were rated as unclear. Studies were assessed on concerns of applicability on the basis of whether the index test methods varied from those specified in the review questions. Concerns about applicability on this domain were assessed as low for 67 percent (n=8) of studies, as high for 25 percent (n=3), and as unclear for 8 percent (n=1).

The potential for bias in the domain of the **reference standard** (i.e., the criteria used to confirm a diagnosis of HF) was judged on the basis of whether the reference standard was likely to correctly classify the target condition and whether the results were interpreted with knowledge of the BNP results. Studies were rated as low risk for 67 percent (n=8) of articles, high for 25 percent (n=3), and as unclear by 8 percent (n=1). Concerns about applicability were assessed as

to whether the target condition, as defined by the reference standard, differed from the target condition specified in the review question. Sixty seven percent (n=8) of studies were assessed as low, 25 percent (n=3) were assessed as high, and 8 percent (n=1) were unclear on this domain.

The potential for bias in the domain of **flow and timing** was assessed on the basis of inappropriate intervals between index test and reference standard, standardized administration of reference standard among patients, and equal inclusion of patients in the analysis. Eighty three percent (n=11) of studies were assessed as low risk and eight percent (n=1) were unclear as to bias for this domain.

NT-proBNP

For studies of diagnostic tests (KQ2), the QUADAS-2 used to assess quality in four key domains: patient selection, index test(s), reference standard, was and flow and timing. The questions in each domain are rated in terms of risk of bias (low, high, unclear) and concerns regarding applicability (low, high, unclear), with associated signaling questions to help with bias and applicability judgments (see Figures 9 and 10, and Appendix I Table I-6).

The potential for bias in the domain of **patient selection** was assessed on the basis of the enrollment of the study sample (consecutive, random, or convenience), the avoidance of a case-control design, and the avoidance of inappropriate patient exclusions. For this domain, 40 percent of studies (n=8) were rated as low risk for bias and 5 percent (n=1) were rated as high risk. The remaining studies (n=11; 55%) were rated as unclear as to risk of bias. Studies were assessed as to patient population, applicability to those targeted by the review question in terms of severity of the target condition, demographic features, presence of differential diagnosis or comorbid conditions, and setting of the study. Overall, 65 percent (n=13) of studies were assessed as high for concerns about applicability on this domain, 20 percent (n=4) were rated as low, and the remainder (n=3; 15%) were rated as unclear on concern regarding applicability on this domain.

The potential for bias in the domain of the **index test** was assessed according to whether results were interpreted without knowledge of the results of the reference standard and whether a prespecified threshold was used for NT-proBNP cutpoints. Forty-five percent (n=9) of studies were rated as low risk and 35 percent were rated as high risk (n=7) and 20 percent (n=4) were deemed unclear on this domain. Studies were assessed on concerns of applicability on the basis of whether the index test methods varied from those specified in the review questions. Concerns about applicability on this domain were assessed as low for 70 percent (n=14) of studies and as high for 30 percent (n=6).

The potential for bias in the domain of the **reference standard** (i.e., the criteria used to confirm a diagnosis of HF) was judged on the basis of whether the reference standard was likely to correctly classify the target condition and whether the results were interpreted with knowledge of the NT-proBNP results. Seventy percent of studies (n=14) were rated as low risk, 10 percent (n=2) were rated as high, and 20 percent (n=4) were rated as unclear on this domain. Concerns about applicability were assessed as to whether the target condition, as defined by the reference standard, differed from the target condition specified in the review question. Sixty-five percent (n=13) of studies were assessed as low and 35 percent (n=7) were assessed as high on this domain.

The potential for bias in the domain of **flow and timing** was assessed on the basis of inappropriate intervals between index test and reference standard, standardized administration of reference standard among patients, and equal inclusion of patients in the analysis. Ninety percent

(n=18) of studies were assessed as low risk of bias and 10 percent (n=2) were assessed as unclear on the domain of flow and timing.

Strength of Evidence for Studies With Primary Care Settings

BNP/NT-proBNP

Two primary outcomes were chosen to be assessed: sensitivity and specificity. For all studies that presented sensitivity and specificity data (BNP n=11;[148-154,156-159] NT-proBNP n=17[156-159,161-170,172-174]), the SOE was examined using a variety of cutpoints. For BNP the lowest cutpoint provided, the manufacturers' suggested, and the optimal cutpoint identified by the author were used. For NT-proBNP we used the lowest and optimal cutpoints.

The SOE for both BNP (Appendix I Tables I-7a to I-7c) and NT-proBNP (Appendix I Table I-8a to I-8c) were determined to be high for sensitivity and moderate for specificity at all cutpoints examined.

Risk of Bias

Using the QUADAS-2 tool, the risk of bias was rated for both sensitivity and specificity (Figures 7 to 10). The tests for publication bias exposed no significant bias in the following conditions in our meta-analysis of BNP and NT-proBNP diagnostic use in primary care: (1) optimum cutpoint, (2) lowest cutpoint, and (3) manufacturers cutpoint (see Appendix I Table I-9 and Figure I-21)**.** In the domains of reference standard and flow and timing, the majority of the studies showed a low risk of bias. In terms of patient selection, 58 percent of the studies had an unclear risk of bias. The domain of index test, 33 percent of the studies, had a high risk of bias. Despite the potential high risk of bias in the index test, the overall risk of bias was rated low.

Figure 7. Proportion (%) of all diagnostic studies using BNP with low, high, or unclear concerns regarding risk of bias in primary care

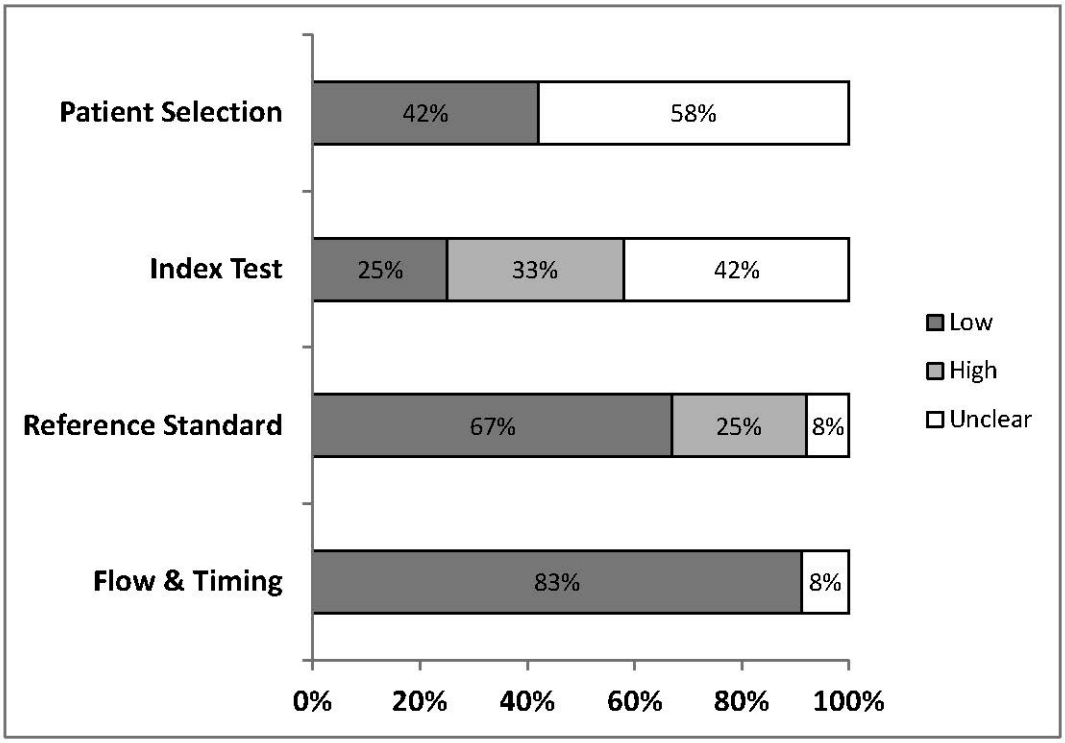


Figure 8. Proportion (%) of diagnostic studies using BNP with low, high, or unclear concerns regarding applicability in primary care

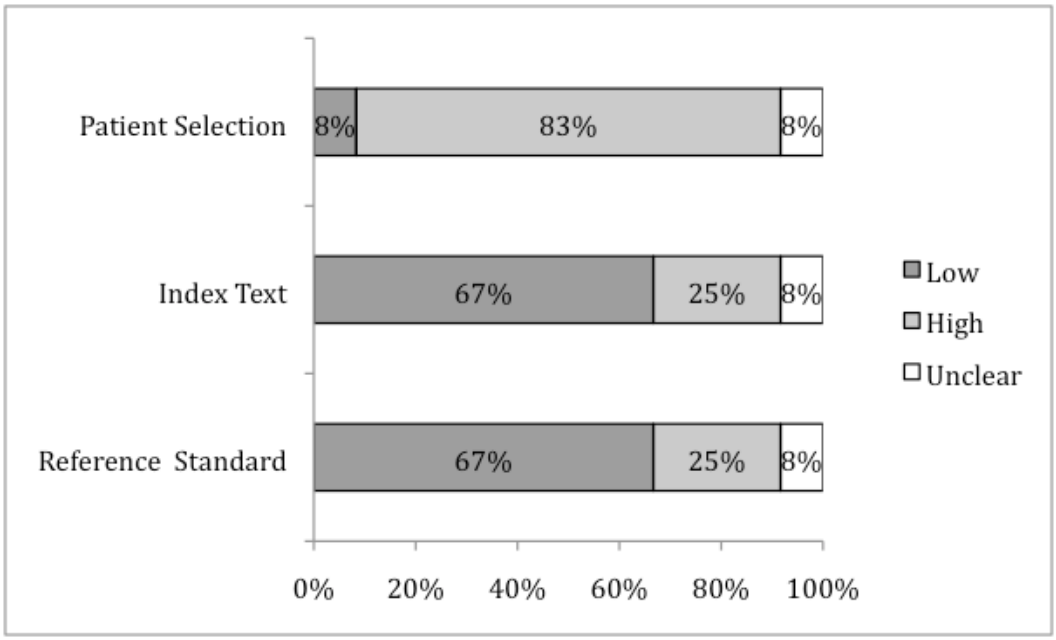


Figure 9. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding risk of bias in primary care

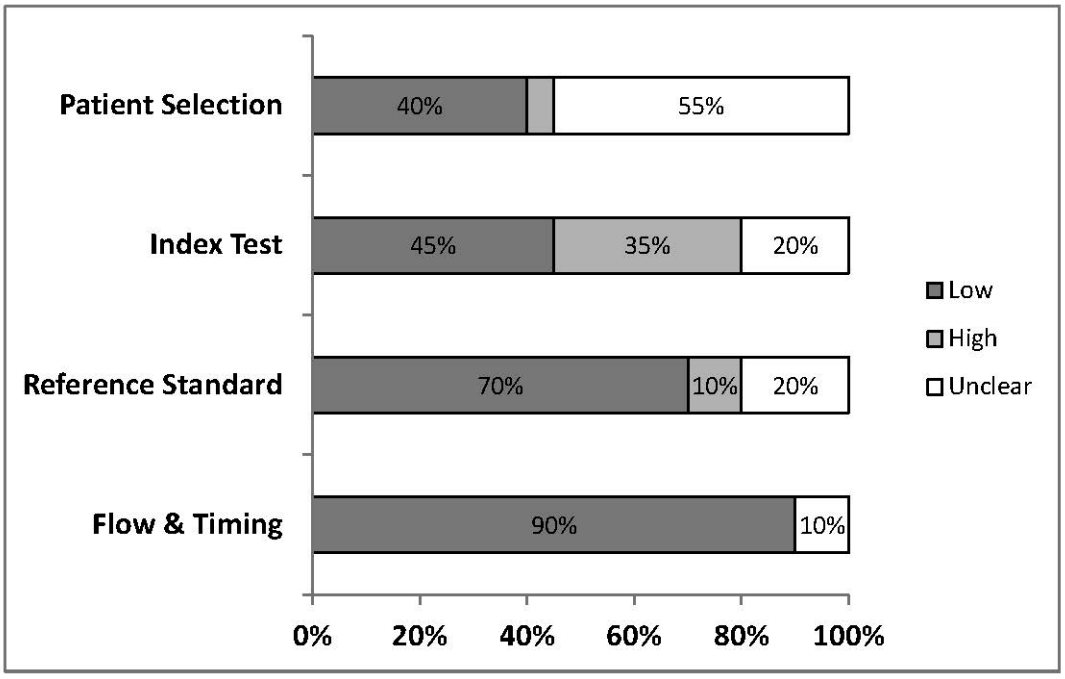
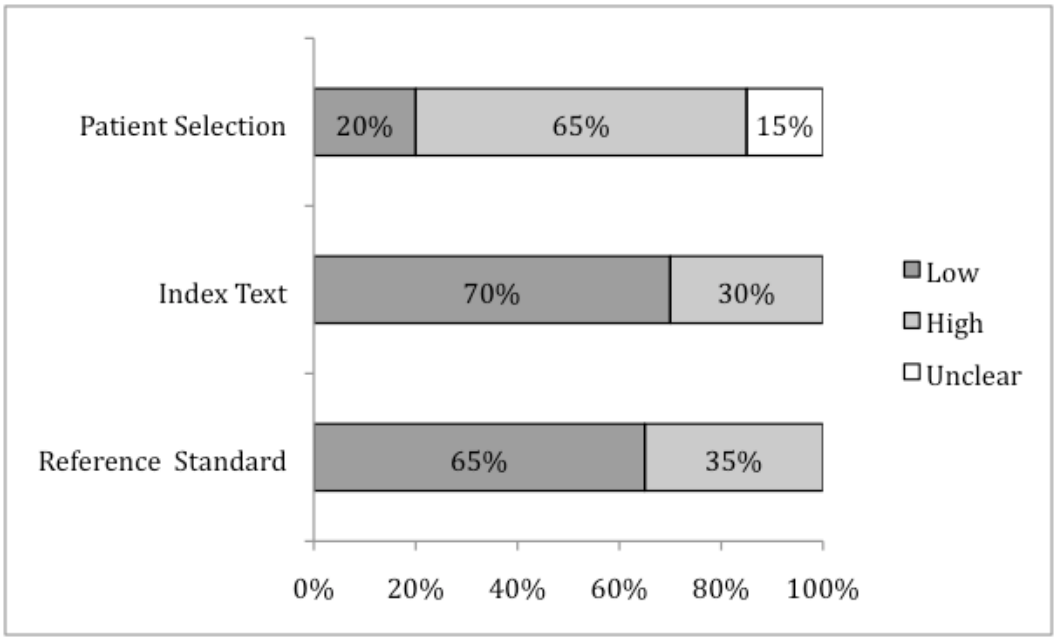


Figure 10. Proportion (%) of diagnostic studies using NT-ProBNP with low, high, or unclear concerns regarding applicability in primary care



Directness

The question of diagnostic accuracy is asked in KQ2 and sensitivity and specificity in a primary care population are being assessed. This domain was rated as direct, as these are concepts that are generally understood by clinicians and can be applied directly to diagnosis of HF in a similar clinical setting.

Precision

For both BNP and NT-proBNP, the CIs around the summary estimates for sensitivity and specificity for BNP and NT-proBNP are not precise. This domain was rated as imprecise (Table 20).

Consistency

In terms of BNP sensitivity, the directions of the estimates are consistent, and with the exception of a single study,[153] are very similar. In terms of NT-proBNP sensitivity, because the directions of the estimates are consistent and the CIs are small, this domain was rated as consistent for both BNP and NT-proBNP. However, the specificity was rated as inconsistent because the range of estimates across studies for both BNP and NT-proBNP are large (Table 20).

Table 20. Statistical summary of test performance characteristics based on the manufacturer, optimum, and lowest cutpoints in the primary care settings

Test	Cutpoint	Assay type	n study	Sensitivity			Specificity			LR+			LR-			log DOR			AUC	
				Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI	I^2	Est	95% CI
PC-BNP	Manu-facturer	D	8	0.74	0.63, 0.84	94	0.67	0.50, 0.85	99.1	2.6	1.69, 4.00	96.9	0.38	0.23, 0.62	92.7	2.02	1.24, 2.80	90.2	0.8	0.71, 0.88
	Optimum	D	8	0.8	0.71, 0.89	92.9	0.61	0.43, 0.80	98.4	2.27	1.59, 3.24	96.1	0.3	0.16, 0.55	93.4	2.07	1.20, 2.94	90.9	0.8	0.71, 0.90
	Lowest	D	10	0.85	0.77, 0.92	95.8	0.54	0.42, 0.66	97.3	1.87	1.50, 2.34	94.1	0.22	0.11, 0.44	93.7	2.18	1.41, 2.95	87.9	0.81	0.73, 0.90
PC-NT-proBNP	Manu-facturer	E	2	0.82	0.66, 0.98	86.7	0.58	0.54, 0.62	12.3	1.96	1.45, 2.66	87.7	0.29	0.10, 0.88	75.7	1.9	0.56, 3.25	78.9	-	-
	Optimum	E	11	0.86	0.79, 0.93	87.8	0.58	0.42, 0.75	99	2.18	1.81, 2.63	89.2	0.23	0.16, 0.34	75.5	2.5	1.87, 3.13	80.2	0.85	0.79, 0.90
	Lowest	E	12	0.9	0.85, 0.95	84.7	0.5	0.41, 0.60	96.4	1.87	1.59, 2.20	91	0.19	0.12, 0.29	73.1	2.38	1.86, 2.91	71.6	0.84	0.78, 0.89

NOTE: AUC were calculated for the group with 4 or more studies
ASSAY: A-ADVIA -Centaur® BNP Assay, B-Abbott AxSYM® B-Type, C-TRIAGE -B-Type Beckman, D-TRIAGE -B-Type Test, E-ELECSYS -proBNP Immunoassay
Abbreviations: AUC = area under the curve; CI = confidence interval; DOR = diagnostic odds ratio; Est = estimate; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; n=sample size; PC= primary care

Key Question 3: In HF populations, is BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge, an independent predictor of morbidity and mortality outcomes?

Interpretation of the results from prognostic studies may require some caution with respect to comparison across studies. Establishing the prognostic value of a marker within a single study requires consideration of the type of statistical computational methods (e.g., cox regression), the manner in which the BNP/NT-proBNP is operationalized within these computations (e.g., continuous, dichotomous, log-transformed), the number and types of covariates included as explanatory variables, and the threshold/cutpoint used to consider high and low risk groups within categorical analyses. Thus, the magnitude of a hazard ratio (HR) in one study is not comparable to that in another study when any of the features detailed above are different. Where provided within the text of eligible studies, aspects of the statistical model/computations are reported (e.g., the type and number of covariates, how BNP/NT-proBNP was operationalized within the statistical model, any applicable cutpoints). See Appendix J KQ3 Evidence Set.

BNP Levels in Decompensated Heart Failure Patients Using BNP and Prognosis

Characteristics of Studies in Decompensated Heart Failure Patients Using BNP Levels

Study Characteristics

The prognostic ability of BNP among patients with decompensated HF was assessed in 38 publications that dealt specifically with BNP.[106,176-212] A further six publications evaluated both BNP and NT-proBNP in this population.[3,213-217] One study[218] reported only multivariable correlation coefficient with BNP levels and the outcome of length of stay and as such is not suitable for prediction of outcomes. In total, 44 publications are presented for evaluating the predictive contribution of BNP levels in decompensated HF patients.

One article was an RCT examining outcomes in participants randomized to regular BNP measurements versus no regular BNP measurement.[194] Two articles were secondary analyses of data initially collected in RCTs; however, the secondary analyses did not account for the groups to which participants were randomized.[210,211] One[191] used a non-randomized controlled design, and six were retrospective[193,196,197,201,203,216] cohort studies. It was unclear in one article as to what study design was used. The remaining (n=33) used a prospective cohort design. The selected articles were published between 2004 and 2012 and were conducted world-wide including: nine in North America,[176,179,185,189,193,197,207,212,213] 28 in Europe,[106,177,178,180,182-184,186-188,190-192,195,198-206,208,209,211,215,219] and one in Asia.[181] Five studies were conducted in multinational sites.[3,196,210,216,217]

Companion Papers

Several publications reported on the same cohorts, including subjects from the Rapid Emergency Department Heart Failure Trial (REDHOT) study,[176] REDHOT II,[194] and from an Austrian HF specialty clinic.[182,204] Another study[216] included the subjects from the Austrian HF clinic with subjects from the PRIDE study.[213,216] Several other included papers were based on

large study cohorts including: one from the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial,[196] one from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study,[210] two from the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) trial,[211,220] two from the BASEL[188,220] study, and two from BACH.[3,221] Additionally, there were several publications that derived data from cumulative patient registries that overlapped in time (subsets of same patient pool) from the cardiology departments of Valencia, Spain[198,205] and Cuneo, Italy[178,184,199,201,203] acute care hospitals.

Risk of Bias

The risk of bias was assessed based on the Hayden criteria[58] as described in the methods section (Appendix E) and results across studies are seen in Figure 11 (see also Appendix J Table J-1 for individual study ratings).

For the studies including patients with decompensated HF and evaluating the predictive strength of BNP levels, there is low risk of bias for population description and selection, attrition, description of statistical analysis, and for how prognostic factors were addressed, with the exception that most studies did not provide reasons for indeterminate test results or missing data (item 3e).

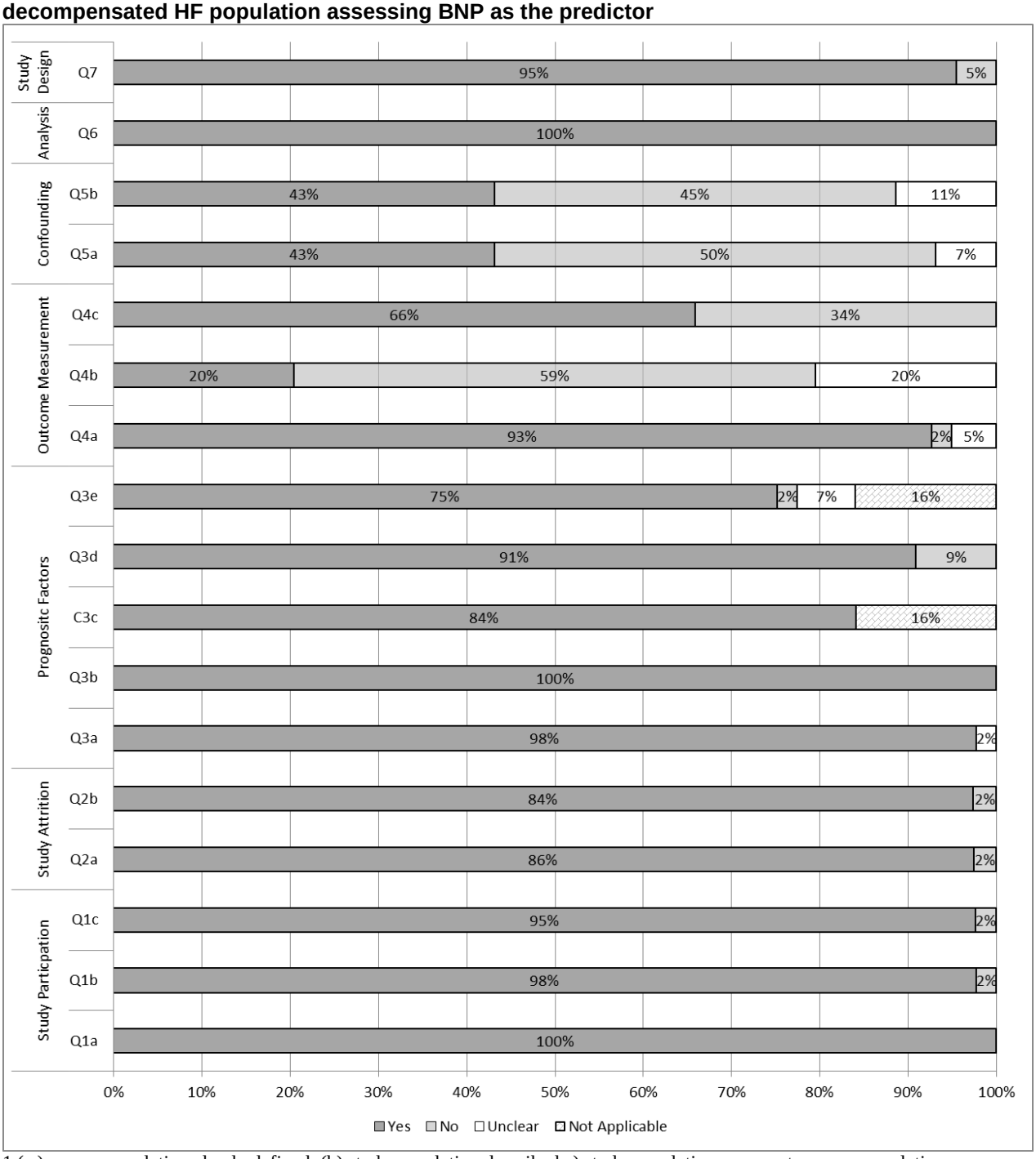
Although, the outcome measurement was adequately defined in most studies, the majority of publications did not adequately measure the outcome (item 4b), and many studies reported data for composite outcomes only (item 4c). The risk of bias is high for the BNP studies in decompensated patients with respect to adequate measurement of outcomes and avoiding composite outcomes.

Confounding was particularly poorly addressed in this group of studies. Based on the a priori criteria, studies were assessed for selection of important confounders such as age, sex, BMI, and renal function as important covariates within the prognostic model. Within these 44 publications, only 43 percent of studies met criteria for measuring confounders or accounting for them in the design or analysis (items 5a, 5b). The risk of bias is high for confounding and most studies omitted at least one of the key confounders (BMI in particular).

Most of the study designs were observational cohorts (prospective) and the majority of studies established research questions specifically to assess BNP levels. However, some studies evaluated other cardiac markers and the focus of the research and the development of the prognostic models included evaluation of the BNP but was not primarily focused on BNP.

In summary, the overall risk of bias in studies evaluating BNP levels as a predictor of outcome in decompensated patients for HF, was rated as moderate because of concerns with adequacy of outcome measurement, use of composite outcomes only, and problems with identification and adjustment for key confounders.

Figure 11. Assessment of risk of bias using the Hayden criteria for prognostic studies in decompensated HF population assessing BNP as the predictor



1.(a) source population clearly defined, (b) study population described c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

All tables showing the prognostic studies can be found in Appendix J.

BNP Levels Predicting Risk for All-Cause Mortality

Appendix J and Table 21 describe study outcomes and followup.

Admission, Discharge, and Change in BNP Levels and Prognosis Up to 31 Days

Five studies[183,194,196,215,217] assessed admission BNP levels and attempted to evaluate all-cause mortality up to 30 or 31 days (Appendix J Table J-2). Two studies recruited subjects from emergency settings. One study[217] reported that admission BNP levels were independent predictors of 14 day mortality. The REDHOT II study[194] recruited subjects with BNP levels greater than 100 pg/mL; patients were randomized to having serial BNP measurements (admission, 3, 6, 9, and 12 hours post admission) that were communicated to the physician; the control group did not have serial measurement and assessment of BNP was at the discretion of the physician. The findings from the REDHOT II study suggest that knowledge of serial BNP measurements has a protective effect with respect to predicting 30 day mortality but this was not statistically significant. This study could also be classified as one assessing the impact of the use of BNP to guide treatment.

Three studies enrolling subjects admitted to hospital[183,196,215] attempted to evaluate the association between baseline BNP and subsequent 30 day mortality. Two studies evaluated serial measurements of BNP, including admission, 24 hours,[196,215] 48 hours,[215] and at days three and five.[196] Neither study reported the predictive strength of admission BNP levels and subsequent mortality. Both these studies would suggest that serial measurements at 24 and 48 hours are significant predictors of 30 day mortality. One study[196] showed that change from baseline (reduction in BNP levels) was protective with respect to 30 day mortality. A single study[183] that was at high risk of bias evaluated patients admitted to an acute care center with BNP levels >100 pg/mL but reported no results from the logistic regression specific to BNP.

Admission, Discharge, and Change in BNP Levels and Prognosis From 2 to 3 Months

Four studies[3,176,214,217] attempted to evaluate the predictive strength of BNP levels and all-cause mortality at 3 months (Appendix J Table J-3). All but one study recruited subjects from the emergency setting.[214] Two publications[3,217] evaluated the subjects from the BACH study but differed in the number of subjects with final adjudication of acute HF; both BACH publications showed admission BNP levels to be independent predictors of 90 day mortality. One of these publications[3] showed admission BNP to be an independent predictor when considered as both a categorical, continuous, and log transformed variable in a simple statistical model (age, sex, BMI, creatinine) but not in a more complex model. The REDHOT trial,[176] showed that knowledge of serial BNP levels (admission, 3, 6,9, and 12 hour) was an independent predictor of 90 day all-cause mortality. A single study[214] recruited subjects admitted to hospital, evaluated a 10 percent change (decrease) relative to admission BNP levels and showed that this change in BNP levels was not a statistically significant predictor of 90 day mortality.

Admission, Discharge, and Change in BNP Levels and Prognosis at 6 to 11 Months

Five publications[196,198,200,205,210] evaluated BNP levels and prediction of all-cause mortality from 6 to 11 months (Appendix J Table J-4). Two publications[198,205] had overlapping samples recruited from the same hospital center. One of these publications[205] used log transformed BNP and showed it to be an independent predictor. The companion article[198] used admission BNP levels and showed a dose response effect; with increasing thresholds (quintiles) of BNP levels, the HR increased (from HR=2.75 (95% CI, 1.17 to 6.46) to HR=5.82 (95% CI, 2.62 to 12.97)). There was some concern with outcome measurement and the adjustment of confounders in these companion papers, suggesting the potential for increased risk of bias in these two publications. Another study[210] recruiting subjects form emergency settings and evaluating admission BNP levels showed that higher levels of BNP increased the HR for 6 month mortality (HR=1.84 (95% CI, 1.25 to 2.71) to (HR=3.22 (95% CI, 2.27 to 4.55)).

The two remaining studies evaluated change in BNP levels[196] and discharge BNP levels[200] as predictors of all-cause mortality. In one study,[196] a decrease of BNP levels greater than 30 percent relative to admission (or <800 pg/mL) showed a protective effect from mortality. In the second study,[222] combining subjects who had discharge BNP levels greater than or equal to 360 pg/mL and a decrease of less than 50 percent, or increase (Group 3 vs. 1) showed the highest HR (Appendix J Table J-4).

Admission, Discharge, and Change in BNP Levels and Prognosis at 12 to 23 Months

There were seven publications that evaluated admission BNP levels from the BASEL cohort,[106,188] a German study (overlapping samples),[182,204] the PRIDE study,[213,216] and an independent study[193] for predicting 12 month all-cause mortality. Two studies[211,215] evaluated change or discharge levels of BNP.

All but two studies[193,211] recruited patients from emergency settings. All but one study[215] recruited subjects from emergency settings and evaluated admission BNP levels as predictors. One additional[193] study evaluated admission BNP levels but recruited subjects admitted to hospital but with a mixed population with 29.7 percent of subjects recruited from the community The seven publications[106,182,188,204,213,215,216] that recruited patients from emergency settings, were generally at low risk of bias, with the exception of some concerns regarding verification or validity of the outcomes and potential confounding. One study with two publications,[182,204] undertook different model computations on the same dataset. (Appendix J Table J-5) shows the differences in the estimate of the HR varying from HR=2.45 (95% CI, 1.29 to 4.65) to HR=3.34 (95% CI, 1.61 to 6.97). Similarly, two studies from the PRIDE cohort[216] and the Boston site of the PRIDE cohort,[213] showed that admission BNP levels were independent predictors of all-cause mortality (HR=2.12 [95% CI, 1.37 to 3.27] and HR=2.53 [95% CI, 1.53 to 6.21]) at 12 months.

Two publications[106,223] based on subjects from the BASEL study, modeled admission BNP levels as a dichotomous and continuous variable, and both were independent predictors of 12 month mortality. The final study evaluating admission BNP levels also showed that BNP was an independent predictor of mortality at 12 months.[193]

Two studies did not assess the prognostic value of admission BNP levels assessed but serial measurements[215] and discharge BNP levels.[211,215] The first study[215] showed that 24 and 48 hour and discharge BNP levels were all significant independent predictors of 12 month mortality. The second study[211] had a primary aim to evaluate the prognostic merit of Type D personality type

(distressed) as a predictor of mortality but did not find this factor (or symptoms of depression) to be significant; rather, discharge BNP was shown to be an independent predictor at 18 months.

Admission, Discharge, and Change in BNP Levels and Prognosis at 24 Months and Greater

There were three studies,[179,192,208] that evaluated prognosis at 24 months (Appendix J Table J-6). The single study[208] evaluating admission BNP levels as a predictor of 24 month all-cause mortality had a primary objective to compare the value of human growth factor as a predictor; BNP was the reference biomarker, and was shown to be a significant predictor. A second study[192] compared admission and discharge BNP levels and both were shown to be independent predictors at 24 months. The final study[179] evaluating prediction of 24 month all-cause mortality evaluated discharge BNP levels and this was not statistically significant.

Table 21. Outcomes by length of time interval in decompensated population assessing BNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Kellett,[183] 2008	A																							
Singer,[194] 2009	A																							
Maisel,[176] 2004	A																							
Boisot,[214] 2008	A	D	C																					
Peacock,[217] 2011	A																							
Maisel,[3] 2010	A																							
Cohen-Solal,[196] 2009	A	D	C																					
Nunez,[205] 2010	A																							
Allen,[210] 2011	A																							
Núñez,[198] 2008	A																							
Arenja,[106] 2011	A																							
Dieplinger,[204] 2009	A																							
Reichlin,[188] 2010	A																							
Dunlay,[193] 2009	A																							
Noveanu,[215] 2011	A	S	D																					
Rehman,[216] 2008	A																							
Sakhuja,[213] 2007	A																							
Gegenhuber,[182] 2007	A																							
Coyne,[211] 2011	A																							
Neuhold,[192] 2010	D	C																						
Rychli,[208] 2011	A																							
Stoiser,[179] 2006	D																							

Table 21. Outcomes by length of time interval in decompensated population assessing BNP (continued)

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cardiovascular mortality																								
Arques,[209] 2011	NR	A																						
Zairis,[187] 2010	A																							
Nunez,[205] 2010	A																							
Sun,[181] 2007	A																							
Rychli,[208] 2011	A																							
All-cause morbidity																								
Allen,[210] 2011	A																							
CV morbidity																								
Singer,[194] 2009	A																							
Stoiser,[179] 2006	D																							
Neuhold,[192] 2010	D	C																						
Cardiovascular mortality and cardiovascular morbidity																								
Parissis,[202] 2007	A																							
Valle,[184] 2005	A																							
Cournot,[180] 2006	A	D	C																					
Cournot,[200] 2008	D	C																						
Nahum,[189] 2010	A																							
Dokainish,[185] 2005	A	D																						
Composite of all-cause mortality and cardiovascular morbidity																								
Maisel,[212] 2011	A	D																						
Pimenta,[206] 2009	D																							
Maisel,[176] 2004	A																							
Xue,[207] 2010	D																							
Aspromonte,[178] 2007	D																							
Valle,[203] 2008	A	D																						
Faggiano,[190] 2009	A																							

Table 21. Outcomes by length of time interval in decompensated population assessing BNP (continued)

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Farmakis,[191] 2008	A	C																						
Feola,[199] 2008	D																							
Logeart,[177] 2004	A	D																						
Parissis,[195] 2009	A																							
Dhaliwal,[197] 2009	A	D	C																					
Stoiser,[179] 2006	D																							
Composite of all-cause mortality and all-cause morbidity																								
Di Somma,[186] 2010	A	D																						
Valle,[201] 2008	D	C																						
Allen,[210] 2011	A																							

xI vertical line indicates intermittent endpoint measurement

* mean; **median; A=Admission BNP used; D=Discharge BNP used, C=Change in BNP for admission to discharge used

BNP Levels Predicting Cardiovascular Mortality

Five studies evaluated the prognostic value of admission BNP levels and cardiovascular mortality from 31 days,[187,209] 6 months,[205] 12 months,[181] and 24 months.[208] Two studies[3,214] measured cardiovascular mortality at 90 days but did not report data evaluating the predictive value of admission BNP (Appendix J Table J-7).

Two studies[187,209] at low risk of bias (except for potential measurement of confounding) evaluated admission BNP levels and prognostic value at 31 days for cardiovascular mortality. These studies included similar patient populations (older patients with severe HF) and cutpoints; their findings suggest that admission BNP is an independent predictor adding incremental prognostic value[187] and showing increasing odds (for log transformed BNP) of cardiovascular mortality.

One study[205] that evaluated cardiovascular mortality at 6 months showed that the log transformed admission BNP was an independent predictor (HR=1.48 (95% CI, 1.24 to1.77)). This same study reported similar values for HF mortality (HR=1.47 (95% CI, 1.19 to 1.81)).

Two studies[181,208] evaluated cardiovascular mortality for longer term followup (12 and 24 months), and one[181] reported the prognostic strength of admission BNP (odds ratio (OR)=1.21 (95% CI, 1.06 to 2.32)) and the other indicating that admission BNP levels was a significant independent predictor.[208]

BNP Levels Predicting Morbidity Outcomes

Four studies[179,192,194,210] reported on morbidity outcomes using admission and discharge BNP for followup periods of 1,[194] 6,[210] and 24 months.[179,192] A single study[194] evaluated serial BNP levels for predicting 6 month cardiovascular morbidity (readmission) and their findings suggest that knowledge of BNP values had a protective effect (Appendix J Table J-8).

Two other studies[179,192] evaluated cardiovascular readmission outcomes but evaluated discharge BNP levels as the prognostic indicator at 24 months; one study showed that discharge BNP levels was an independent predictor[179] and the other[192] showed that it was not significant but this paper was suspect with respect to the selection and adjustment of confounders. One other paper[210] used discharge BNP levels to predict unfavorable quality of life (QOL) or hospitalization at 6 months and showed that BNP was a significant predictor only for the hospitalization outcome at both thresholds for BNP levels.

BNP Levels Predicting Composite Outcomes

All-Cause Mortality and All-Cause Morbidity

Two studies evaluated the composite outcome of all-cause mortality and all-cause morbidity at 3 months[186] and 6 months.[210] One study[186] evaluated discharge and change from admission in isolation or in combination to predict a composite outcome; when combining change less than 46 percent and BNP greater than 300 pg/mL at discharge, the greatest risk (OR=9.61 (95% CI, 4.51 to 20.47), $p<0.001$) was observed. The second study[210] also used discharge BNP levels and found it to be an independent predictor. (Appendix J Table J-9)

All-Cause Mortality and Cardiovascular Morbidity

Fourteen publications[176-179,190,191,195,197,199,201,203,206,207,212] evaluated the composite outcome of all-cause mortality and cardiovascular morbidity. Two studies evaluated this outcome at 1 month where one study[212] showed that admission BNP levels and the other[206] discharge BNP levels

both were independent predictors. Similarly, two studies evaluated prediction at 3 months and one[176] showed that admission BNP levels were significant; however, the second study[207] showed that BNP was not a significant predictor when selecting a dichotomous predictor (threshold 360 pg/mL) but was statistically significant when placed in the prognostic model as a continuous variable (Appendix J Table J-10).

Five publications[178,190,199,201,203] evaluated overlapping patient populations from related clinics in Italy, and all used discharge BNP levels as the prognostic indicator which was consistently shown to be an independent predictor at 6 months. Two other studies evaluated composite outcome at 6 months. One study[191] showed only change from baseline (less than 58 percent) to be a significant predictor and admission BNP levels were not. The second study[177] evaluated discharge BNP levels as predictors in the study sample but also in a validation cohort; discharge BNP levels were predictive of this composite outcome, but the risk was significantly increased in the validation sample.

Three remaining studies evaluated BNP levels as predictors of longer term composite outcome at 12 months,[195] 392 days,[197] and 24 months.[179] One study[195] evaluated admission BNP levels as a predictor in patients with depression and showed that it was a significant predictor (HR=1.002, p=0.001). The remaining two studies evaluated post admission change from baseline or discharge BNP levels as predictors. One study[197] evaluated patients post admission (interval not specified) and combined data of BNP levels with some data from patients up to 30 days post discharge; their findings suggest that BNP levels measured post admission were significant predictors of 12 month composite outcome. In this group, discharge and percent change from discharge were evaluated; the latter showed a protective effect (HR=0.7 (95% CI, 0.6 to 0.9), p=0.006). The third study[179] reported that adding BNP improved model performance and was a significant predictor.

Cardiovascular Mortality and Cardiovascular Morbidity

Six publications[180,184,185,189,200,202,222] evaluated the composite outcome of cardiovascular mortality and cardiovascular morbidity; two publications[180,200] may have overlapping samples (Appendix J Table J-11). Two studies[184,202] evaluated admission BNP levels and prediction of this composite outcome at 6 months and both showed it to be an independent predictor, with increasing risk when levels were higher.[184] Two related studies[180,222] showed that change in BNP levels (as a decrease alone or in combination with a discharge BNP threshold) was a significant predictor at 7 months. From the two remaining studies, one publication[189] showed that admission BNP was not a significant predictor, and the other[185] showed that discharge BNP levels contributed to the prognostic model and was significant.

NT-proBNP Levels in Decompensated Heart Failure Patients and Prognosis

Characteristics of Studies in Decompensated Heart Failure Patients Using NT-proBNP Levels

Study Characteristics

The prognostic ability of NT-proBNP among patients admitted to hospital was assessed in 35 publications that deal specifically with NT-proBNP.[1,2,224-256] A further six publications looked at both BNP and NT-proBNP.[3,213-217] In total, 41 publications are discussed in this section. Study

design was unclear in one paper,[245] five used a retrospective cohort study design,[216,232,235,240,256] and the remaining (n=35) were prospective cohort studies. The selected articles were published between 2004 and 2012 and were conducted world-wide including: four in North America,[1,213,214,253]19 in Europe,[215,224,226,230-233,236,237,240-242,244-247,250,251,254] three in Asia,[234,235,252] one in South America,[227] and one in Australia.[243] Eight studies were conducted in multinational sites,[2,3,216,217,225,228,238,239] and one did not report region of conduct.[249]

Companion Papers

Several included papers were based on large study cohorts including: two[225,228] from the ICON study, one[256] from the Echo Cardiography and Heart Outcome Study (ECHOS), two[3,217] from the BACH study, and two[213,228] from the PRIDE study. Four studies used a combination of data sets including, ICON, PRIDE and others,[2,238,239] and PRIDE and other.[216] Additionally, two articles published results on companion data sets.[230,248] The remaining papers were independent studies using unique data sets.

Risk of Bias

The risk of bias was assessed based on the Hayden Criteria[58] as described in the methods section of this report. Figure 12 shows the proportion of studies meeting the criteria assessed for risk of bias (see Appendix J Table J-12 for individual study ratings).

For the studies including patients with decompensated HF and evaluating the predictive strength of NT-proBNP levels, there is low risk of bias for population description and selection, attrition, description of statistical analysis, and for how prognostic factors were addressed, with the exception that most studies did not provide reasons for indeterminate test results or missing data (item 3e).

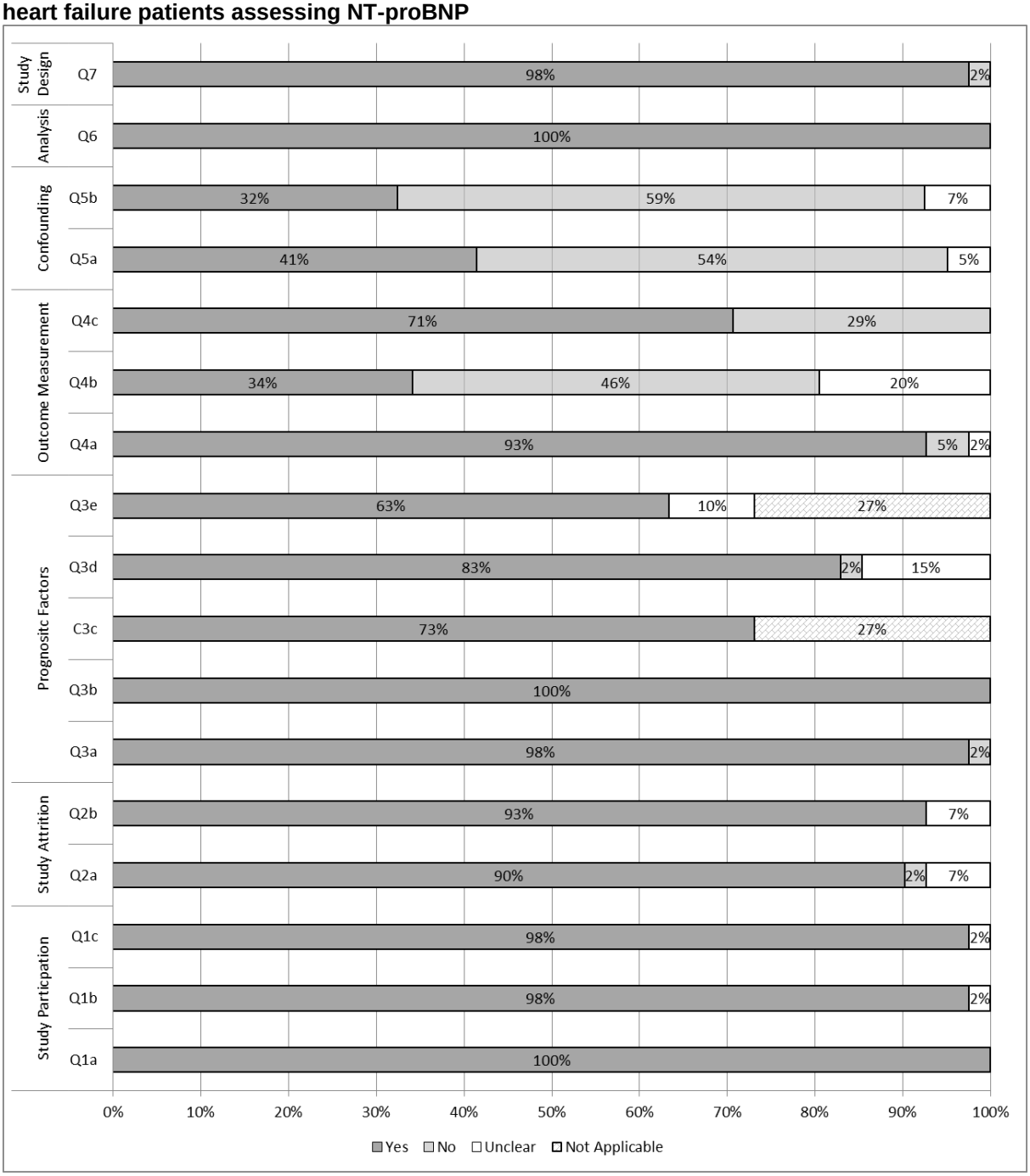
Although, the outcome measurement was adequately defined in most studies, the majority of studies (66%) did not adequately measure the outcome (item 4b), and at least one third of the studies reported data for composite outcomes only (item 4c). The risk of bias is high for this group of studies with respect to adequate measurement of outcomes and avoiding composite outcomes.

Confounding was particularly poorly addressed in the studies evaluating NT-proBNP in decompensated HF patients. The a priori criteria for confounding assessed studies with respect to a minimum set of confounders that included age, sex, BMI, and renal function as important covariates. Only 41 percent of studies in this group met the criteria for measuring confounders (item 5a) and 32 percent accounted for them in the design or analysis (item 5b). The risk of bias is high for confounding (BMI in particular) in these studies.

Most of the study designs were observational cohorts (prospective) and the majority of studies established research questions specifically to assess BNP levels. However, some studies evaluated other cardiac markers and the focus of the research (and covariates in the prognostic models) was not primarily focused on BNP.

In summary, the overall risk of bias in studies evaluating BNP levels as a predictor of outcome in decompensated patients rated overall as moderate.

Figure 12. Risk of bias for prognostic studies using the Hayden criteria for both decompensated heart failure patients assessing NT-proBNP



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Study Outcomes and Followup Periods

Table 22 shows study outcomes and followup period for patients admitted to hospital for decompensated HF. Twenty-three[1-3,213-217,224,225,228,234,238-240,242,243,245,247,248,250,251,256] of the 41 publications assessed all-cause mortality as a primary outcome using followup periods ranging from 2 months[1,225,228] to 81 months.[256] The majority of these studies, with the exception of three,[214,217,247] used NT-proBNP collected at admission as a prognostic indicator for all-cause mortality. Four papers[224,234,242,243] used discharge NT-proBNP and change in NT-proBNP from admission to discharge, along with admission NT-proBNP, as covariates in their models. One article[247] used NT-proBNP measurements taken serially in combination with discharge, while another[215] added admission NT-proBNP to serial and discharge measures. One article[217] just used serial measurements of NT-proBNP. Five articles[229,230,236,246,249] assessed cardiovascular mortality as an outcome, with followup periods ranging from one month[249] to 15 months.[246] All, but one,[249] used admission NT-proBNP to predict cardiovascular mortality. Two articles[230,249] used serial measurements, along with change in NT-proBNP, in their models.

All-cause morbidity was assessed in three articles,[234,243,253] and cardiovascular morbidity outcomes were assessed in one.[229] The remaining outcome measures consisted of composite outcomes combining various combinations including: cardiovascular mortality and cardiovascular morbidity,[231,237,252,255,257] all-cause mortality and cardiovascular morbidity,[1,226,227,241,254,258] all-cause mortality and all-cause morbidity,[232-234,250,253,259] and cardiovascular mortality and all-cause morbidity.[244] Of the articles assessing morbidity or composite outcomes, 10 used admission NT-proBNP alone as a prognostic indicator.[1,234,235,237,241,250,252,254,255,260] The remaining publications used various combinations of admission, discharge, and change scores of NT-proBNP to predict morbidity and composite outcomes.

Results

NT-proBNP Levels Predicting Risk for All-Cause Mortality

Admission and Predischarge NT-proBNP Levels and Prognosis Up to 31 Days

Two studies evaluated NT-proBNP levels and predicted all-cause mortality within 31 days post admission. One study[217] evaluated admission NT-proBNP in patients admitted to the emergency department and with a final diagnosis of acute HF; findings suggested that NT-proBNP was not a significant predictor for 14 day mortality and that MR-proADM and copeptin may provide superior prediction relative to NT-proBNP. The second study evaluated 24 and 48 hour post admission and predischarge levels and assessed prediction of 30 day all-cause mortality.[215] This study showed that only predischarge NT-proBNP was a significant predictor (Appendix J Table J-13).

Admission and Discharge NT-proBNP Levels and Prognosis From 2 to 3 Months

All-cause mortality was assessed in seven NT-proBNP publications for admission levels[1-3,217,225,228] and post admission/predischarge[214] levels as a prognostic indicator (Appendix J Table J-14).

Four publications were related with respect to overlapping subjects and evaluated predictive ability for 90 day all-cause mortality; two were companion articles reporting on data from the ICON study,[225,228] one was from the PRIDE study,[1] and one included data from ICON and the

PRIDE studies combined.[2] Three of these related publications showed that admission NT-proBNP was an independent and statistically significant predictor of 60 day all-cause mortality; the study evaluating the PRIDE cohort[1] showed an odds ratio (OR) of similar magnitude to the other related studies but unlike the other studies, did not show statistical significance.

Two publications evaluated subjects from the BACH study. One publication evaluated the entire BACH sample[3] and showed that admission NT-proBNP was a significant independent predictor only when MDproADM and troponin were not added to the predictive model. The second study evaluated a subset of subjects who subsequently had a confirmed diagnosis of acute HF[217] from the BACH study and showed that admission NT-proBNP added predictive value to the prognostic model.

A single paper[214] measured admission and discharge NT-proBNP levels but reported predictive ability for a change in admission levels (decrease by 3 percent); this study showed the OR to be less than 1 (OR=0.19) suggesting a statistically significant protective effect for 90 day mortality.

Admission and Discharge NT-proBNP Levels and Prognosis From 6 to 11 Months

All-cause mortality was assessed at 6 months by five studies[224,234,240,243,247] using NT-proBNP as a prognostic indicator (Appendix J Table J-15). Two related papers evaluated a subset of participants[240] from a larger population[224] with the New York Heart Association (NYHA) III and IV only. One[240] of these companion studies evaluated the ability to predict mortality based on an analysis with extreme tertiles of admission NT-proBNP levels and showed the highest NT-proBNP levels to be the strongest predictor of death. The study with the larger sample[224] evaluated change or increase of 30 percent relative to baseline and showed NT-proBNP to be a significant predictor.

One study[243] compared admission and discharge NT-proBNP levels and both were independent predictors, but discharge levels were of greater magnitude (HR=3.25 vs. HR=7.05). Another study[234] compared admission NT-proBNP levels at two admission thresholds (>17.86 pg/mL and <8.49 pg/mL) relative to a decrease of 35 percent from admission; both threshold NT-proBNP levels were independent predictors but the decrease in NT-proBNP showed a protective effect (OR=0.19, p=0.071). The final study[247] evaluated only the predictive ability of greater than 3,000 pg/mL discharge NT-proBNP levels and showed the largest HR (HR=13.63) for predicting 6 month mortality.

Admission and Discharge NT-proBNP Levels and Prognosis From 12 to 23 Months

Eight publications reported on the prognostic ability of NT-proBNP to predict all-cause mortality at 12 months (Appendix J Table J-16). Four related publications evaluated subjects in the PRIDE only,[213] PRIDE combined with other sample,[216] and ICON cohorts[238,239] (which included PRIDE subjects) and these studies all showed admission NT-proBNP to be an independent predictor of 12 month mortality. Two of these studies[213,216] were rated as problematic with respect to outcome measurement, relying on hospital records only to assess outcome. Three additional studies evaluated admission NT-proBNP and risk of subsequent mortality at 12 months and only one of these[250] did not show that it was a significant predictor. Another study[215] compared 24 and 48 hour admission levels and subsequent mortality prediction; only 48 hour NT-proBNP levels were a significant predictor.

Two studies[215,242] evaluated discharge or after clinical stabilization NT-proBNP levels and showed HR of similar magnitude but different increments for added risk (500 vs. 1,000 pg/mL) (Appendix J Table J-16).

Admission and Discharge NT-proBNP Levels and Prognosis at 24 Months or Greater

Three studies assessed admission NT-proBNP levels and all-cause mortality at 24/25 months,[245,251] and 6.8 years.[256] All studies showed that admission NT-proBNP was an independent predictor despite differing prognostic models. One study[245] showed an increasing HR with an increasing threshold for NT-proBNP levels (Appendix J Table J-17) but only those greater than 5,000 pg/mL were statistically significant.

Table 22. Outcomes by length of time interval in decompensated population assessing NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
van Kimmenade,[228] 2006	**A**																							
van Kimmenade,[1] 2006	**A**																							
Baggish,[225] 2007	**A**																							
Januzzi,[2] 2006	**A**		2.6																					
Boisot,[214] 2008	**a**	**d**	C																					
Peacock,[217] 2011	**S**																							
Maisel,[3] 2010	**A**																							
Lourenco,[240] 2009	**A**																							
Paul,[243] 2008	**A**	**D**	C																					
Siswanto,[234] 2006	**A**	**D**	C																					
Metra,[247] 2007	**S**	**D**																						
Bettencourt,[224] 2004	**A**	**D**	C																					
Sakhuja,[213] 2007	**A**																							
Rehman,[216] 2008	**A**																							
Noveanu,[215] 2011	**A**	**S**	D																					
Mohammed,[238] 2010	**A**																							
Baggish,[239] 2010	**A**																							
Kubler,[242] 2008	**A**	**D**	C																					
Lassus,[248] 2007	**A**																							
Carrasco-Sanchez,[250] 2011	**A**																							
Andersson,[245] 2008	**A**																							
Pascual-Figal,[251] 2011	**A**																							
Harutyunyan,[256] 2012	**A**																						81	..>

Table 22. Outcomes by length of time interval in decompensated population assessing NT-proBNP (continued)

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cardiovascular mortality																								
Luers,[249] 2010	a	S		C[x]																				
Davutoglu,[236] 2010	A																							
Marcucci,[229] 2006	A							8.5																
Bayes-Genis,[230] 2005	A	S	C																					
Petretta,[246] 2007	A																							
All-cause morbidity																								
Paul,[243] 2008	**A**	**D**	C																					
Siswanto,[234] 2006	**A**	C																						
Michtalik,[253] 2011	**A**	d																						
Cardiovascular morbidity																								
Marcucci,[229] 2006	A							8.5																
Cardiovascular mortality and cardiovascular morbidity																								
Bayes-Genis,[231] 2006	**A**	S	C																					
Park,[235] 2010	**A**																							
Ho,[252] 2011	**A**																							
Dini,[237] 2010	**A**																							
Krackhardt,[255] 2011	**A**																						**107**	**..>**
Composite of all-cause mortality and cardiovascular morbidity																								
van Kimmenade,[1] 2006	**A**																							
Metra,[247] 2007	**S**	D	C																					
Bettencourt,[226] 2007	**A**	D	C																					
Perna,[227] 2006	**A**	D																						
Fernández,[241] 2009	**A**							8.7																
Korewicki,[254] 2011	**A**																							

Table 22. Outcomes by length of time interval in decompensated population assessing NT-proBNP (continued)

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of all-cause mortality and all-cause morbidity*																								
Ferreira,[232] 2007	**A**	D																						
Pimenta,[233] 2007	**A**	D																						
Siswanto,[234] 2006	**A**																							
Bettencourt,[224] 2004	**A**	D	C																					
Michtalik,[253] 2011	**A**	D																						
Carrasco-Sanchez,[250] 2011	**A**																							
Composite of cardiovascular mortality and all-cause morbidity																								
Verdiani,[244] 2008	**A**	D	C																					

XI vertical line indicates intermittent endpoint measurement

* mean; **median; A=Admission NT-proBNP used; D=Discharge NT-proBNP used, C=Change in NT-proBNP for admission to discharge used; lower case ACD indicates measured by not used; ->study duration and endpoint greater than 24 months

X = 12 hours Y = 24 hours

NT-proBNP Levels Predicting Cardiovascular Mortality

A single study[249] evaluated NT-proBNP levels at admission, at 12 hours post admission and the change from admission to 12 hour post admission to predict 30 day cardiovascular mortality (Appendix J Table J-18). These results were also stratified by subgroups of HF patients (chronic ischemic cardiomyopathy (ICM), decompensated non-ischemic cardiomyopathy (NONICM) and acute ischemia (AMI)). The findings in this study suggest that NT-proBNP levels after admission (at 12 hours or increase from baseline at 12 hours) are predictive of mortality but admission levels are not. There was some variation in statistical significance within the HF subgroups; the sample sizes were small relative to the covariates included in the model for the AMI and NONICM groups.

Two papers evaluated admission NT-proBNP levels at 6 months[236] and 8.5 months[229] as predictors of cardiovascular mortality (Appendix J Table J-19). Both studies showed that NT-proBNP was not a significant predictor, but both studies did not include important covariates in their prognostic models.

A single study evaluated NT-proBNP levels and cardiovascular mortality at 12[230] and 15.5 months (Appendix J Table J-19). One study used the reduction of NT-proBNP levels greater than 30 percent relative to admission levels, as predictive of cardiovascular mortality; this study was rated as having some deficiencies with respect to identification and control of confounders. A second study compared admission NT-proBNP and log transformed NT-proBNP as predictors of cardiovascular mortality; although both HR estimates were significant, the log transformed value doubled the magnitude of the risk

Admission and Discharge NT-proBNP Levels and Morbidity Outcomes

Four studies assessed NT-proBNP levels and all-cause hospitalization at 30 days,[253] at 6 months,[234,243] and HF hospitalization at 8.5 months[229] (Appendix J Table J-20). One study[253] that was rated as problematic with respect to outcome measurement and confounding, showed that change in NT-proBNP relative to admission levels (less than 50 percent reduction) was a predictor of 30 day mortality but it was not statistically significant. In contrast, another study[234] evaluated change in NT-proBNP levels (reduction of greater than 35 percent relative to baseline) and showed that it had a protective effect for hospital readmission.

Another study[243] compared admission and discharge NT-proBNP levels; although both were significant predictors of 6 month hospital readmission, the HR for discharge was of greater magnitude.

Admission and Discharge NT-proBNP Levels Predicting Composite Outcomes

All-Cause Mortality and All-Cause Morbidity

Seven publications evaluated the composite outcome of all-cause mortality and all-cause morbidity (primarily rehospitalization) (Appendix J Table J-21) at 6 months.[226,232] From these, four publications[224,226,232,233] evaluated subjects from the same registry that were partial[224] or completely overlapping samples[226,232,233] and followed subjects up to 6 months. Three[224,226,232] of these related publications evaluated change in NT-proBNP levels as: (1) change-decrease of greater than or equal to 30 percent (group 1); (2) changed greater than 30 percent (group 2); or (3) change-increase greater than 30 percent. The fourth publication[233] evaluated decrease less than and greater than 30 percent and discharge levels. Although all three of these thresholds were

independent predictors, the increase by greater than 30 percent had the HR of greatest magnitude across all three studies for predicting 6 month composite outcome. Additionally, all four publications show that a decrease less than 30 percent relative to admission in NT-proBNP levels incurs an increased risk for death or rehospitalization (Appendix J Table J-21). This was observed for patients with and without renal failure.[233] In contrast, one study[234] evaluating decrease in NT-proBNP levels greater than 35 percent from baseline discharge NT-proBNP, showed a protective effect (HR=0.42 (95% CI, 0.12 to 0.76), p=0.010) from mortality and rehospitalization at 6 months.

Two studies evaluated the predicting composite outcome of all-cause mortality and all-cause morbidity at 12 months. One study[250] reported that admission NT-proBNP was not a significant predictor. The second study[253] showed that 50 percent change (relative to admission levels) was an independent predictor of outcome.

All-Cause Mortality and Cardiovascular Morbidity

Five studies evaluated all-cause mortality and cardiovascular endpoints at 2 months,[1] 184 days,[247] 252 days,[227] 261 days,[241] and 601 days.[254] All but two studies evaluated all-cause mortality and HF or cardiovascular readmission; one study[1] evaluated all-cause mortality and recurrent HF and the other study[254] measured all-cause mortality and heart transplant list (Appendix J Table J-22). Despite the different prognostic models and time intervals, all were shown to be independent predictors of the composite outcomes; only one of these was not statistically significant for predicting all-cause mortality and recurrence of HF at 2 months.[1]

Cardiovascular Mortality and All-Cause Morbidity

A single study[244] evaluated predictive ability of change in NT-proBNP levels (reduction less than 30 percent) for the composite endpoint of cardiovascular mortality and hospital readmission at 6 months (Appendix J Table J-23). This study showed that a reduction less than 30 percent increased the risk of this endpoint (HR=2.04 (95% CI, 1.02 to 4.08), p=0.04).

Cardiovascular Mortality and Cardiovascular Morbidity

Five studies evaluated the composite outcome of cardiovascular mortality and cardiovascular morbidity at 3 months,[231,235] 6 months,[252] 24 months,[237] and 6.8 years.[255] Two of these studies did not show a statistical significance for predicting composite endpoint at 3 months[235] and 24 months.[237] Two studies[252,255] showed that admission NT-proBNP was a significant predictor for this composite outcome. The final study[231] showed that a decrease at 2 weeks post admission had a protective effect (HR=0.79 (95% CI, 0.70 to 0.88), p<0.001) for this composite endpoint (Appendix J Table J-23).

Comparing Prognostic Value of BNP and NT-proBNP in Decompensated Heart Failure Patients

Six studies[3,213-217] evaluated BNP and NP-proBNP concurrently in acutely ill HF patients (Appendix J Table J-24). All studies recruited patients from emergency settings with the exception of one.[214] Four of five publications recruited subjects from emergency settings evaluated admission BNP and NT-proBNP levels[3,213,216,217] and one study[215] evaluated post-admission and pre-discharge from hospital levels. The single study[214] recruiting subjects admitted for decompensated HF also evaluated admission levels. The studies evaluated both short term prediction (14 to 90 days) and longer term prediction (1 year). All studies evaluated

all-cause mortality only. Two publications based their analyses on the same study cohort (BACH trial).

In general, these six publications were at low risk of bias, but the majority of studies[3,213-216] measured the outcome based on hospital records or did not specify exact outcome and as such, are prone to misclassification bias. Appendix J Table J-24 shows the findings from these six publications and comparisons between predictive ability of BNP versus NT-proBNP can be evaluated. Two studies evaluated prognostic strength in the short term.[215,217] One study[217] showed that both assays were not statistically significant predictors of 14 day all-cause mortality. The second study[215] showed differences in prediction between assays collected at 24 and 48 hours with only BNP being a significant predictor; predischarge values for predicting 30 day all-cause mortality were significant for both assays.

When considering 90 day all-cause mortality, three publications (two studies)[3,214,217] showed mixed results depending on the assay.

The single study[214] evaluating patients admitted to hospital showed a decrease in BNP (<10% relative to baseline) that was not statistically significant (p=0.817) but a decrease in NT-proBNP (<3% relative to baseline) that was significant (p=0.005). Two publications evaluating subjects from the BACH trial (differing sample sizes) showed that both markers added incremental value to the model,[3,217] but showed mixed results as a predictor, as only one model with NT-proBNP was significant. Three studies[213,215,216] compared BNP and NT-proBNP for predicting 1 year all-cause mortality.

The single study[215] that compared BNP and NT-proBNP levels at 24 and 48 hours post admission and also at predischarge, showed in the multivariable analysis that all three levels for both assays were significant predictors of subsequent 1 year mortality; only NT-proBNP at 24 hours was not statistically significant. The two other studies[213,216] evaluated admission BNP/NT-proBNP levels and showed that both assays were statistically significant predictors of 1 year mortality despite having different covariates within the multivariable models.

Overall, these studies present mixed findings to suggest that BNP and NT-proBNP have differences with respect to predicting shorter term mortality (14 to 90 days). The three studies evaluating longer term mortality (1 year) would suggest that both assays are predictors of mortality and may not differ in their predictive strength.

Chronic Stable Heart Failure and BNP Assay

Design Characteristics of Studies

The prognostic value of BNP among patients with chronic stable HF was assessed in 15 publications.[222,261-274] All of the included studies measured BNP at admission to the study. As this group of studies examined stable HF, the measurement of BNP at discharge or change in BNP between admission and discharge are not relevant to the question. One article measured both BNP and NT-proBNP and is included in this section for a total of 16 papers.[275] One article[222] used an RCT design and the remaining studies (n=15) used prospective cohort designs. The selected articles were published between 2003 and 2011 and were conducted world-wide including: four in North America,[261-263,267] and seven in Europe.[264,265,268,270,273-275] Two publications were from studies conducted in multinational sites,[269,271] one from Turkey[266] and two were unclear as to region of conduct.[222,261]

Four articles reported patient population with mean or median ages ranging from 60 to 69 years.[222,261,266,270] Three had a somewhat older patient populations with mean or median ages

between 70 and 79 years.[272-274] Nine articles had populations with mean ages less than 60.[262-265,267-269,271,275] Two papers reported age ranges of 15 to 84.[263,275] The percentage of males enrolled in each study ranged from 59 percent[261] to 89 percent[264] (mean=68.2%, median=72.5%). Sample size populations ranged from 46[272] to 1,294[274] (mean=398, median=254).

Table 23 shows study outcomes and durations for each publication grouped by the outcomes. Some papers reported study duration as endpoints of years or months and reported durations ranging from 6 months to 24 months. Most reported mean or median study durations ranging to a median of 68 or a mean of 55.8 months followup.

Heart Failure Diagnosis and Severity at Admission

The diagnosis of HF was established in a number of ways, but was usually confirmed using echocardiography, carried out as part of the study or obtained from previous medical records at study enrollment or by clinical assessment. The subjects included were defined as having stable HF according to the inclusion criteria with the exception of one study which recruited subjects with chronic HF that was worsening.[268] The majority of studies included subjects across all levels of the NYHA classification levels I to IV at enrollment. The exceptions were two articles[222,261] enrolling patients at NYHA classification levels III and IV only. Many studies assessed LVEF of enrolled patients at various thresholds including: less than 30 percent,[264] less than 35 percent,[265] less than 40 percent,[262,263,270] and less than 45 percent.[266,268]

BNP Tests and Threshold Values

The majority of publications (n=13) used the TRIAGE -B-Type Natriuretic Peptide (BNP) Test to measure BNP. Two articles,[268,272] used the ADVIA-Centaur® B -Type Natriuretic Peptide (BNP) and one article Abbott Architect BNP reagent Kit.[267]

Six papers categorizing high and low BNP cutpoints based on ROC results.[263,268,271,275] Papers reported other rationales for BNP threshold selection including previously reported prognostic cutpoints[261] and mean or median BNP levels.[262,265-267,270,273,274] The remaining articles[222,264,269,272] used BNP as a continuous variable.

Companion Articles

Most articles (n=14) were independent studies, publishing results on unique data sets, with the exception of one[269] that published results on a companion data set, and one[275] where study affiliation could not be identified.

Definition of Outcomes

Most articles assessed the prognostic value of BNP on mortality. The majority (n=10) examined all-cause mortality,[261-264,268-271,274,275] one assessed sudden cardiac death,[222] and one examined cardiovascular mortality and pump failure mortality.[261] Heart failure hospitalization admissions was assessed by one article.[274]

Several studies evaluated composite outcomes that combined all-cause mortality with nonfatal events. The composite of all-cause mortality and cardiovascular morbidity was reported by seven studies.[262,266-268,272-274] Other outcome assessed included all-cause hospital readmission[274] and heart transplantation.[262,268] One assessed a composite of cardiovascular mortality and morbidity.[265] (Table 23)

Table 23. Outcomes by length of time interval in stable population assessing BNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Vrtovec,[261] 2003																								
Ralli,[263] 2005																								
Horwich,[262] 2006																								
Boffa,[268] 2009	*																							
Meyer,[264] 2005																								
Adlbrecht,[269] 2009																								
Neuhold,[271] 2008																								
Scardovi,[270] 2008	*																						25	->
Bermingham,[274] 2011																							33	->
Moertl,[275] 2009	**																						68	->
Cardiovascular mortality																								
Vrtovec,[261] 2003																								
Cardiovascular mortality (continued)																								
Vrtovec,[222] 2008																								
Heart failure hospital admission																								
Bermingham,[274] 2011																							33	->
Composite of cardiovascular mortality and cardiovascular morbidity																								
Kruger,[265] 2005	*																							

Table 23. Outcomes by length of time interval in stable population assessing BNP (continued)

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of all-cause mortality and cardiovascular morbidity																								
Horwich,[262] 2006																								
Boffa,[268] 2009																								
Kozdag,[266] 2010																								
Scardovi,[273] 2007																								
Popescu,[272] 2007																								
Dries,[267] 2010																							**30**	**->**
Composite of all-cause mortality and all-cause morbidity																								
Bermingham,[274] 2011																							**33**	**->**

XI vertical line indicates intermittent endpoint measurement

* mean; **median; measured by not used; ->study duration and endpoint greater than 24 months

Risk of Bias

The risk of bias was assessed based on the Hayden criteria[58] as described in the methods section (Appendix E) and findings are shown in Figure 13 (also Appendix J Table J-25).

The populations for this group of studies was mostly suitably defined, described, and represented the population of interest. Only one paper did not define the population adequately,[271] and one paper's[268] population was considered not representative of the study's source population or population of interest. There is low risk of bias for population description and selection.

The description of attrition was not adequately described in a number of papers.[222,268,270,272,274,275] Overall, the risk of bias is moderate for study attrition.

The prognostic factors were fairly well addressed. BNP was appropriately defined and measured in all but two papers.[268,274] The other prognostic factors were well defined and measured in all but one paper.[275] The indeterminate results or missing data was less well addressed by a few papers.[222,270,272-274] There is low risk of bias for the BNP and low risk of bias for the other prognostic factors.

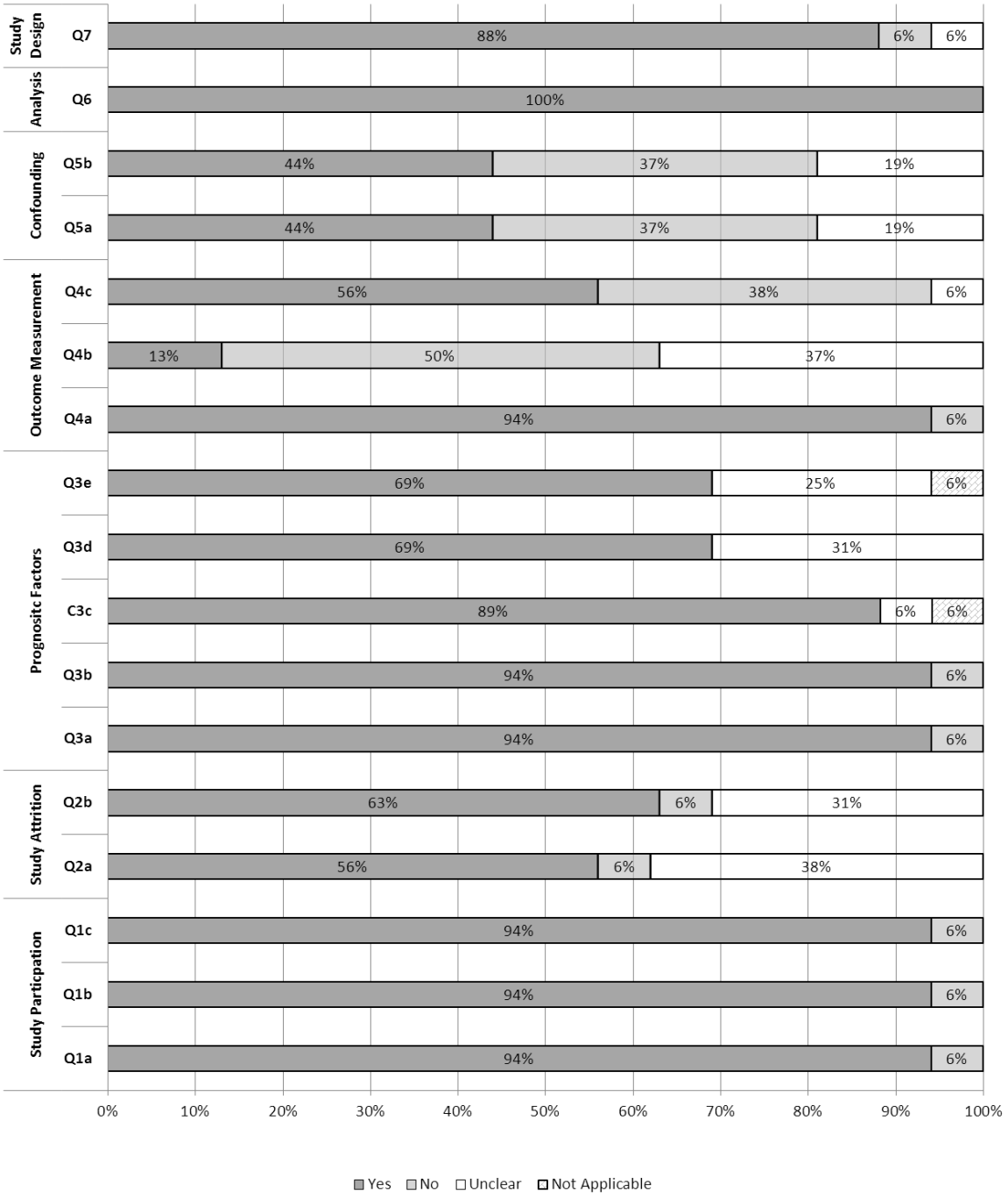
Outcome measurement was defined by most studies, with the exception of one.[271] We set fairly stringent criteria for obtaining accurate data and only two studies met these criteria.[267,275] Composite outcomes are not recommended by Hayden and as we included composite outcomes a number of studies did not meet this criterion.[264-268,272,273] The risk of bias for the outcomes is moderate.

Confounding was particularly poorly addressed. According to the criteria we expected studies to consider age, sex, BMI, and renal function as important covariants. Some studies met these criteria.[262,263,267-269,272,275] The risk of bias from confounders (BMI in particular) is high (Figure 13)

Analysis was appropriately conducted in all the studies. Most of study the designs were observational cohorts and the question posed for the reports most often looked at the predictive value of BNP in the population described. There is low risk of bias for analysis.

In summary, the risk of bias in this group of papers for KQ3 is rated as moderate.

Figure 13. Risk of bias for prognostic studies using the Hayden criteria for stable population assessing BNP



1.(a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4.(a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5.(a) confounders measured, (b) confounders accounted for
6.(a) analysis described;
7 (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

BNP Independent Prediction of Single Outcomes

All-cause mortality was the outcome in 10 articles (Appendix J Table J-26).[261-264,268-271,274,275] One article had followup periods of 6 months or less,[261] and showed a significant adjusted HR for cutpoint BNP>1,000 pg/mL (HR=1.99 (95% CI, 1.18 to 3.36)) in a population with NHYA class III or IV HF. One article[263] had a followup period of 12 months and showed significant adjusted relative risk (RR) for patients with advanced HF (RR=17.34 (95% CI, 2.23 to 134.9)) in a population with LVEF <40 percent. This study also investigated anemia and BNP>485 pg/mL remained a significant predictor in both the anemic and non-anemic subjects. There were five papers reporting on followup periods between 12 and 24 months. A significant adjusted HR with BNP and logBNP measured at various levels of BMI was demonstrated but an HR for the entire population was not reported.[262] In patients with United Network of Organ Sharing (UNOS) status 2, logBNP remained an independent predictor of all-cause mortality.[264] In more general populations of chronic HF outpatients,[268,269,271] non-significant statistics were reported. One of these studies reported a model with BNP (non-significant) and a model with logBNP (HR=1.32 (95% CI, 1.16 to 1.50)).[269] Three articles had followup periods greater than 24 months, two[274,275] assessed the prognostic ability of logBNP in predicting all-cause mortality among HF patients attending a disease management program (HR=1.53 (95% CI, 1.33 to 1.75)),[274] and in a general chronic HF population (HF=1.34 (95% CI, 1.34 to 1.49)).[275] The final paper assessing a followup period of greater than 24 months[270] showed significant results for outpatients with stable mild to moderate HF and LVEF <40 percent (BNP>250 vs. ≤250), adjusting for left bundle branch block (LBBB) and beta blockers (HR=1.59 (95% CI, 1.07 to 2.36)).

Sudden cardiac death was not associated with a significant adjusted HR using a BNP cutpoint of 700 pg/mL (HR=1.03 (95% CI, 0.65 to 1.32)),[222] while pump failure mortality showed a significant HR for 1,000 pg/mL (HR=3.78 (95% CI, 1.63 to 8.78))[261] Cardiac mortality demonstrated a significant adjusted HR for BNP >1,000 pg/mL (HR=1.76 (95% CI, 1.01 to 3.07)).[261] (Appendix J Table J-27).

The natural log of BNP (lnBNP) was a predictor of HF hospitalization (HR=1.53 (95% CI, 1.33 to 1.75)) over a 33 month period (Appendix J Table J-28).[274]

BNP Independent Prediction of Composite Outcomes

A composite outcome of cardiovascular mortality and morbidity was used by one paper and demonstrated a non-significant HR (Appendix J Table J-29).[265]

The composite outcome of all-cause mortality and cardiovascular morbidity (Appendix J Table J-30) was reported by six studies.[262,266-268,272,273] One these studies reported a non-significant HR using heart transplant as the cardiovascular morbidity.[268] The other studies reported significant HR ranging from HR=1.1 (95% CI, 1.1 to 1.2)[267] to HR=3.194 (95% CI, 1.625 to 6.277).[266] The factors used to adjust the multivariable model varied in these studies but included: age, sex, race, tobacco use, creatinine, BMI, LVEF and other echocardiographic measures, etiology of HF (ischemic and non-ischemic), NYHA class, Hb, IL-6, hypertension, albumin, FT3, and medications.

A composite outcome of all-cause mortality and all-cause hospitalization was used by one paper using lnBNP (HR=1.28 (95% CI, 1.17 to 1.41)) over a 33 month period (Appendix J Table J-31).[274]

Chronic Stable Heart Failure and NT-proBNP Assay

Design Characteristics of Studies

The prognostic value of NT-proBNP among patients with chronic stable HF was assessed in 88 publications.[4,53,275-362] One additional article[275] measured both BNP and NT-proBNP and is also included in this section, for a total of 89 papers.

Two articles were RCTs of NT-proBNP-guided therapies versus non NT-proBNP-guided therapies.[4,53] Four articles were secondary analyses of data initially collected in RCTs; however, the secondary analyses did not account for the groups to which participants were randomized.[279,286,301,309] One was a nonrandomized controlled clinical trial,[298] and one[317] was a post hoc analysis of an RCT. One study[342] used a cross-sectional design and two did not report the study design used.[322,346] Three papers[275,352,360] used a retrospective cohort design and the remaining 76 publications used prospective cohort designs. All articles were published between 2001 and 2012 and were conducted in the following parts of the world: five in North America,[293,305,314,338,345] 11 in Asia,[289,290,297,298,302,311,313,327,332,336,346] and one in Austria.[4] Sixteen publications were from studies conducted in multinational sites,[53,284,286,301,307,309,317,318,322,328,331,339,340,344,351,356] and four[276,334,335,341] were unclear as to region of conduct. The remainder (n=52) were published in Europe.

Companion Articles

Several authors published results from large studies, including one[279] from the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, one[333] from the MUerte Sûbita en Insuficiencia (MUSIC) study, three[301,309,351] from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), two[53,345] from the Cardiovascular Health Study (CHS), and one[305]from the Assessment of Doppler Econocardiography Study in Prognosis and Therapy. One article[275] was unclear as to study affiliation and nine published results on companion data sets.[280,281,286,288,297,298,313,326,327] The remaining articles (n=71) were independent studies, publishing results on unique data sets.

Risk of Bias

The risk of bias was assessed based on the Hayden criteria[58] as described in the Methods section, Appendix E, Figure 14, and Appendix J Table J-32, shows the percentage ratings for risk of bias for studies evaluating NT-proBNP in stable HF populations.

As seen in Figure 14 the populations for this group of studies were, for the most part, suitably defined (98 percent) and described (99 percent) with the exception of two papers.[310,353] It was clear in 96 percent of papers that the study population represented the source population or the population of interest, with one paper's[304] population not representing the source population or the population of interest and three[295,337,353] being unclear as to whether this was the case. Therefore, all of the domains within this area of bias are rated as low risk of bias; the overall rating for this area of bias is also low.

Eighty-one percent of articles described their study's completeness of followup and 82 percent were assessed as having adequate completeness of followup. Attrition was not adequately described in two articles,[305,323] and we could not ascertain whether attrition was adequately described and complete in nine articles.[275,298,300,327,328,342,345,351,360] In four other articles,[288,289,344,349] completeness of followup was adequate, yet the description of followup was either unclear[289,349] or inadequate.[288,344] In two articles,[276,348] attrition was not adequately

described and we could not ascertain whether followup was completed. A rating of unclear was assigned to each domain and an overall rating of unclear to the risk of bias for study attrition.

NT-proBNP and other prognostic factors were appropriately defined and measured in all except two included article.[282,290] The issue of indeterminate results or missing data for both NT-proBNP and other prognostic factors were less well addressed by a some papers,[278,280,289,298-300,302,320,324,328,342,348,353,357,360,361] although the published reports do not suggest results were biased. The domain-specific and overall risk of bias rating for prognostic factor measurement is low.

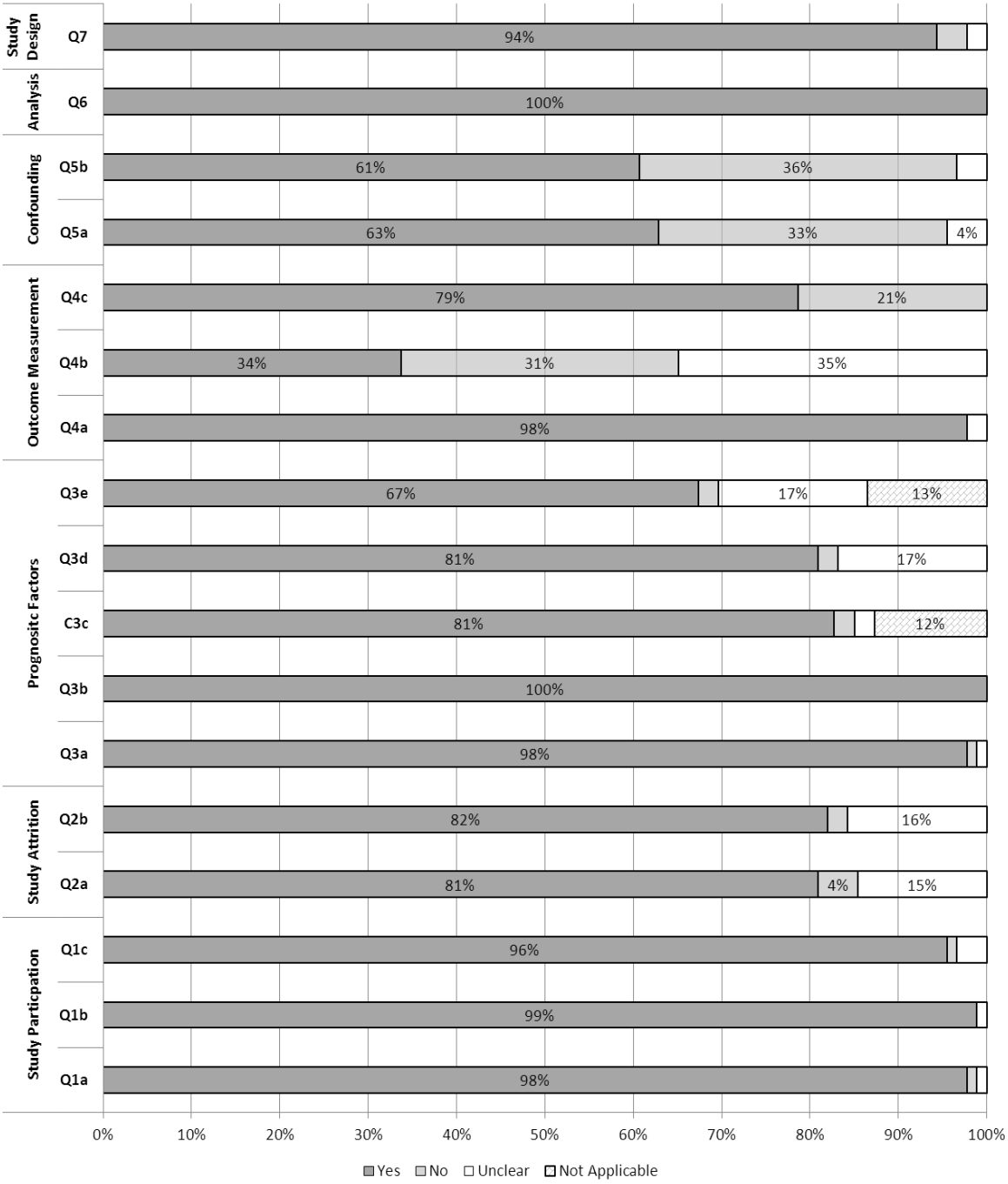
Outcomes were defined in 98 percent of publications (low risk of bias), with the exception of two articles.[298,327] Fairly stringent criteria for obtaining accurate data on outcomes were set and only 30 of the 89 included articles (34 percent)[53,275,280,281,283,286,288,296,303,312,320,321,323,329,338,339,341,347,350-360,362] measured the outcomes appropriately (high risk of bias). Twenty-one percent of studies (n=19) used composite outcomes only in their analysis and did not analyze any single outcome in multivariable analyses.[53,285,287,294,303,305,306,311,317,321,322,324,333,336-338,340,348,353] The overall risk of bias for outcome measurement is high.

Confounding was particularly poorly addressed. According to the a priori criteria, studies were expected to measure age, sex, BMI, and renal function as important covariates. Fifty-six (63 percent) of the 89 articles met these criteria (low risk of bias). In publications that measured confounders, the means of adjustment was typically a multivariable regression analysis (low risk of bias). The overall risk of bias for measuring and accounting for confounding is high.

Analyses were appropriately conducted in all of the included articles. Most of the study designs were observational cohorts and the question posed for the reports most often looked at the predictive value of NT-proBNP in the population described. Consequently, a low risk of bias was assigned to this area.

For the seventh potential area of bias, it was considered whether the included articles were designed to test the prognostic value of NT-proBNP, rather than being secondary analyses of data collected for other purposes. All except five papers[298,317,332,339,341] were adequately designed for prognostic study, earning a low risk of bias to this area.

Figure 14. Risk of bias for prognostic studies using the Hayden criteria for stable population assessing NT-proBNP



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

Chronic Stable Heart Failure and NT-proBNP Predicting All-Cause Mortality

Table 24 describes study outcomes and followup periods for studies assessing mortality outcomes (n=69). Sudden death was considered to be part of all-cause death. Pump failure death was not a primary study outcome. Since we included articles that performed multivariable analyses, measures of association reported in the text are adjusted in the analyses for the influence of covariates. Two articles within which the authors failed to report the length of followup were not considered.[301,309]

Fifty-two articles included all-cause mortality as an outcome in the assessment of the predictive value of NT-proBNP in persons with chronic and stable HF (including the two publications that did not reports lengths of followup) (Appendix J Table J-33).[4,275-282,284,286,288,290-292,295,296,299-302,307-309,311,313-315,317,320,321,326-332,336,342,344,345,348,350,353,355-360,362]

NT-proBNP Levels and Prognosis 6 Months or Less

Two papers[279,321] reported a followup of 6 months or less. In the first paper,[279] an adjusted NT-proBNP value >1,767 pg/mL was a highly significant risk indicator in the model with RR=2.17 (95% CI, 1.33 to 3.54). In the second paper,[321] NT-proBNP level was a strong independent predictor of 6 month mortality, with a seven-fold risk of early death (OR=7.6, 95% CI, 1.4 to 40.8).

NT-proBNP Levels and Prognosis From Greater Than 6 Months to 12 Months

Five papers[4,277,292,344,359] followed up participants for periods between 6 and 12 months, with two articles including persons with mean ages of 63[344] and 65 years.[359] Of the remaining three papers, two[277,292] included persons with a mean age of approximately 50 years and one[4] contained subjects with a mean age of over 71 years. Two papers reported NT-proBNP cutpoints of >1,490[277] and >1,548 pg/mL.[292] One paper[344] reported an adjusted HR=1.43 per standard deviation (SD) unit increase, but did not reach statistical significance (95% CI, 0.89 to 2.3). Three articles reported chi-squares of 20.2 ($p<0.001$),[359] 13.8 ($p=0.0002$),[292] and 6.03 ($p=0.01$),[277] all of which suggest predictive values for NT-proBNP. One article[4] did not report results of the multivariate analysis.

NT-proBNP Levels and Prognosis From Greater Than 12 Months to 24 Months

Eight articles[276,278,286,290,291,320,326,332] reported followups of greater than 12 months and up to 24 months. One of these articles[276] did not report any outcome data and will not be discussed further. Of the remaining papers, three[290,320,332] included persons with mean ages of 71 years, one[278] used populations with mean ages of 82 and 50, and two[291,326] included persons with mean ages of 51 years. One paper[286] did not report on the age of study participants. Reported measures of association in four articles[286,320,326,332] were above 1.0 (indicating NT-proBNP is predictive of all-cause mortality) yet CIs included the null value in two cases,[326,332] the exception were HRs of 1.16 (95% CI, 1.042 to 1.291),[332] 2.58 (95% CI, 1.24 to 5.37),[320] 4.02 (95% CI, 2.63 to 6.11),[286]and 2.07 (95% CI, 1.76 to 2.46).[286] The remaining three articles reported a chi-square of 13.6 ($p<0.001$),[290] 14.2 ($p<0.001$),[291] and 26.95 ($p=0.0001$),[278] all of which suggest predictive values for NT-proBNP.

NT-proBNP Levels and Prognosis From Greater Than 24 Months to 36 Months

Nineteen articles[280-282,284,288,295,296,300,301,307,309,317,327-329,336,353,355,360] reported followups of greater than 24 months and up to 36 months. Sample sizes ranged from 50[295] to 1,503.[317] Mean or median age ranges encompassed 60 to 69 years in 12 articles,[282,284,288,295,296,300,317,327,328,336,355,360] and 70 to 79 years in five publications.[280,281,307,329,353] One article did not report on population age. Authors reported cutpoints in 10 articles,[278,281,295,296,317,327,329,336,353,355] ranging from >641 pg/mL[327] to 10,000 pg/mL.[295] Three papers adjusted HR based on decrements including one SD unit increase in NT-proBNP,[282,360] and a 500 pg/mL increase.[284] Reported point-estimate HRs ranged from 1.03 per pg/mL increase[284] to 4.2.[296] All point estimates, except the ones calculated in two articles,[284,331] were statistically significant at the five percent level. In one paper[355] NT-proBNP level was a strong independent predictor of all-cause mortality, with almost a three-fold risk of early death (OR=2.7; 95% CI, 1.3 to 5.7) Three papers[278,327,336] found NT-proBNP to have an independent predictive value, but the authors only reported chi-square test statistics rather than measures of association.

NT-proBNP Levels and Prognosis From Greater Than 36 Months to 48 Months

Nine articles[302,308,313-315,331,342,357,362] reported followups of greater than 36 months and up to 48 months. Sample sizes ranged from 148[342] to 992.[362] Mean or median age ranges encompassed 50 to 59 years in one paper,[314] 60 to 69 years in six articles,[313,315,331,342,357,362] and 70 to 79 years in two publications.[302,308] Three articles reported cutpoints of >796 pg/mL,[313] 1,000 pg/L,[362] and 1,720 pg/mL.[357] Three of the nine papers adjusted HR based on decrements of NT-proBNP. Decrements included a one log unit (1 log pg/mL) increase,[308,331] a change of 2,000 pg/mL,[314] or a 100 pg/mL increase.[315] All adjusted HR indicated positive associations between higher values of NT-proBNP and all-cause mortality. Reported point-estimate ranged from HR=1.01 per 100 pg/mL increase[315] to HR=4.3.[280] One article[313] reported a chi-square of 2.195 (p=0.0282). All point estimates, with the exception of one,[331] were statistically significant at the five percent level.

NT-proBNP Levels and Prognosis From Greater Than 48 Months to 60 Months

Five articles[299,311,350,356,358] reported followups of greater than 48 months and up to 60 months. Sample sizes included 285,[311]and 1,087,[299]and 1,844.[350] Two of the three articles included mean or median age groups ranging from 70 to 75.[299,311,356] One article[350] did not report the age of their study population. Two articles reported statistically significant HRs, indicating positive associations between higher values of NT-proBNP and all-cause mortality. Reported point-estimate included: HR=1.006 (95% CI, 1.004 to 1.009),[311] HR=2.06 (95% CI, 1.68 to 2.52),[299] and HR=3.2 (95% CI, 2.69 to 3.79).[299] In one article,[356] baseline natural logarithm NT-proBNP as a continuous variable was independently associated with an increased risk of all end points, even after adjustment for several other baseline characteristics; however, use of angiotensin receptor blocker Irbesartan was associated with improved outcomes in patients with NT-proBNP below, but not above, the median levels. Adjusted HRs showed positive association between higher values of NT-proBNP and all-cause mortality.[358] The final article[350] did not report outcome data.

NT-proBNP Levels and Prognosis Greater Than 5 Years

Four studies (six reports) examined all-cause mortality for followup periods that were longer than 5 years.[275,330,345,348,356,358] Mean or median age ranges encompassed 50 to 59 years in three

papers,[275,330,348] and 70 to 79 years in the remaining three publications.[345,348,356] Authors reported cutpoints in three articles,[345,348,356] ranging from 190 pg/mL[345] to 808 pg/mL,[348] with one[348] reporting various cutpoints based on sex and beta-blocker use. One paper[275] reported results that were not statistically significant, although a statistically significant result was found after adding midregional pro-atrial natriuretic peptide (MR-proBNP) to a model with BNP and NT-proBNP already included. Prior to the addition of MR-proBNP, NT-proBNP was an independent predictor ($p<0.05$) of all-cause mortality. Another paper[330] found NT-proBNP to have an independent predictive value, but the authors only reported chi-square test statistics rather than measures of association. Of the remaining three papers, two[345,348,358] had adjusted HRs indicating positive associations between higher values of NT-proBNP and all-cause mortality. Reported point-estimate ranged from HR=1.89 per 100 pg/mL increase to HR=3.37.[348] All point estimates were statistically significant at the five percent level (Table 24).

Table 24. Outcomes by length of time interval in stable population assessing mortality for NT-proBNP

Outcome Measures	Study Duration (months)																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Wedel,[309] 2009	**NR**																							
Cleland,[301] 2009	**NR**																							
Hartmann,[279] 2004	**																							
Amir,[321] 2008																								
Gardner,[277] 2003	**																							
Gardner,[292] 2005	**																							
Berger,[4] 2010																								
von Haehling,[344] 2009																								
Al-Najjar,[359] 2012																								
Michowitz,[332] 2007																								
Gardner,[291] 2005	**																							
Dini,[320] 2008																								
Gardner,[326] 2007	**																							
Gardner,[278] 2005	**																							
Masson,[286] 2006																								
Rothenburger,[276] 2004																								
George,[290] 2005																								
Jungbauer,[355] 2011																							25	->
Dini,[296] 2010	**																						25	->
Masson,[317] 2008																							25	->
Güder,[282] 2007	**																						27	->
von Haehling,[328] 2007																							28	->
Schou,[281] 2007	**																						28	->

Table 24. Outcomes by length of time interval in stable population assessing mortality for NT-proBNP (continued)

Outcome Measures	Study Duration (months)																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Schou,[329] 2007	**																						30	->
Christensen,[360] 2012	**																						30	->
Kistorp,[288] 2005	**																						306	->
Tsutamoto,[336] 2007	**																						31	->
Tsutamoto,[327] 2007																							32	->
Corell,[280] 2007	**																						33	->
Bayes-Genis,[353] 2011	**																						33	->
Jankowska,[284] 2006																							36	->
Frankenstein,[300] 2009																							36	->
Frankenstein,[307] 2009																							36	->
Codognotto,[295] 2010:																							36	->
Frankenstein,[315] 2008	**																						37	->
Kubanek,[308] 2009	**																						39	->
Kemph,[331] 2007	**																						40	->
Tsutamoto,[313] 2008																							40	->
Schierbeck,[342] 2011																							415	->
Antonio,[357], 2012	**																						44	->
Charach,[302] 2009																							44	->
Vazquez,[362] 2009	**																						44	->
Hinderliter,[314] 2008	**																						48	->
Anand,[356] 2011																							50	->
Al Najjar,[299] 2009	**																						52	->
Michowitz,[311] 2008																							54	->
Balling,[358] 2012	**																						55	->
Carlsen,[350] 2012																							60	->
Frankenstein,[348] 2011	**																						67	->
Moerti,[275] 2009	**																						68	->
Frankenstein,[330] 2007	**																						91	->
vandenBroek,[345] 2011																							14	Y

Table 24. Outcomes by length of time interval in stable population assessing mortality for NT-proBNP (continued)

Outcome Measures	Study Duration (months)																								
Cardiovascular Mortality																									
Cleland,[301] 2009	**NR**																								
Wedel,[309] 2009	**NR**																								
Jankowska,[340] 2011																									
Tziakas,[352] 2012																									
Raposeiras,[343] 2011	**																								
Petretta,[335] 2007																									
Koc,[324] 2008																								25	->
Poletti,[304] 2009	**																							30	->
Tsutamoto,[297] 2010																								30	->
Sherwood,[293] 2007	**																							36	->
Bayes-Genis,[333] 2007																								36	->
Schierbeck,[342] 2011																								42	->
Vazquez,[362] 2009	**																							44	->
Hinderliter,[314] 2008	**																							48	->
Kawahara,[346] 2011																								500	->
Nishiyama,[298] 2009																								51	->
van den Broek,[345] 2011																								14	Y

Notes: NR not reported; **median (all else mean); ->study duration and endpoint greater than 24 months

NT-proBNP Levels Predicting Cardiovascular Mortality

Seventeen articles[293,297,298,301,304,309,314,324,333,335,340,342,343,345,346,352,362] examined the prognostic value of NT-proBNP for cardiovascular mortality in person with stable HF (Appendix J Table J-34). Two articles which did not report the length of followup were not included.[301,309]

NT-proBNP Levels and Prognosis Less Than 12 Months

No articles reported cardiovascular mortality for periods of less than 12 months.

NT-proBNP Levels and Prognosis From 12 to 24 Months

Four articles[335,340,343,352] contained followup periods of over 12 months and up to 24 months (Appendix J Table J-34). Sample sizes ranged from 82[335] to 491.[340] Mean or median age ranges encompassed 60 to 69 years in three papers,[335,340,352] and 70 to 79 years in one publication.[343] Three of the four papers reported cutpoints of 3,337 pg/mL,[352] 2,465 pg/mL[340] and >844 pg/mL.[335] Three publications reported added predictive value for admission NT-proBNP in terms of cardiovascular mortality. The first article,[340] reported an adjusted HR=3.36 (95% CI, 2.4 to 4.7). The second article[335] found an HR=1.02 (95% CI, 1.01 to 1.03) with the same level of significance ($p < 0.001$) obtained using log-transformed NT-proBNP levels (HR=9.79; (95% CI, 3.02 to 31.8)). The third paper found discharge NT-proBNP to be inversely related to survival, reporting an HR=0.43 (95% CI, 0.23 to 0.79).[352] Another study[343] also found NT-proBNP to be a significant predictor of cardiovascular mortality (HR=1.039 (95% CI, 1.014 to 1.065) per 100 pg/mL).

NT-proBNP Levels and Prognosis Greater Than 24 Months

Followup was greater than 24 months in 11 papers (Appendix J Table J-34).[293,297,298,304,314,324,333,342,345,346,362] Two articles[314,342] did not report quantitative results and will not be mentioned further in this subsection. Sample sizes spanned from 75[324] to 992.[362] Two papers included persons with a mean age of 53[324] or 57[293] years. Five articles[297,298,304,333,346,362] included subjects with a mean age between 62 and 68 years. The remaining article included persons with a mean age of 75.2 years.[345] Cutpoints varied from a low of ≥190 pg/mL[345] to a high of >908 pg/mL.[333] One article[324] did not report cutpoints, although it calculated adjusted OR for participants at rest for each 50 pg/mL decrement of NT-proBNP (OR=0.91; 95% CI, 0.656 to 1.269) and for each 20 pg/mL change in NT-proBNP (OR=1.106; 95% CI, 1.022 to 1.197) Eight articles[293,297,298,304,333,345,346,362] reported adjusted HRs that indicted that NT-proBNP had predictive ability for cardiovascular mortality. These values were statistically significant at the five percent level and ranged from 1.42 (n=204)[293] to 6.8(n=95);[346] the adjusted HR in the largest sample (n=992)[362] was HR=2.87 (95% CI, 1.80 to 4.57) for NT-proBNP levels >1,000 pg/l. One article[346] also reported chi-squares of 19.2 ($p<0.001$) for baseline NT-proBNP and 16.3 ($p<0.0001$), for discharge NT-proBNP; both of which suggest predictive values for NT-proBNP.

NT-proBNP Levels Predicting All-Cause and Cardiovascular Morbidity

Table 25 describes study outcomes and followup period for articles assessing all-cause and cardiovascular morbidity outcomes (n=12).

Twelve studies[4,276,281,283,286,290,302,308,309,319,332,347] examined the prognostic value of NT-proBNP for all-cause and cardiovascular morbidity in persons with stable HF (Appendix J Table J-35 and Table J-36) Eight studies[281,286,290,302,308,309,319,332] investigated morbidity as some form of hospitalization, including first cardiovascular hospitalization[308,309] or time to first

hospitalization,[302] hospital admission for HF,[286,290,332] all-cause hospitalization,[281] or rehospitalization with worsening HF.[319] Three of these eight studies[290,302,309] also included a composite outcome of hospitalization and all-cause mortality.

Three studies defined morbidity as a decision to initiate cardiac transplant,[276] change in NYHA class and quality-of-life,[283] or worsening renal function.[347] One study[4] reported that NT-proBNP was the strongest prognostic indicator of first HF rehospitalization and a composite outcome of first HF rehospitalization and death; however, the authors did not show any regression results and this study will consequently not be considered further in this section.

Eleven studies included samples drawn from HF clinics. Mean ages of participants ranged from 56[276] to 73;[309] five studies[290,302,308,309,332] included persons with mean ages between 71 and 73. One study[283] stratified mean age data by participant subgroup, with the highest mean age being 70 years. Another study[286] reported that 71 percent of the sample was aged less than 70 years, while 29 percent were aged 70 years or above. One study[281] stratified participants by NT-proBNP cutpoint and reported a mean age of 69 years (<1,381 pg/mL) or 75 years (>1381 pg/mL). A majority of participants were male in all studies, with the proportion of males ranging from 0.55[283] to 0.84.[332]

Nine studies reported mean lengths of followup in the range of 12[283] to 48 months.[308] One study[276] indicated followup lasted anywhere from 3 to 6 months, depending on the participant; one study reported a median length of followup of 28 months.[281] Sample sizes ranged from 78[283] to 3,916.[309] Mean sample size was 875, including the two largest studies (n=3,342,[309] n=3,916[286]). Excluding the two largest studies, mean sample size was 264.

For most outcomes, higher levels of NT-proBNP were predictive of increased morbidity in persons with stable HF. Results in all except one study[283] showed this positive association. In only one study[302] did the results fail to achieve statistical significance.

Hospitalization

Findings for morbidity measured as some form of hospitalization did not vary in terms of mean age, proportion of males, or length of followup. The largest effect was observed in a 48 month study of 354 persons,[308] where baseline log NT-proBNP and log NT-proBNP measured after 6 months of followup, were both associated with increased unplanned cardiovascular hospitalizations. Adjusted HRs and 95% CIs (shown in brackets) were 3.16 (2.24 to 4.46) for baseline log NT-proBNP and 2.45 (1.50 to 4.01) for 6 month log NT-proBNP. The next largest effect was observed in a 23 month study (n=3,916) where the adjusted HR=2.66 (2.19 to 3.22) for persons above a cutpoint of 895 pg/mL. The authors found a cutpoint of 1,007 pg/mL to be optimal for prognostic purposes, with an AUC of 0.69, sensitivity of 70 percent, and specificity of 59 percent. In the other large study, consisting of 3,342 participants and an average followup of 32 months,[309] the adjusted HR for a first cardiovascular hospitalization was HR=1.36 (1.29 to 1.44) for each 1-unit increase in log NT-proBNP.

In a study lasting 14 months,[332] the positive association between NT-proBNP and hospitalization was more muted, with an adjusted HR=1.07 (1.00 to 1.14; p=0.03).[332] Note, though, that a 44 month study of time to first hospitalization found an adjusted HR=1.01 (0.96 to 1.05).[302]

One 21 month study[319] of rehospitalization due to worsening HF dichotomized NT-proBNP at a cutpoint of 1,474 pg/mL. Persons with NT-proBNP values above 1,474 pg/mL had faster times to rehospitalization (HR=1.26; 95% CI, 1.03 to 1.55). Similar results were reported in a study with a median followup of 28 months, where NT-proBNP values above 1,381 pg/mL were associated with faster times to hospitalization (HR=1.71; 95% CI, 1.24 to 2.36).[281] This study

also reported that a doubling of NT-proBNP levels would lead to faster hospitalization (HR for $\log_2$ NT-proBNP: HR=1.19; 95% CI, 1.09 to 1.31). Another study[290] involving 24 months of followup claimed higher NT-proBNP levels were positively associated with hospitalization for HF, but the authors only reported a chi-square test statistic (11.2) and p-value ($p < 0.01$). This study[290] also showed Kaplan-Meier curves depicting greater hospitalization for persons with NT-proBNP levels >1,556 pg/mL.

Three studies featured a composite outcome of hospitalization and mortality. One 24 month study[290] only provided a Kaplan-Meier curve, which showed shorter times to either outcome in persons with NT-proBNP levels >1,556 pg/mL. A 32 month study[309] found an adjusted HR=1.64 (95% CI, 1.54 to 1.74) and a 44 month study[302] found a non-significant adjusted HR=1.03 (95% CI, 1.00 to 1.06).

Besides the studies discussed above,[290,319] the only other hospitalization study that provided cutpoints was the 48 month investigation of first unplanned cardiovascular hospitalization.[308] This study reported elevated risks of hospitalization at each of five levels of NT-proBNP, with the levels based on quintiles of baseline NT-proBNP (i.e., ≤474, 475 to 1,090, 1,091 to 2,529, 2,530 to 5,532, ≥5,533 (all values in pg/mL).

Other Morbidity Outcomes

Three studies[276,283,347] examined other morbidity outcomes besides hospitalization; all found strong predictive effects for NT-proBNP. The odds of being recommended for cardiac transplant were 10.6 times greater (95% CI, 3.7 to 14.5) in persons with an NT-proBNP value greater than 1,000 pg/mL in a study of 550 HF patients.[276] In a study of 125 persons with HF, the risk of worsening renal function was 3.6 times greater (95% CI, 1.9 to 7.0) per standard deviation unit increase in log NT-proBNP.[347] At a cutpoint of 696 pg/mL, NT-proBNP showed 92.9 percent sensitivity, 54.6 percent specificity, and an AUC of 0.80 (95% CI, 0.72 to 0.89) to predict worsening renal function.

A 12 month study examined two outcomes, namely improvements in NYHA class (n=78) or quality-of-life (n=71).[283] The authors measured quality of life using the Minnesota Living with Heart Failure Questionnaire.[363] Resistance to improvement in NYHA class was associated with low baseline NT-proBNP (OR=0.49; 95% CI, 0.31 to 0.78 on log NT-proBNP). Thus, high pre-treatment NT-proBNP levels suggested potential improvement in functional status. The authors did not report multivariable results for quality-of-life because model fit was poor.

Table 25. Outcomes by length of time interval in stable population assessing morbidity for NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause morbidity																								
Pfister,[347] 2011																								
Schou,[281] 2002																							**28**	**->**
Cardiovascular morbidity																								
Berger,[4] 2010																								
Mikkelsen,[283] 2006																								
Michowitz,[332] 2007																								
Bruch,[319] 2008																								
Masson/Cohn,[286] 2006/2001																								
Rothenburger,[276] 2004																								
George,[290] 2005																								
Wedel,[309] 2009																							**32**	**->**
Kubanek,[308] 2009																							**39**	**->**
Charach,[302] 2009																							**44**	**->**

xI vertical line indicates intermittent endpoint measurement

* mean; **median; ->study duration and endpoint greater than 24 months

NT-proBNP Levels Predicting All-Cause Mortality and All-Cause Morbidity

Table 26 describes study outcomes and followup period for articles assessing all-cause mortality and all-cause morbidity outcomes (n=3).

Three studies[279,286,293] examined all-cause mortality and all-cause morbidity, which was defined as hospitalization[279,293] in two studies. The third study[286] reported a composite outcome of "mortality and morbidity", yet the authors did not clearly define morbidity. The studies included outpatients with HF. Proportions of males and mean ages were 0.81 and 63 years,[279] 0.68 and 57 years,[293] and 0.80 with mean age unreported.[286] Sample sizes and lengths of followup were 1,011 participants and a mean of 5.3 months,[279] 204 participants and a median of 36 months,[293] and 3,916 participants and a mean of 23 months.[286]

In all cases, higher levels of NT-proBNP were associated with the composite outcomes. The adjusted relative risk was 2.11 (95% CI, 1.54 to 2.90) in the 5.3 month study for persons with an NT-proBNP level >1,767 pg/mL; adjusted HRs (CIs) were 1.23 (1.12 to 1.35) for persons with a level >1,000 pg/mL in the 36 month study[293] and 2.20 (1.92 to 2.51) for participants with a level >895 pg/mL in the 23 month study.[286] (Appendix J Table J-37)

NT-proBNP Levels Predicting Cardiovascular Mortality and Cardiovascular Morbidity

Table 27 describes study outcomes and followup period for articles assessing cardiovascular mortality and cardiovascular morbidity outcomes (n=8).

Eight studies in 12 publications[285,287,294,301,309,310,312,318,319,334,349,351] examined cardiovascular mortality and cardiovascular morbidity (Appendix J Table J-38). Three publications[301,309,351] used data from the CORONA study and another three publications[285,287,319] used data from a HF clinic in Germany. The main study publications for these two sets of papers were the ones with the most participants.[301,319] All eight studies included outpatients with HF. Proportions of males ranged from 0.65[318] to 1.00.[294] Mean ages ranged from 54[310] to 73[301] years. The smallest sample size was 100[310] and the largest was 3,664.[301] The mean sample size was 601 including CORONA (n=3,664)[301] and 164 excluding CORONA. Mean lengths of followup were 6 months,[334] 17 months,[318] 20 months,[319] 22 months,[312] and greater than 24 months.[294,301,310,349]

A 6 month study[334] found NT-proBNP levels above 2061 pg/mL to be positively associated with a composite outcome of cardiac death, heart transplantation, or HF hospitalization (HR=2.56; 95% CI, 1.36 to 4.82). A 17 month study[318] examined three different cutpoints and found similar positive associations with a composite outcome of cardiovascular mortality, HF hospitalization, myocardial infarction, or stroke. Adjusted HRs (CIs) for each cutpoint were 3.1 (1.20 to 8.20) for >100 pg/mL, 5.8 (1.3 to 26.4) for >300 pg/mL, and 8.0 (2.6 to 24.8) for >600 pg/mL.

The longest of the three German HF clinic papers[319] reported a mean followup of 20 months. This article contained information on 341 persons recruited between March 2003 and November 2005. The composite outcome was cardiac death, need for a cardiac assist device, or urgent cardiac transplantation. Time to event was faster in persons with NT-proBNP levels greater than or equal to 1,474 pg/mL (HR=1.56; 95% CI, 1.23 to 1.98). An earlier publication[285] from the same clinic reported on 162 persons recruited between March 2003 and November 2004. These persons were followed for a mean of 13 months. Time to a composite outcome of cardiac death or urgent cardiac transplantation was faster in persons with NT-proBNP levels above 1,129 pg/mL (HR=3.79; 95% CI, 1.62 to 8.89). The first publication[287] from this research group

reported on 73 participants followed for a mean of 5.6 months. The composite outcome was rehospitalization due to worsening HF, cardiac death, or urgent cardiac transplantation. The adjusted HR for a cutpoint of 2,283 pg/mL was HR=8.33 (95% CI, 2.65 to 26.20).

A study of 103 persons with mean followup of 22 months found NT-proBNP was not associated (p=0.2) with cardiovascular mortality or HF rehospitalization.[312] The authors did not report HRs for NT-proBNP or any other variables that were non-significant in their multivariable regression model.

Besides the CORONA publications,[301,309,351] three other studies[294,310,349] followed participants for over 24 months. A 100-person study[310] with 25 months of mean followup reported an odds ratio of 1.27 (95% CI, 1.07 to 1.51) for a cutpoint of 1,000 pg/mL. The composite outcome was cardiovascular mortality and HF hospitalization. A 28 month study[294] examined the occurrence of cardiovascular mortality or cardiovascular hospitalization in 163 men. When the multivariable regression model included dichotomized covariates for dehydroepiandrosterone sulphate levels and Beck Depression Inventory scores, men with NT-proBNP levels >500 pg/mL had a small increase in risk for the outcome (HR=1.02; 95% CI, 1.01 to 1.03). When these covariates were treated as continuous in the model, the increase in risk was statistically nonsignificant (HR=1.01; 95% CI, 1.00 to 1.03; p=0.09). A 37 month study[349] of 107 persons showed an increased odds of cardiovascular mortality or HF hospitalization in participants with a log-transformed NT-proBNP level at or above a log-transformed cutpoint of 2.47 pg/mL (OR=4.16; 95% CI, 1.29 to 13.44).

Turning to the three CORONA articles,[301,309,351] participants were followed for a mean of 32 months. The primary composite outcome was cardiovascular mortality, nonfatal MI, or nonfatal stroke. A secondary composite outcome was any coronary event, which included sudden death, fatal or nonfatal MI, coronary revascularization, ventricular defibrillation by an implantable defibrillator, resuscitation from cardiac arrest, or hospitalization for unstable angina. The authors also had a post hoc outcome called atherothrombotic endpoint (i.e., fatal or nonfatal MI or fatal or nonfatal non-hemorrhagic stroke). The paper[301] with the largest sample size (n=3,664) reported the impact of log-transformed NT-proBNP on the aforementioned three composite outcomes. These same results were also reported in a slightly earlier paper[309] where the CORONA team analyzed 3,342 persons who had complete data for all of the variables that were included in the regression analyses. Adjusted HRs (CIs) for each log unit change in NT-proBNP were 1.59 (1.48 to 1.71) for the primary outcome, 1.47 (1.36 to 1.59) for any coronary event, and 1.24 (1.10 to 1.40) for atherothrombotic outcomes.[301,309] The third CORONA paper in this series analyzed a subset of 1,449 persons for whom researchers had measured soluble ST2.[351] In this subgroup, each log unit increase in NT-proBNP was positively associated with the primary outcome (HR=1.59; 95% CI, 1.42 to 1.79).

Table 26. Outcomes by length of time interval in stable population assessing all-cause mortality and all-cause morbidity for NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of all-cause mortality and all-cause morbidity																								
Hartmann,[279] 2004																								
Masson,[286] 2006																								
Sherwood,[293] 2007																							**36**	**->**

XI vertical line indicates intermittent endpoint measurement
->study duration and endpoint greater than 24 months

Table 27. Outcomes by length of time interval in stable population assessing cardiovascular mortality and cardiovascular morbidity for NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of cardiovascular mortality and cardiovascular morbidity																								
Yin,[334] 2007																								
Bruch,[287] 2006																								
Bruch,[285] 2006																								
Grewal,[318] 2008																								
Bruch,[319] 2008																								
Honold,[312] 2008																								
Koç,[310] 2009																							**25**	**->**
Jankowska,[294] 2010																							**28**	**->**
Broch,[351] 2012																							**32**	**->**
Cleland,[301] 2009																							**32**	**->**
Wedel,[309] 2009																							**32**	**->**
Bajraktari,[349] 2011																							**37**	**->**

XI vertical line indicates intermittent endpoint measurement
->study duration and endpoint greater than 24 months

NT-proBNP Levels Predicting All-Cause Mortality and Cardiovascular Morbidity

Table 28 describes study outcomes and followup period for articles assessing all-cause mortality and cardiovascular morbidity outcomes (n=26).

Twenty-six publications[4,277,278,289,291,292,301-303,305,306,309,316,320,322,323,325,326,330,335,337-339,341,354,356] measured composite outcomes relating to all-cause mortality and cardiovascular morbidity (Appendix J Table J-39). Two publications[4,330] did not report HRs or test statistics, so neither will be discussed further in this section. Five publications[277,278,291,292,326] pertained to a single study in Scotland, two[306,320] involved a single study in Italy, and two[301,309] came from the CORONA study. The remaining papers reported on individual studies. For summarizing study characteristics and risk of bias, the publications[301,306,326] with the largest sample sizes were chosen to represent all of the Scottish, Italian, and CORONA papers. Thus, this section reports on 18 unique studies.

The included studies took place in medical settings (e.g., HF clinics). Proportions of males and mean ages ranged from 0.65[323] to 0.88[303,339] and 49[303,337] to 72[289] years. One paper[356] did not report either characteristic. Another study[305] reported proportions of males across three different strata based on tertiles of sACE2 plasma activity: 0.68, 0.73, and 0.89.[305] Sample sizes ranged from 71[322] to 3,664;[301] mean sample size was 608. Lengths of followup were between six and 12 months for four publications,[303,322,337,354] 13 to 24 months for 12 publications,[277,278,289,291,292,320,323,325,326,335,338,339] and greater than 24 months for eight publications.[301,302,305,306,309,316,341,356]

Four studies[303,322,337,354] followed participants for between six and 12 months. A 658 person[303] study with a mean followup of six months reported an adjusted HR=1.06 (95% CI, 1.03 to 1.08) per unit change in NT-proBNP. The outcome was all-cause mortality or urgent cardiac transplant. The other four studies reported a mean followup of 12 months. The largest (n=504) 12 month study[354] employed an outcome of death, heart transplant, or HF hospitalization and found adjusted HRs (CIs) of 0.45 (0.45 to 1.46) and 2.43 (1.39 to 4.28) when NT-proBNP was measured at baseline and six months respectively. A 91 person study[337] measuring all-cause mortality or worsening HF reported an adjusted HR=1.001 (p=0.036) for each one unit change in NT-proBNP. A study[322] examining all-cause mortality and HF hospitalization in 71 persons found no predictive value for NT-proBNP (HR=1.00; p=0.53).

Twelve publications[277,278,289,291,292,320,323,325,326,335,338,339] reported 13- to 24- month followup periods. Five of these publications[277,278,291,292,326] pertained to a single study in Scotland and two publications to a single study in Italy,[306,320] while the remaining five reports each covered individual studies.[323,325,335,338,339]

The shortest followup in the 13 to 24 month category was a 13 month study[338] of 210 persons; NT-proBNP values >581 pg/mL were associated with higher all-cause mortality, HF hospitalization, number of emergency department visits (HR=2.02; 95% CI, 1.08 to 3.78). A 17 month study[325] of 290 participants evaluated log NT-proBNP in two separate multivariable regression models. This study found positive associations between each one-unit standard deviation increase in the peptide and a composite outcome of all-cause mortality, HF hospitalization, or urgent cardiac transplant (HR=1.9; 95% CI, 1.50 to 2.40 and adjusted HR=1.7; 95% CI, 1.30 to 2.30). Two 18 month studies also found positive associations between NT-proBNP and a composite outcome. The first study[335] involved 82 persons who had a higher risk of death or HF hospitalization at an NT-proBNP cutpoint above 844 pg/mL (HR=4.50; 95%

CI, 2.22 to 9.15). The second 18 month study[323] recruited 166 persons and examined the same composite outcome; however, the authors only reported chi-square test statistics and p-values, so the magnitude of the positive association could not be assessed.

The five publications from the Scottish study[277,278,291,292,326] reported on a rolling cohort of patients recruited between April 2001 and March 2004. Followups ranged from 13 to 22 months. The composite outcome was all-cause mortality or urgent cardiac transplant and multivariable regression analyses showed positive associations between higher NT-proBNP levels and incidences of the outcome. Since the analyses were repeated on an ever-increasing number of patients over time, median cutpoints varied in the publications. The last publication[326] in this group reported a sample size of 182; NT-proBNP was positively associated with the outcome above 1,506 pg/mL (HR=2.7; 95% CI, 1.10 to 6.40).

The two publications from Italy appeared to include overlapping patients. The first study[320] involved 142 patients followed for a mean of 20 months and the second[306] contained 232 patients followed for a mean of 29 months. The combined outcome in both studies was all-cause mortality or HF hospitalization. Positive associations between peptide level and outcome were found in both studies. At a cutpoint ≥544 pg/mL, the adjusted HR=2.66 (1.24 to 5.71);[306] at a cutpoint ≥3,283 pg/mL, the adjusted HR=2.16 (1.27 to 3.67).[320]

Two 24 month studies[289,339] also found positive associations between NT-proBNP levels and composite outcomes. An investigation of 546 persons[339] found a one log unit increase in NT-proBNP to be associated with higher event rates for all-cause death or heart transplantation (HR=1.42; 95% CI, 1.19 to 1.71). An 88-person study[289] only reported a chi-square test statistic and p-value for the positive association between NT-proBNP and all-cause death or HF rehospitalization.

Seven papers[301,302,305,309,316,341,356] besides the second Italian publication[306] reported followups between 25 and 60 months. Two papers[301,309] came from the CORONA study and the remaining four papers each pertained to an individual study. The CORONA papers reported on all-cause mortality or hospitalization for worsening HF at a mean of 32 months of followup. In both papers, each one-unit increase in log NT-proBNP was associated with increased mortality or hospitalization (HR=1.64 in both publications; 95% CI, 1.54 to 1.74 reported in one paper).[309]

The remaining five papers all contained results that were consistent with the above findings. A 30 month examination[316] of 149 participants found various permutations of NT-proBNP to be statistically significantly associated with all-cause mortality or heart transplant. Permutations included the risk per 100 pg/mL increase in NT-proBNP, as well as assessments at cutpoints of ≥760 pg/mL, ≥1,164 pg/mL, and ≥1,460 pg/mL. Adjusted HRs ranged from 1.07 to 15.85. A 34 month study[305] of 113 participants investigated a three-pronged outcome of all-cause mortality, cardiac transplant, or HF hospitalization and found an adjusted HR=1.55 (95% CI, 1.01 to 2.33) in participants above a cutpoint of 1,240 pg/mL. The same three-pronged outcome was used in a 37 month study of 136 persons,[341] with an adjusted HR=2.12 (95% CI, 1.08 to 4.42) in persons at or above a cutpoint of 1,158 pg/mL. A 44 month investigation of 284 persons[302] found a non-significant higher risk of all-cause mortality or first hospitalization with each one-unit increase in NT-proBNP (HR=1.03; 95% CI, 1.00 to 1.06; p=0.099). In a large (n=3,480) 49 month study involving all-cause mortality or cardiovascular hospitalizations, the adjusted HR=1.46 (95% CI, 1.37 to 1.57) per log unit increase in NT-proBNP.

Table 28. Outcomes by length of time interval in stable population assessing all-cause mortality and cardiovascular morbidity for NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of all-cause mortality and cardiovascular morbidity																								
Zielinski,[303] 2009																								
Franke,[354] 2011																								
MacGowan,[337] 2010																								
Berger,[4] 2010																								
Pascual-Figal,[322] 2008																								
Song,[338] 2010																								
Gardner,[277] 2003																								
Gardner,[292] 2005																								
Pfister,[325] 2008																								
Moertl,[323] 2008																								
Gardner,[291] 2005																								
Petretta,[335] 2007																								
Dini,[320] 2008																								
Gardner,[326] 2007																								
Gardner,[278] 2005																								
George,[289] 2005																								
Jankowska,[339] 2010																								
Dini,[306] 2009																							**29**	**->**
Kallistratos,[316] 2008																							**30**	**->**
Cleland,[301] 2009																							**32**	**->**
Wedel,[309] 2009																							**32**	**->**
Epelman,[305] 2009																							**34**	**->**
Tang,[341] 2011																							**37**	**->**
Charach,[302] 2009																							**44**	**->**
Anand,[356] 2011																							**49**	**->**
Frankenstein,[330] 2007																							**91**	**->**

xI vertical line indicates intermittent endpoint measurement

->study duration and endpoint greater than 24 months

NT-proBNP Levels Predicting Cardiovascular Mortality and All-Cause Morbidity

Table 29 describes study outcomes and followup period for articles assessing cardiovascular mortality and all-cause morbidity outcomes (n=3).

Three studies[293,343,356] investigated the composite outcome of cardiovascular mortality and all-cause morbidity (Appendix J Table J-40). Participants were persons with HF who were two-thirds male;[293,343] mean ages were 72[343] or 57 years.[293] In one study,[356] the proportion of males and the mean age of participants was reported in two strata defined by a median NT-proBNP value of 339 pg/mL (below median: 37 percent, 70 years; above median: 41 percent, 74 years). Sample sizes were 106,[343] 204,[293] and 3,474.[356] Mean followups were 16[343] or 50[356] months, or a median of 36 months.[293] Mortality and morbidity were defined as cardiovascular/HF death and hospitalization in all three studies.

In all three studies, higher levels of NT-proBNP were positively associated with the composite outcome of mortality and hospitalization. Adjusted HRs (CIs) were 1.02 (1.01 to 1.03) per 100 pg/mL in the 16 month study,[343] 1.28 (1.16 to 1.42) for NT-proBNP levels above 1,000 pg/mL in the median 36 month study,[293] and 1.77 (1.43 to 2.20) for levels above 339 pg/mL in the large 50 month study.[356] The 50 month study also reported other adjusted HRs: 1.44 (1.31 to 1.58) per log unit change in NT-proBNP; 1.13 (0.94 to 1.37) in the subgroup (n=1,737) with NT-proBNP >339 pg/mL; 0.57 (0.41 to 0.80) in the subgroup (n=1,737) with NT-proBNP <339 pg/mL. This study also found increasing point-estimate adjusted HRs for each quartile of NT-proBNP compared to the first quartile (Appendix J Table J-40).[356]

Table 29. Outcomes by length of time interval in stable population assessing cardiovascular mortality and all-cause morbidity for NT-proBNP

Outcome Measures	Followup Months																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of cardiovascular mortality and all-cause morbidity																								
Raposeiras-Roubin,[343] 2011																								
Sherwood,[293] 2007																							**36**	**->**
Anand,[356] 2011																							**49**	**->**

XI vertical line indicates intermittent endpoint measurement
->study duration and endpoint greater than 24 months

Surgical BNP

Design Characteristics of Studies

Six studies[364-369] investigated the prognostic value of baseline BNP in persons with HF who received some type of surgery or dialysis (Table 30, and Appendix J Table J-41). Five studies[364-368] were undertaken in stable HF populations and one study[369] involved persons with acute decompensated HF. Surgeries included cardiac resynchronization therapy (CRT),[366-368] cardiac resynchronization defibrillator therapy (CRT-D),[364] or noncardiac surgery (e.g., abdominal, orthopedic).[365] One study[369] involved peritoneal dialysis.

Mean ages ranged from 61[368] to 77 years.[365] Percentages of males ranged from 41[365] to 98 percent[364] and mean lengths of followup ranged from 1[365] to 18 months (Table 29, and Appendix J Table J-41).[367] The smallest sample size was 32[367] and the largest was 164.[366] The mean sample size across all six studies was 87. Three studies used the Triage B-Type Natriuretic Peptide Test[364,366,369] and three used the ADVIA-Centaur immunoassay.[365,367,368]

Risk of Bias

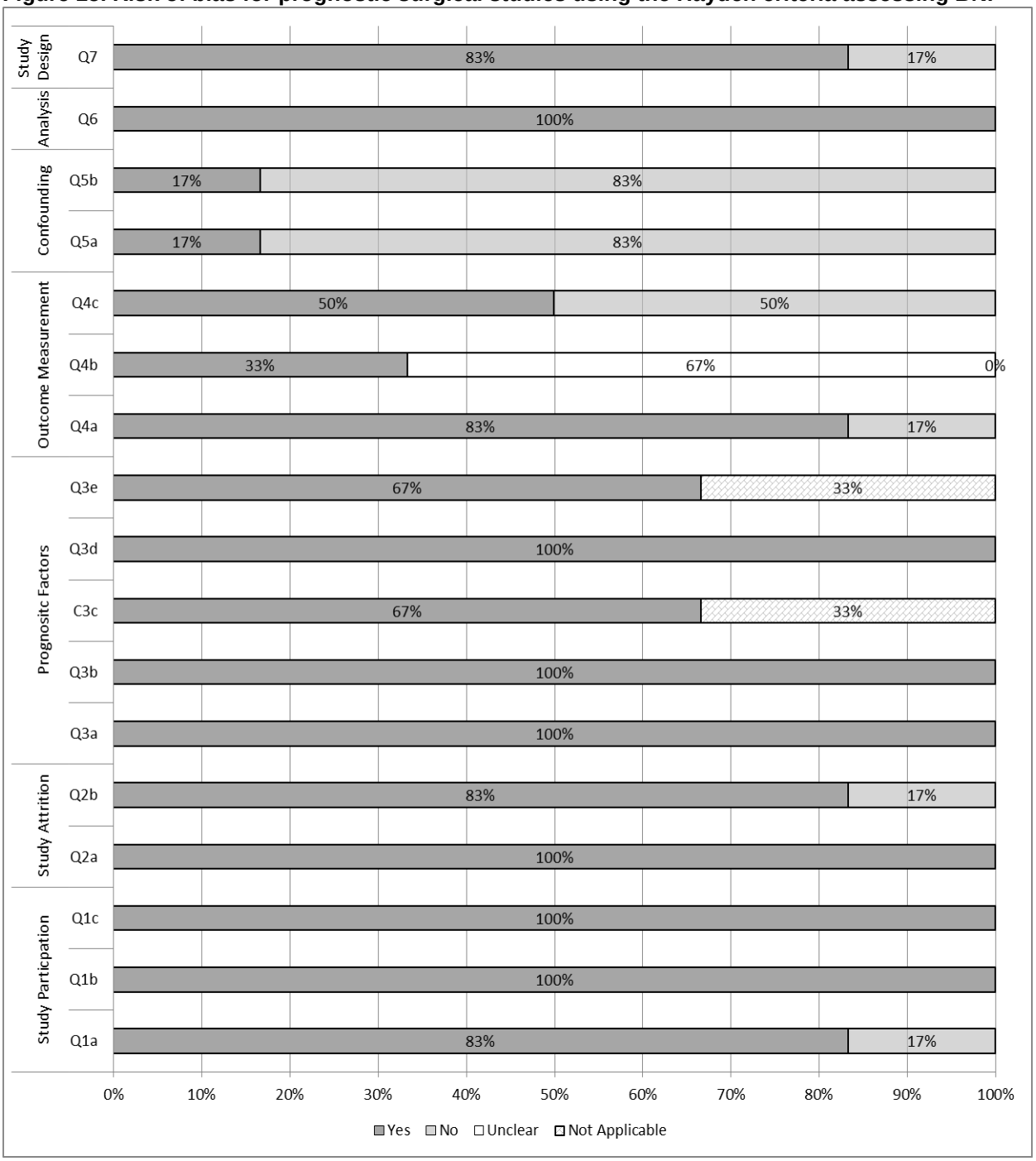
Overall risk of bias was low when the Hayden criteria were taken together for all of the studies (Figure 15, Appendix J Table J-41). Specific areas where risk of bias could be problematic included uncertainty over appropriate measuring of outcomes in four studies,[365-368] as well as inadequate measuring and accounting for confounders in five studies.[364-368]

Table 30. Outcomes by length of time interval in surgical population assessing BNP

Outcome Measures	Follow-up Months																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Koch,[369] 2011	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒											
Glick,[367] 2006	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	**17.7**						
El Saed,[364] 2009	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	17.5						
Cardiovascular mortality																								
Glick,[367] 2006	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	**17.7**						
El Saed,[364] 2009	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	17.5						
Cardiovascular mortality and cardiovascular morbidity																								
Lellouche,[366] 2007	▒	▒	▒	▒	▒	▒																		
Pitzalis,[368] 2006	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒					
All-cause mortality and cardiovascular morbidity																								
Leibowitz,[365] 2007	▒	▒	▒	▒	▒	▒																		

XI vertical line indicates intermittent endpoint measurement

Figure 15. Risk of bias for prognostic surgical studies using the Hayden criteria assessing BNP



1. (a) source population clearly defined, (b) study population described c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

In stable HF populations, three studies[366-368] examined the prognostic value of BNP, measured at baseline, following CRT. In two studies,[366,367] effect sizes per unit change in BNP were close to unity. In one of these two studies, higher levels of BNP were associated with positive responses to CRT, (i.e., no HF hospitalization or improvement of at least 1 NYHA grade [95% CI, 1.001 to 1.003; p <0.01]).[366] Conversely, in the second of these two studies, higher BNP levels were shown to be associated with HF hospitalization following CRT (adjusted HR=1.001; 95% CI, 1.000 to 1.002; p=0.024).[367] In this second study,[367] the authors found no association between higher BNP and all-cause mortality, although they did not provide numerical results to illustrate their finding. The last study[368] involving CRT evaluated a composite outcome called HF progression, which included death, urgent transplant, HF hospitalization, or symptoms of HF progression. The adjusted HR per unit change in log BNP was 2.07 (95% CI, 1.19 to 3.62). See Appendix J Table J-42.

In the CRT-D study,[364] persons with BNP levels at or above a cutpoint of 492 pg/mL had higher risks of all-cause mortality (adjusted HR=2.89; 95% CI, 1.06 to 7.88) or HF hospitalization (adjusted HR=4.23; 95% CI, 1.68 to 10.60).

The study evaluating the prognostic utility of BNP following noncardiac surgery reported a positive association between BNP levels and a composite outcome of all-cause mortality, acute coronary syndrome, or development/worsening HF.[365] However, the authors reported a p-value (p=0.023), which does not show the magnitude of the association.

The lone study of 118 acute decompensated HF patients[369] found a nonsignificant positive association between each one-unit change in BNP level and all-cause mortality following peritoneal dialysis (adjusted HR=1.38; 95% CI, 0.93 to 2.06).

Surgical NT-proBNP

Design Characteristics of Studies

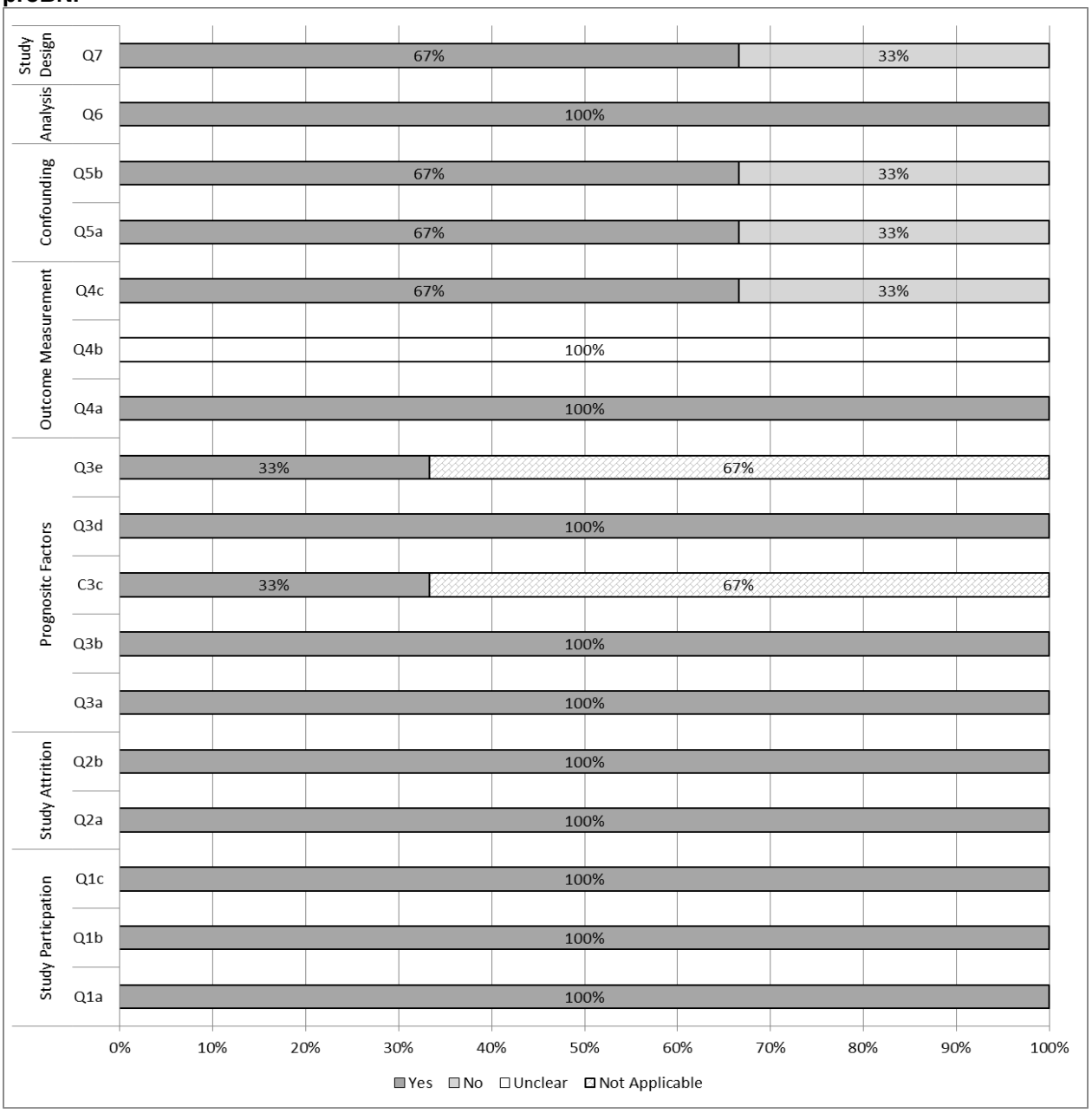
Three papers[370-372] (Table 31 and Appendix J Table J-43) pertaining to two trials, TOPCARE-CHD,[370] CARE-HF,[371,372] reported on the prognostic value of NT-proBNP following surgery in persons with stable HF. For TOPCARE-CHD,[370] mean age was 62 years, 87% of participants were male, mean length of followup was 19 months, and sample size was 121 persons. The intervention under study was intracoronary infusion of bone marrow-derived mononuclear progenitor cells. NT-proBNP was measured using the Elecsys 2010.

In the CARE-HF papers,[371,372] the age range was 55 to 75 years, 67% of participants were male, the median length of followup was 37.6 months, and 813 persons were studied. The intervention was cardiac resynchronization therapy and medical therapy compared to medical therapy alone. NT-proBNP was also measured using the Elecsys 2010.

Risk of Bias

Overall, risk of bias for the three publications was low (Figure 16, Appendix J Table J-43). However, a few specific questions on the Hayden instrument suggested potential issues with bias. Risk of bias was “uncertain” for appropriate measuring of outcomes in the case of all three articles. High risk of bias in the manner of measuring and accounting for confounders was possible in one paper.[371] One publication[372] was not designed to test the prognostic value of NT-proBNP.

Figure 16. Risk of bias for prognostic surgical studies using the Hayden criteria assessing NT-proBNP



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

In the TOPCARE-CHD paper,[370] baseline NT-proBNP was shown to be positively associated with all-cause mortality. The adjusted hazard ratio was 7.2 (95% CI, 2.4 to 22.2) per one-unit increase in log NT-proBNP. All-cause mortality was also assessed in the CARE-HF papers: the adjusted HR for a one-unit increase in baseline log NT-proBNP was 1.56 (95% CI, 1.34 to 1.82);[371] the adjusted HR in a time-dependent model examining log NT-proBNP measured three months after randomization was 1.62 (95% CI, 1.41 to 1.85) per unit increase[372] (Table 31). See Appendix J Table J-44.

One of the CARE-HF papers[371] also examined the prognostic value of one-unit changes in baseline log NT-proBNP on sudden death (adjusted HR=1.33; 95% CI, 1.11 to 1.60) and death from pump failure (adjusted HR=1.92; 95% CI, 1.58 to 2.34).

Table 31. Outcomes by length of time interval in surgical population assessing NT-proBNP

Outcome Measures	Followup Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Berger,[371] 2009																								
Assmus,[370] 2007																								
Cleland,[372] 2008																							37.6	..>
Cardiovascular mortality																								
Berger,[371] 2009																								

XI vertical line indicates intermittent endpoint measurement
->study duration and endpoint greater than 24 month

Comparing Prognostic Value of BNP and NT-proBNP in Decompensated and Stable Heart Failure Patients

Design Characteristics of Studies

Two publications[373,374] included both decompensated and stable HF patients in their study populations. Both are part of the same population prospectively recruited in a hospital in Pisa Italy, with one article[373] assessing a sub-population of the other (Table 32 and Appendix J Table J-45).[374]

Risk of Bias

The risk of bias was assessed based on the Hayden criteria[58] as described in the methods section and Appendix E. Both articles[373,374] (Figure 17, Appendix J Table J-46) scored well on assessment of study participation, study attrition and prognostic factors. Both articles adequately measured and defined the study outcomes. However, since one publication[373] used a composite outcome comprised of mortality and morbidity, it was rated low on the question asking whether "composite outcomes were avoided." Both publications[373,374] failed to adequately measure and account for the important covariates, specified according to the a priori criteria set out (age, sex, body mass index and renal function). Analyses were appropriately conducted in both articles and both were adequately designed for prognostic study.[373,374]

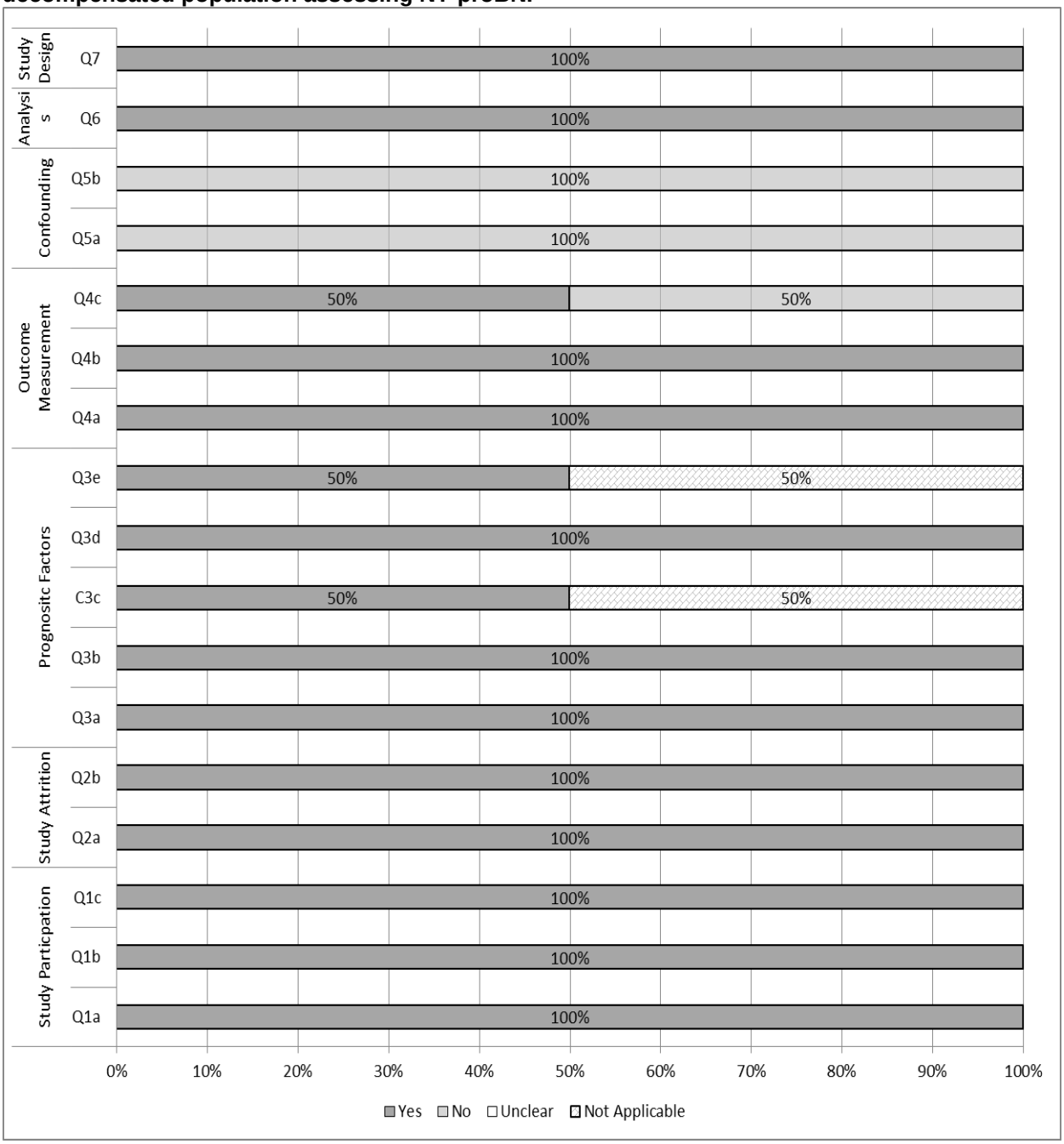
Results

Decompensated and Stable NT-proBNP

One of the articles[374] looked at all-cause mortality over 32 months (Table 32), in a population of 400 people with a mean age of 69 years. For the overall group of patients, the authors reported a statistically significant HR (HR=2.04; 95% CI,1.25 to 3.36), indicating a positive association between higher values of log NT-proBNP and all-cause mortality. In patients with decompensated HF, log NT-proBNP was slightly above 1.0 (HR= 1.01; 95% CI, 1.00 to 1.01; p=.060), yet confidence intervals included the null value. Multivariable results for stable HF patients were not reported in the article.[374] See Appendix J Table J-46.

The other article[373] examined a composite outcome of all-cause mortality and cardiovascular morbidity over 22 months, in a population of 313 individuals with a mean age of 69. The publication performed multivariable analyses on varying cutpoints. In patients with stable HF, NT-pro-BNP >1,129 pg/mL (HR=2.84; 95% CI,1.44 to 5.62) was a significant predictor of the end point in multivariate analysis. Likewise, in patients with decompensated HF, NT-pro-BNP >3,430 pg/mL was significant at HR=2.06 (95% CI, 1.16 to 3.67). For both stable and decompensated groups combined, NT-pro BNP >1,492 pg/mL was a significant predictor of all-cause mortality and cardiovascular morbidity (HR=2.94; 95% CI, 1.83 to 4.72).[373]

Figure 17. Risk of bias for prognostic studies using the Hayden criteria for both stable and decompensated population assessing NT-proBNP



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4.(a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5.(a) confounders measured, (b) confounders accounted for
6.(a) analysis described;
7 (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table 32. Outcomes by length of time interval in both decompensated and stable population assessing NT-proBNP

Outcome Measures	Followup Months																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
Dini,[374] 2012																							->	32
All-cause mortality and cardiovascular morbidity																								
Dini,[373] 2008																								

XI vertical line indicates intermittent endpoint measurement
->study duration and endpoint greater than 24 month

Key Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge, add incremental predictive information to established risk factors for morbidity and mortality outcomes?

All studies eligible for KQ3 were further screened for appropriate statistical methods used to demonstrate additional incremental predictive value of adding BNP /NT-proBNP to prognostic models predicting future outcomes of mortality, morbidity, and composite outcomes. Incremental predictive value could be evaluated in a number of ways including the use of discrimination, calibration, or reclassification statistics. An abbreviated summary of these complex statistics follows to guide the reader to interpret the study findings described below.

The c-statistics or c-index, which is one of the more frequently reported incremental value statistics, is a measure of discrimination; it indicates how variables improve the discriminatory ability of prognostic models for risk prediction between the groups of individuals classified as high risk and low risk. The accuracy, or calibration, of risk prediction is also an important measure of a risk marker. The calibration of a risk predictor can be measured by comparing the predicted frequency of events with the observed frequency and this is determined by assessing the goodness of model fit (Hosmer-Lemeshow goodness-of-fit test). The likelihood-based measures (such as global chi-square or LR chi-square and log LR) show whether the addition of BNP/NT-proBNP, or other markers, to base models provides a better model fit and increase in predictive value for mortality or morbidity. Measures of risk classification (including net reclassification index (NRI) and incremental discrimination improvement (IDI) index) assess the degree to which the addition of BNP/NT-proBNP improves discrimination between groups of individuals classified with and without the test. NRI and IDI are considered to be improvements over measures of discrimination (AUC and c-statistic), calibration (goodness-of-fit, Hosmer-Lemeshow statistic), and global model-fit statistics (likelihood-based measures).[44]

From 183 eligible studies in KQ3, 39 publications used methods that would allow assessment of the incremental value of adding BNP or NT-proBNP when predicting subsequent outcomes. From these 39 publications, two studies[2,247] reported that they undertook statistical computations but did not present any data for incremental value. Additionally, 15 studies included BNP in the base prognostic model,[106,196,210,212,273] in the NT-proBNP predictive model,[282,303,316,339,343,348,352,362,375] or both assays in the model.[217] Including these assays in the base model does not allow assessment of predictive incremental value for BNP/NT-proBNP. The study findings from the remaining 22 publications (12 unique studies [cohort of patients])[3,187,193,198,205,251,256,283,286,301,306,309,320,329,340,344,349,353,357,360,373,376] are presented in grouped sections accounting for incremental value estimates in studies with decompensated or stable populations with HF. See Appendix K. KQ4 Evidence Set.

Evidence for Incremental Value of BNP and NT-proBNP in Decompensated Heart Failure Patients

There were seven publications (6 studies) that included patients with decompensated HF and evaluated the incremental value of admission BNP[3,187,193,198,205] and admission NT-proBNP.[251,256] One study[3] evaluated both BNP and NT-proBNP but reported results only for BNP. One study[198] had overlapping samples of consecutive patients recruited from the same center; findings from both publications are reported even though the cohorts overlap and are considered a single study.

Design Characteristics of Studies

From the five[3,187,193,198,205] publications evaluating BNP in acute decompensated populations, only one recruited participants from emergency settings,[3] while the other four recruited participants from among persons admitted to hospital.[187,193,198,205] All BNP studies were cohort designs that included relatively equal proportions of men and women. One BNP study included only patients with NYHA class III and IV severity.[187] Sample sizes of BNP studies varied from 568 to 1,111 subjects. All studies evaluated BNP/NT-proBNP levels at admission and did not assess any serial or discharge from hospital levels.

Table 33 shows the outcomes and time intervals of studies who evaluated and presented data on incremental value of BNP/NT-proBNP. The studies evaluating the incremental value of BNP as a predictor evaluated only mortality related outcomes. Time intervals for outcome prediction varied from 3 months to 12 months in these studies the studies were undertaken in Greece,[187] Spain,[198,205] the United States,[193] and multinational settings.[3] The assays used in these BNP studies included the Abbott AxSym,[187] the ELECSYS-proBNP,[3,205] the TRIAGE-BNP,[193] and the ADVIA-Centaur.[198] Other study characteristics are described in Appendix K Tables K-1 and K-2.

Two studies evaluated NT-proBNP in patients with decompensated HF presenting to the emergency department in Spain[251]or admitted to hospital in Denmark.[256] The Elecsys 2010 analyser assay was used in both studies to assess NT-proBNP levels. The mean age of the samples and proportion of males are described in Appendix K Table K-3.

Risk of Bias

Figure 18 (also Appendix K Table K-4) shows the distribution of risk of bias across the five BNP studies and single NT-proBNP study. Generally, these six publications were at low risk of bias. Studies tended to be problematic with respect to describing and accounting for confounders,[187,198,205] and with appropriate measurement of the outcome,[187,193,205] or unclear outcome measurement.[3,198]

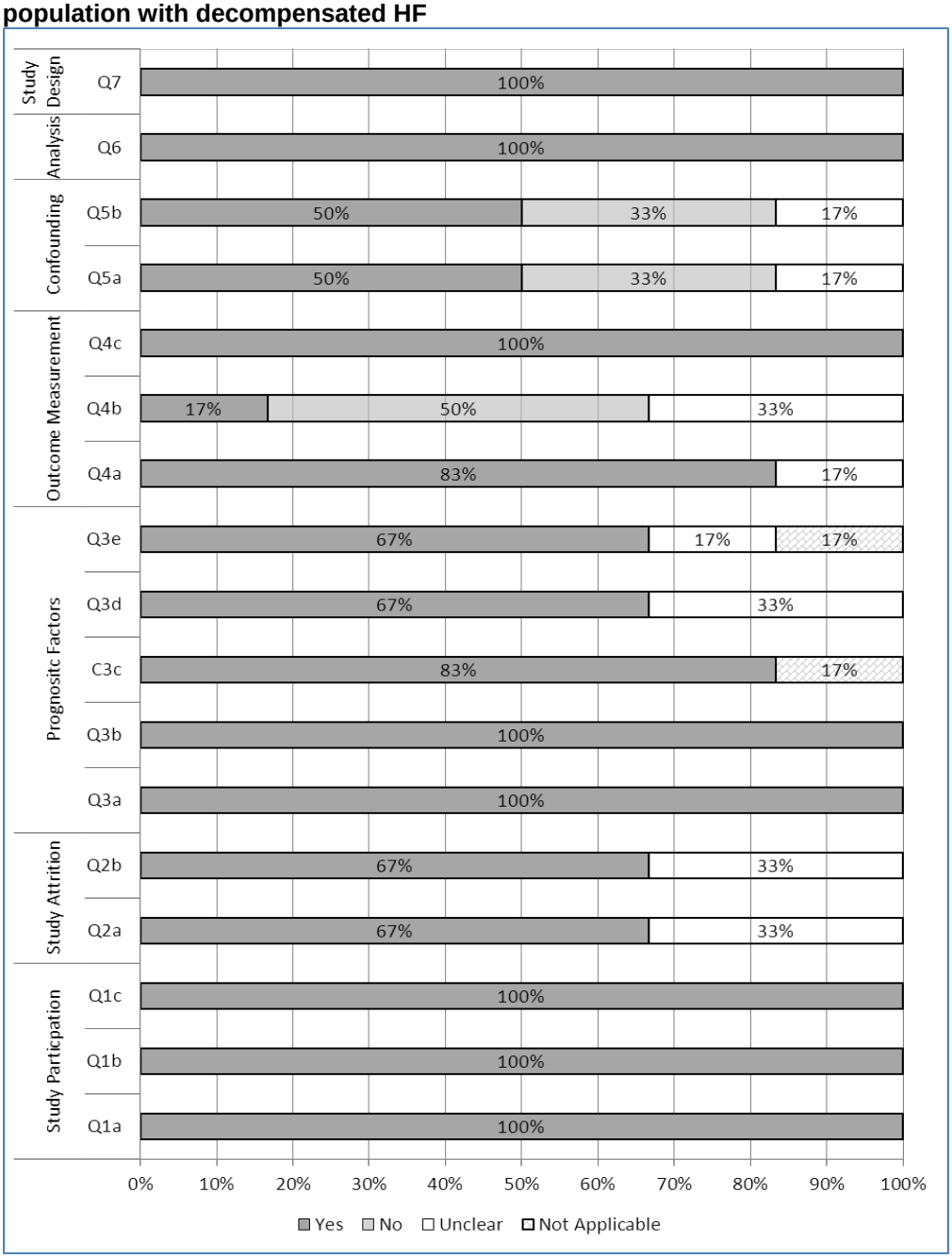
The single study that evaluated NT-proBNP in decompensated patients[251] was the only publication within that group that rated adequate for all criteria; however, this study also had the smallest sample size (n=107) of the studies with decompensated patients.

Table 33. Study outcomes and followup period for patients with decompensated heart failure

Outcome Measures	Study Duration (months)																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
BNP																								
Maisel,[3] 2010	**A**																							
Nunez,[205] 2010	**A**																							
Nunez,[198] 2008	**A**																							
Dunlay,[193] 2009	**A**																							
NT-proBNP																								
Pascual-Figal,[251] 2011	**A**																						**25**	**-->**
Harutyunyan,[256] 2012	**A**																						**82**	**-->**
Cardiovascular mortality																								
BNP																								
Zairis,[187] 2010	**A**																							
Nunez,[205] 2010	**A**																							

XI vertical line indicates intermittent endpoint measurement (followup);
A = admission BNP
Abbreviations: BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide
->study duration and endpoint greater than 24 month

Figure 18. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for population with decompensated HF



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

BNP Levels Adding Incremental Value in Predicting Risk for Mortality

None of the BNP publications included in this group undertook internal or external model validation computations. Only mortality outcomes were evaluated in these studies. Note that these studies evaluated admission BNP levels and none evaluated the incremental value of discharge or change in BNP levels. None of the studies overlapped with respect to the lengths of followup, which varied from 31 days to 12 months (see Table 33).

All-Cause Mortality

Four publications assessed all-cause mortality[3,193,198,205] and two assessed cardiovascular mortality[187,205] in studies using BNP levels as the predictor. Appendix K Table K-1 shows the primary findings of these studies evaluating the incremental value of using BNP levels to predict all-cause mortality.

Two studies used measures of reclassification and both evaluated all-cause mortality in the short-term, at 3 months,[3] and 6 months.[205] Both studies estimated the IDI index, which shows how BNP (or other markers) improves the level of discrimination between groups of individuals classified as high or low risk for the outcome (in this case, mortality). Comparison across these two studies is limited as one publication[3] used a cutpoint of 350 pg/mL as the threshold in the model and the second study[205] used BNP (per increase of 1 interquartile range (IQR)). Nunez et al.[205] showed that the base model with BNP had a lower IDI than the base model with tumor marker carbohydrate antigen 125 (CA125). When both BNP and CA125 were added to the base model, the greatest percentage increase in IDI was achieved. This study also evaluated two other mortality outcomes, cardiovascular and HF, and when comparing all three, all-cause mortality showed the largest percentage improvement in IDI for the base model with BNP added (1.51% for all-cause vs. 1.23% for cardiovascular or 0.95% for HF mortality). These data suggest that there may be differences in risk prediction by type of mortality outcome, but also that BNP combined with CA125 had the best level of discrimination. Maisel et al.[3] used two different base models but reported incremental value for log transformed BNP combined with log transformed midregional pro-adrenomedullin (MR-proADM). In this study, the combined model versus BNP alone, showed an NRI of 39 percent change, reflecting the percentage of individuals in the population who are correctly reclassified into clinically meaningful prespecified risk categories (three probability groups for risk: less than 6%, between 6% and 20%, and greater than 20%). An IDI of 5.24 percent was achieved reflecting this degree of improvement in discrimination. In summary, for short-term prediction of all-cause mortality, these two studies would suggest that NT-proBNP has incremental predictive value, but to a lesser degree than when combined with CA125[205] or MR-proADM.[3] One of these studies[205] was at high risk of bias with concerns about followup, description of included covariates, and confounders.

Two studies evaluated the incremental value of BNP for predicting all-cause mortality in the longer term, at 9 months[198] or 12 months.[193] One study[198] recruited subjects from emergency departments and followed them for a median of 9 months; the Harrell's c-statistic was greater in the prognostic model that included admission BNP (continuous and for quintiles) compared to the same model without BNP (c-statistic=0.801 vs. 0.781) for predicting all-cause mortality. The second study,[193] which included patients admitted to hospital, compared the incremental prognostic value of BNP and a number of different markers, showing increases in the c-statistic when admission BNP was added to the base model, as well as for the addition of C-reactive

protein (CRP) and troponinT (TnT) (Appendix K Table K-1). Similarly, the IDI was 4.3 percent (p=0.001) and NRI was 16.2 percent (p=0.003) when BNP alone was added. However, in this study both the c-statistic and IDI and NRI estimates showed slightly greater values for CRP and TnT relative to the incremental value of BNP; the greatest increment was obtained when all three markers were added to the base model. In summary, for longer term prediction of all-cause mortality of 9 and 12 months, these two studies would suggest that BNP adds incremental value. One study[193] suggests that BNP is not superior to CRP and TnT with respect to 9incremental predictive value for all-cause mortality.

Cardiovascular Mortality

Two studies[187,205] that included patients admitted to hospital evaluated the incremental value of BNP and other markers for predicting cardiovascular related mortality. One study[187] evaluated cardiovascular mortality at 31 days and showed incremental value in the c-statistic when admission BNP was added to the base model. The incremental value of BNP was compared to CRP and to cardiac troponin I, and the c-statistic values suggest that BNP showed the largest increase relative to these other markers; however, it is not clear if these are significantly different. A second study[205] evaluated both cardiovascular and HF mortality at 9 months; using IDI estimates this study[205] showed that BNP provided incremental predictive value for cardiovascular and for HF mortality but to a lesser magnitude for the latter mortality (Appendix K Table K-2). This study also compared the incremental value for three types of mortality and BNP relative to CA125. A similar trend was seen across the three mortality outcomes; the base model with BNP had a lower IDI than the base model with CA125. However, when both BNP and CA125 were added to the base model, the greatest percentage of IDI was achieved. Cardiovascular mortality showed the largest IDI when the base model was combined with both BNP and CA125 (IDI=3.65 vs. 3.45 or 2.47%). In summary, these two studies would suggest that BNP adds incremental value in predicting cardiovascular mortality in the short term (31 days) and longer term (9 months). However, both these studies were at high risk of bias with respect to adequacy of measurement of the outcome, and dealing with important confounders.

BNP Levels Adding Incremental Value in Predicting Risk for Morbidity

None of the studies using BNP levels as predictors of outcome assessed the incremental value for outcomes of morbidity.

BNP Levels Adding Incremental Value in Predicting Risk for Composite Outcomes

None of the studies using BNP levels as predictors of outcome assessed the incremental value for composite outcomes.

NT-proBNP Levels Adding Incremental Value To Predicting Risk for All-Cause Mortality

Two studies[251,256] evaluated the incremental prognostic value of NT-proBNP in decompensated patients. One study[251] undertook discrimination, calibration, reclassification, and internal validation computations to assess the incremental prognostic value of NT-proBNP in subjects admitted to hospital with decompensated HF. All-cause mortality was the predicted outcome at a median followup of 22 months. The discrimination statistic showed that when NT-proBNP was added to the model, the value increased but was not statistically significant

(Appendix K Table K-3). For calibration, the Hosmer-Lemeshow statistic decreased (base model 0.56 to 0.29), suggesting that the goodness-of-fit deteriorated when NT-proBNP was added. Considering reclassification statistics, this study considered the integrated discrimination of improvement (IDI) based on the inclusion of several markers in the base model. The inclusion of NT-proBNP alone to the base model failed to show a statistically significantly improvement in the IDI (2%, p=0.532 vs. base model). The highest improvement in the IDI was achieved when the NT-proBNP was combined with other markers in the form of a multimarker risk score, based on optimal cutpoints, using an ROC analysis, and showed an IDI equal to 25 percent (p=0.004) relative to the base model and IDI equal to 22 percent (p=0.003) compared to the base model with NT-proBNP alone (Appendix K Table K-4).

The second study[256] evaluated only the goodness of fit to the model when NT-proBNP was added and showed it added incremental value for predicting all-cause mortality at 6.8 years and was statistically significant.

NT-proBNP Levels Adding Incremental Value in Predicting Risk for Morbidity

None of the studies using NT-proBNP levels as predictors of outcome assessed the incremental value for outcomes of morbidity.

NT-proBNP Levels Adding Incremental Value in Predicting Risk for Composite Outcomes

None of the studies using NT-proBNP levels as predictors of outcome assessed the incremental value for composite outcomes.

Evidence for Incremental Value of BNP in Stable Heart Failure Patients

Added Value of BNP to Prognostic Risk Prediction

There were no studies that evaluated the incremental value of adding BNP in chronic HF patients.

Added Value of NT-proBNP to Prognostic Risk Prediction

Fifteen publications[283,286,301,306,309,320,329,340,344,349,353,357,360,373,376] evaluating patients with chronic stable HF considered the prognostic value of NT-proBNP.

Design Characteristics of Studies

The majority of these studies were publications based on related patient cohorts from Italy,[306,320,349,373,376] from Spain,[353,357] from Europe,[340,344] and from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) with subjects recruited across Europe.[301,309] The remaining studies were conducted in Denmark,[283,329,360] and from multinational sites (16 countries).[286]

Three publications were based on randomized trials from the CORONA trial[301,309] and Valsartan Heart Failure Trial (Val-HeFT);[286] both studies had large sample sizes ranging from 3,342 to 3,916 . The remaining studies were prospective cohort designs and sample sizes varied

from 107 to 891 subjects. All 15 studies used the ELECSYS -proBNP Immunoassay to evaluate the NT-proBNP.

Table 34 shows the length of followup and outcomes evaluated in the studies. The majority of studies evaluated mortality outcomes with fewer studies evaluating morbidity and composite outcomes. Appendix K Tables K-5 to K-8 detail the mean age and percentage of males for each estimate of incremental value of NT-proBNP.

Risk of Bias

Figure 19 (also Appendix K Table K-9) shows the proportion of studies meeting various criteria assessed for risk of bias. Appendix E shows the individual study ratings for risk of bias. Almost all studies clearly defined their source of the population and this was representative of our target population. Similarly, all studies provided adequate description of their statistical analyses and used adequate designs to address this question of prognosis. Four of five related studies[306,320,373,376] had problems with reporting which confounders were measured and how these were dealt with within the analysis, which accounted for the majority of studies with problems in this criteria.

Table 34. Study outcomes and followup period for patients with stable heart failure

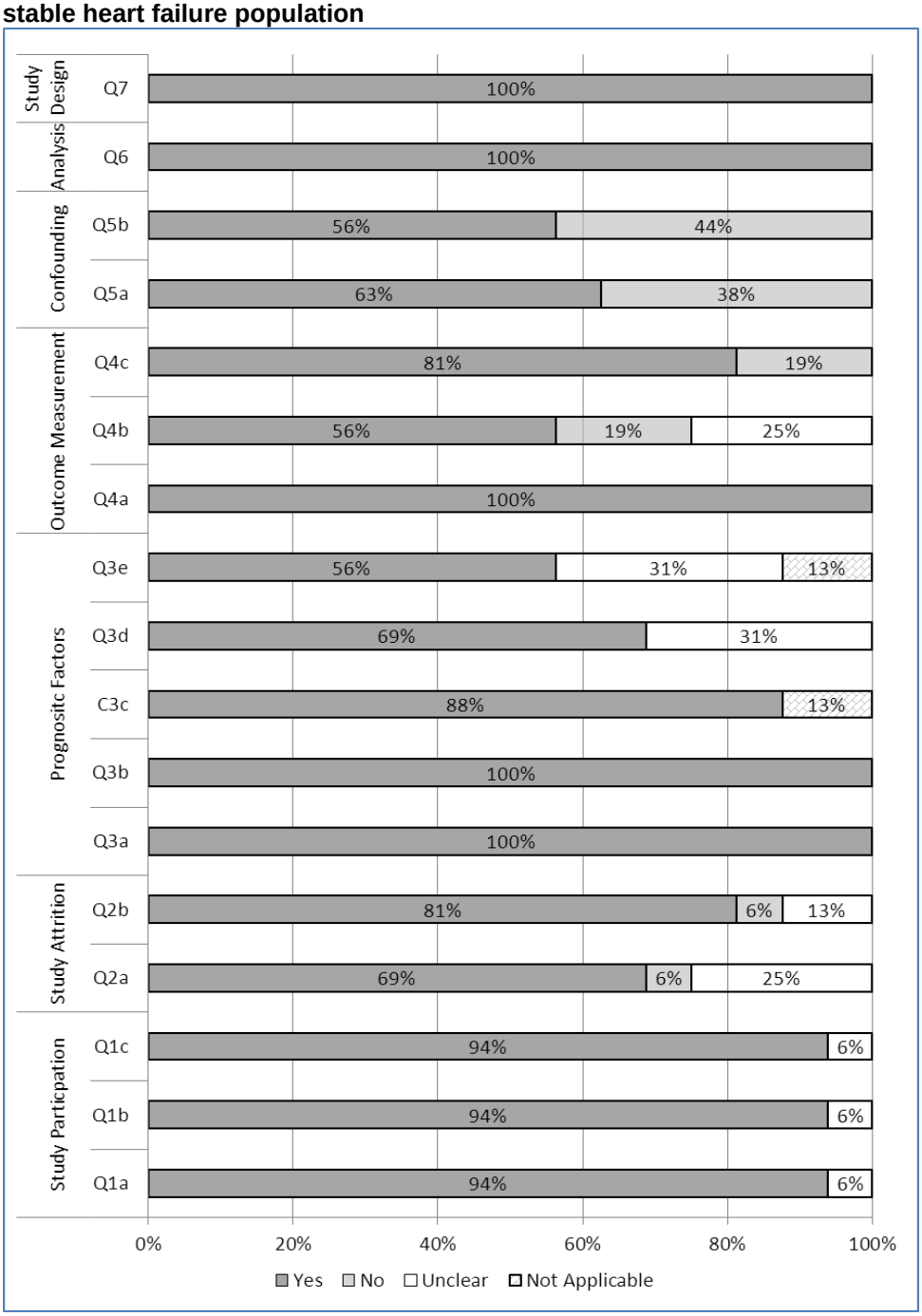
Outcome Measures	Study Duration (months)																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All-cause mortality																								
NT-proBNP																								
von Haehling,[344] 2009																								
Dini,[320] 2008																								
Masson,[286] 2006																								
Cleland,[301] 2009																								
Schou,[329] 2007																							30	-->
Christensen,[360] 2012																							30	-->
Wedel,[309] 2009																							31	-->
Bayes-Genis,[353] 2011																							33	-->
Antonio,[357] 2012																							33	-->
Cardiovascular mortality																								
NT-proBNP																								
Jankowska,[340] 2011																								
Cleland,[301] 2009																								
Dini,[376] 2008																							25	-->
Wedel,[309] 2009																							31	-->
Cardiovascular morbidity																								
NT-proBNP																								
Mikkelsen,[283] 2009																								
Masson,[286] 2006																								
Composite of all-cause mortality and cardiovascular morbidity																								
NT-proBNP																								
Dini,[373] 2008																								
Cleland,[301] 2009																								
Dini,[306] 2009																							29	-->
Wedel,[309] 2009																							31	-->

Table 34. Study outcomes and followup period for patients with stable heart failure (continued)

Outcome Measures	Study Duration (months)																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Composite of all-cause mortality and all-cause morbidity																								
NT-proBNP																								
Masson,[286] 2006																								
Composite of cardiovascular mortality and cardiovascular morbidity																								
NT-proBNP																								
Cleland,[301] 2009																								
Wedel,[309] 2009																							31	-->
Bajraktari,[349] 2011																							37	-->

XI vertical line indicates intermittent endpoint measurement (followup);
A = admission BNP
Abbreviations: BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide ->study duration and endpoint greater than 24 month

Figure 19. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for stable heart failure population



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured,(b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

NT-proBNP Levels Adding Incremental Value To Predicting Risk for All-Cause Mortality

Nine publications[286,301,309,320,329,344,353,357,360] reported on the incremental value of adding NT-proBNP to the model and predicting all-cause mortality at time intervals that varied from 12 months, to 37 months. All but one study[360] presented assessment of the incremental value of NT-proBNP with respect to assessing the goodness of fit; fewer studies used the c-statistic,[309,353,357,360] the Hosmer-Lemeshow statistic,[353,357] IDI,[353,357,360] and validation methods.[353,357]

A single study[344] at low risk of bias evaluated the incremental value of log10 transformed NT-proBNP for predicting all-cause mortality at 12 months and showed no statistical difference (p=0.32) in the AUC by adding either NT-proBNP or midregional proadrenomedullin (MR-proADM). However, when either of these two biomarkers were added to the base model, the prognostic value of the base model significantly increased (p=0.038, p=0.0001). When MR-proADM was already included in the base model, the addition of NT-proBNP was significant; in contrast when NT-proBNP was in the base model and MR-proADM was added, there was no incremental value.

Four publications[286,301,309,320] evaluated incremental value for predicting all-cause mortality at approximately 24 months; subjects in all studies were predominately male subjects (>70%). One study[320] with a smaller sample size (n=142) showed that adding NT-proBNP increased the chi square value to the base model + tricuspid annular plane systolic excursion + ejection fraction. A study[286] from the Val-HeFT cohort (n=3,916) was at low risk of bias and showed that NT-proBNP added to the base model improved predictive ability at 23 months for all-cause mortality. Two related publications[301,309] evaluating the CORONA cohort do not state the followup time interval but based on other CORONA publications this is reported as 24 months (mean or a median of 33.4 months). Both publications report the same number of events but differing sample sizes at risk. The base models differ between the publications but both studies report increases in the chi square value when adding the log transformed NT-proBNP to the base model. One of these publications[309] shows the value of the c-statistic increases to 0.719 when NT-proBNP is added to the base model relative to an increase to 0.684 when lipids alone are added to the base model. The findings from these four publications with relatively large sample sizes, suggest that there is added value in using NT-proBNP to predict all-cause mortality at approximately two years. However, the model covariates differed between studies, as did the NT-proBNP cutpoints.

Four studies evaluated predictive ability of NT-proBNP at 30 months[329,360] and 33.4[353,357] months. Two publications evaluated the same cohort of patients (n=891, n=876) and the same base model, but one study[353] compared NT-proBNP relative to ST2 receptor cardiac biomarker and the other publication[357] compared the logNT-proBNP relative to high sensitivity cardiac troponin T (hs-cTnT). Both publications show that the c-statistic increases when NT-proBNP/logNT-proBNP is added to the base model and is statistically significant (p=0.040, p=0.017). Both publications also show that when the comparator cardiac marker (ST2 or hs-cTnT) are added to the base model the c-statistic increased and was statistically significant. When NT-proBNP is added to the model combined with either of these two cardiac markers, the c-statistic increased and was statistically significant; however, the c-statistic value does not appear to differ by a large amount compared to the value where NT-proBNP alone or the other

markers alone were added (Appendix K Table K-5). The other two studies showed that NT-proBNP added to the base model significantly improved model fit[329] and significantly improved the c-statistic relative to base model[360] for predicting all-cause mortality at 30 months. In summary, the studies evaluating longer term all-cause mortality would suggest NT-proBNP adds incremental value to predicting 30 and 34 month all-cause mortality. When incremental predictive value of BNP is compared to Hs-cTnT and ST2, the relative contribution appears similar but the greatest increment was shown when NT-proBNP was combined with either of these two markers and the base model.

NT-proBNP Levels Adding Incremental Value To Predicting Risk for Cardiovascular Mortality

Three studies[309,340,376] reported on the incremental value of NT-proBNP in patients with stable chronic HF for predicting cardiovascular related mortality from 12 to 24 months.

One study[340] used both the c-statistic and the LR chi-square for the outcome cardiovascular mortality at 12 months; both computations showed that the addition of NT-proBNP added incremental value (Appendix K Table K-6). However, in this study the highest incremental values occurred either when NT-proBNP and C-Terminal Pro-Endothelin-1 (CT-proET) were combined (global chi-square: 94.3 vs. 77.0, $p < 0.0001$). When using the c-statistic, NT-proBNP added to the base model showed a greater AUC relative to that of the addition of CT-proET (c-statistic=0.780 vs. 0.774). A second study[376] computed a LR chi-square and showed that the addition NT-proBNP to the base model yielded a significant increase in predictive value for cardiovascular mortality (global chi-square: 119.30 vs. 105.54, $p < 0.0001$). The third study[309] compared two types of mortality (all-cause and HF), but showed a similar trend across both outcomes; the base model without NT-proBNP had a lower discriminatory ability for risk prediction than the base model with NT-proBNP. However, HF mortality showed the highest improvement in c-statistic for the base model with NT-proBNP that was significant ($p=0.0002$).

NT-proBNP Levels Adding Incremental Value To Predicting Risk for Morbidity Outcomes

Two studies[283,286] evaluated morbidity outcomes from 12 to 24 months. A study[283] of small sample size (n=150) at low risk of bias evaluated the morbidity outcome of NYHA class change (same or worsening) at 12 months; the log LR increased and was statistically significant ($p =0.001$) when NT-proBNP was added to the base model. Another study[286] evaluated HF hospitalization at 23 months and also showed incremental value of NT-proBNP as the log LR increased and was statistically significant ($p =0.001$) (Appendix K Table K-7).

NT-proBNP Levels Adding Incremental Value To Predicting Risk for Composite Outcomes

Six publications evaluated the incremental value of adding NT-proBNP predicting five different composite outcomes for time intervals varying from 22 to 37 months. The composite outcomes evaluated included: (1) cardiovascular mortality or nonfatal myocardial infarction (MI) or nonfatal stroke,[301,309] (2) atherothrombotic endpoint (fatal or MI, or fatal or nonfatal non-hemorhagic stroke),[301,309] (3) coronary events (sudden death, fatal or nonfatal MI, coronary revascularization, ventricular defibrillation by an implantable device, resuscitation from cardiac arrest, or hospitalization for unstable angina),[301] (4) death/ all-cause death or worsening HF;[301,306,309,373] and, (5) mortality and morbidity unspecified;[286] cardiac mortality and HF

hospitalization[349] (Appendix K Table K-8). Two publications[301,309]evaluated prediction of four composite outcomes (some events overlapping) at mean followup of 24 months in the CORONA cohort of patients (n=3,664); all four composite outcomes showed that the addition of NT-proBNP improved the base model global fit and was statistically significant. Two related publications[306,373] with overlapping sample of subjects from the same patient registry showed that the addition of NT-pro BNP added incremental value in predicting all-cause mortality and HF hospitalization at 22 and 29 months. Another study[349] also showed that NT-proBNP added incremental value in predicting cardiac mortality and HF hospitalization at 37 months. In summary, the six publications that evaluated five different composite outcomes that combined mortality and morbidity events all suggest that NT-proBNP adds incremental value in predicting these outcomes from 22 to 37 months.

Key Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?

Seven studies[377-383] from 215 citations screened at full text were eligible for inclusion in this section of the systematic review. Defining a "general" population was not straightforward and after consultation with the Technical Expert Panel (TEP), a general population was defined as one randomly selected from a community setting where no specific inclusion or exclusion criteria were specified. Thus, if a study excluded patients with any particular disease (i.e., exclude those at risk of HF) or a particular biomarker result (i.e., exclude those with high urinary excretion of albumin), this was not defined as a general population.

These general population criteria were implemented to best represent the population as a whole that has no predefined natriuretic hormone level. See Appendix L. KQ5 Evidence Set.

Design Characteristics of Studies

Population

Populations were included in the systematic review only if they were unselected for any disease or risk factor for disease. The populations included as general populations were a very elderly population selected at age 85 years of age[378] or from population-based cohorts,[377,379-383] and many of these samples would be considered to be weighted in favor of the elderly population (Appendix L Table L-1). One study used only male subjects[380] and the others recruited from both sexes with varying representation (28-50% male subjects). A total of 16,507 individuals were included in the seven studies. The smallest study included 274 individuals[378] and the largest 5,447[382] (Appendix L Table L-1). The length of followup ranged from 3.5[378] to 13.8[377] years.

Intervention

All seven studies measured NT-proBNP. No studies used BNP.

Comparison

In three studies, no direct comparison measurement was used.[378,381,382] Three studies compared multiple cardiovascular risk markers[377,380,383] but these studies did not select identical comparison markers. The following markers were used for comparison: high-sensitivity C reactive protein,[377,380] troponin T,[379] troponin I,[380] copeptin,[377] midregional pro-adrenomedullin,[377] midregional pro-atrial natriuretic peptide,[377] cystatin C,[377,380] serum

creatinine,[383] and IGF-1.[383] All of these markers have some association with cardiovascular disease (CVD) reported in the literature.[14]

Outcomes

Several primary outcomes were reported for these studies. All-cause mortality was used in three studies.[378-380] Sudden cardiac death was used by one study.[382] A combined cardiovascular endpoint was used by one study.[381] One study considered the onset of AF or HF as the primary outcome.[377] One study[383] used cardiovascular mortality as a primary outcome and two studies[379,381] used death from CVD as a secondary outcome.

Setting

By definition, all of these studies were set in the community with no selection criteria. These papers represent a true general, unselected population.

Risk of Bias

The risk of bias was assessed based on the Hayden et al.[58] criteria as described in the methods section (Figure 20 and Appendix L Table L-2).

The populations for this group of studies were all suitably defined and described, and represent the population of interest. There is low risk of bias for population description and selection (Figure 20).

Most of the papers have complete data or describe attrition in a suitable manner. Two papers were not clear about the adequacy of the completeness of followup[381,382] and one of these did not describe the completeness of followup.[381] Overall, the risk of bias is low for study attrition.

The prognostic factors were fairly well addressed. NT-proBNP was appropriately defined and measured in all seven papers. The other prognostic factors were well defined and measured in all but two papers.[378,383] The indeterminate results or missing data were less well addressed by a few papers.[377,378,381,383] There is low risk of bias for the NT-proBNP factor and moderate risk of bias for the other prognostic factors.

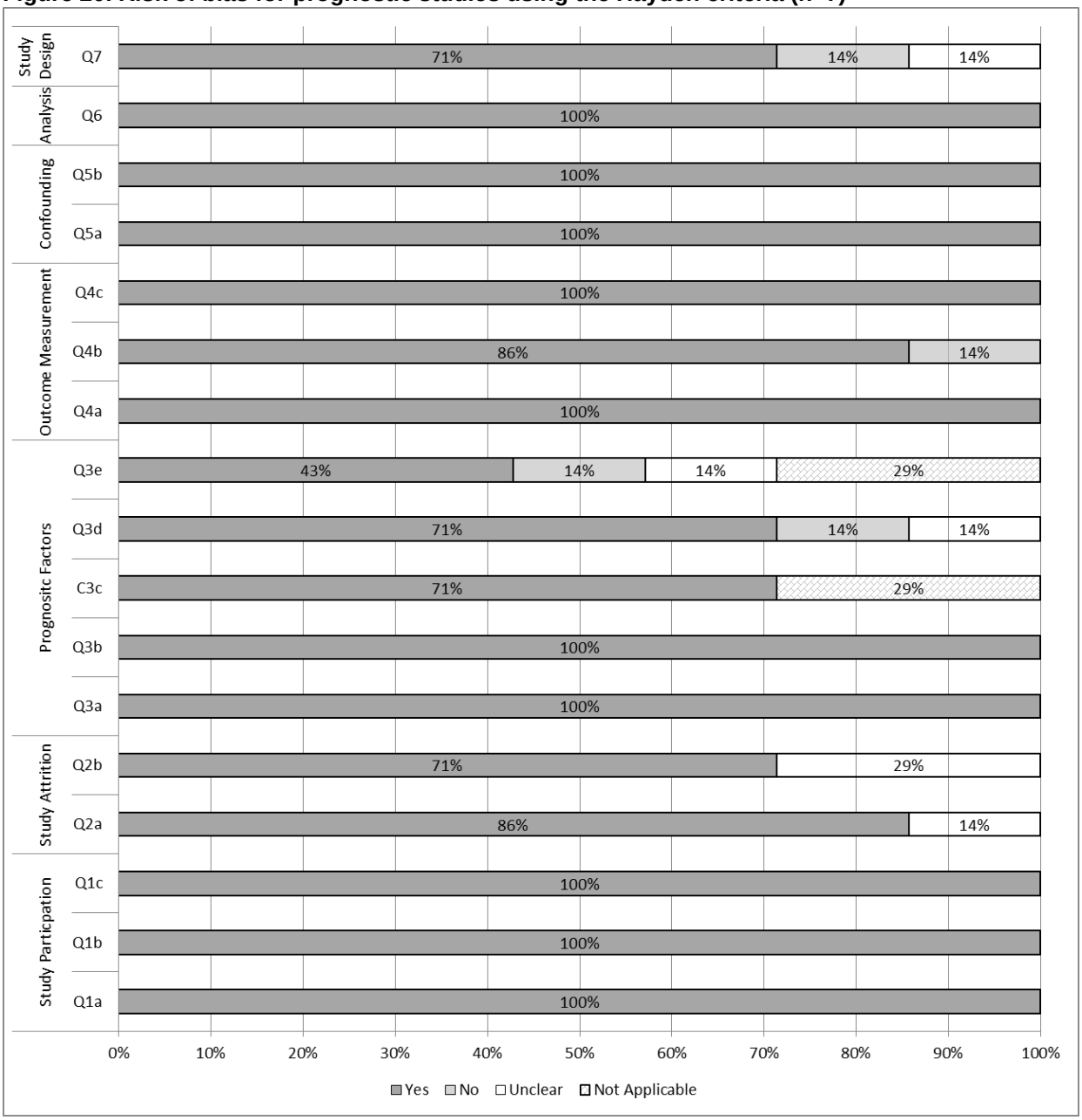
Outcome measurement was also done correctly by most studies. Fairly stringent criteria for obtaining accurate data were set, and only one study did not meet these criteria.[382] However, the authors did address this in their methods and the risk of bias is low for the outcome measurements in this section.

Confounding was considered by all of the papers according to our criteria and the risk of bias is low for confounding. The use of appropriate covariants was appropriate in these seven papers. Studies were expected to consider, age, sex, BMI, and renal function as important covariants. One study did not use BMI but did use waist-to-hip ratio as a covariant.[381]

Analysis was appropriately conducted in all the studies. All the study designs were observational cohorts, and the question posed for the reports most often looked at the predictive value of NT-proBNP in the population described. All reports used stored samples from the population studies to measure NT-proBNP and the other biomarkers of interest.

In summary, the risk of bias in this group of papers is low.

Figure 20. Risk of bias for prognostic studies using the Hayden criteria (n=7)



1. (a) source population clearly defined, (b) study population described (c) study population represents source population, or population of interest
2. (a) completeness of followup described, (b) completeness of followup adequate
3. (a) BNP/NTBNP factors defined, (b) BNP/NTBNP factors measured appropriately, (c) Other factors measured appropriately, (d) For BNP/NTBNP, the extent of and reasons for indeterminate test results or missing data reported, (e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. (a) outcome defined, (b) outcome measured appropriately, (c) a composite outcome was avoided
5. (a) confounders measured, (b) confounders accounted for
6. (a) analysis described;
7. (a) The study was designed to test the prognostic value of BNP/NT-proBNP

Results

Mortality

All-cause mortality was the outcome in three studies[378-380] and in all three there is an increasing adjusted HR with increasing NT-proBNP measured by tertiles,[378] by increases of 1 standard deviation[380] and by log(NT-proBNP).[379] The adjusted HR shown in Appendix L Table L-1 demonstrates the clear relationship between baseline NT-proBNP and all-cause mortality. The relationship appears to be log-linear in nature.

Sudden cardiac death has increasing HR across the quintiles of NT-proBNP and an adjusted HR=1.9 (95% CI, 1.7 to 2.1) for the natural logarithm (ln) ln-NT-proBNP.[382]

Cardiovascular death has a significant adjusted HR for log(NT-proBNP)/SD[381] and log(NT-proBNP).[379] When a cutpoint of 100 pg/mL was applied to a population older than 65 years of age an adjusted HR=1 (95% CI, 1 to 1.001) was reported with a p value of 0.001.[383] However, in a model that was adjusted for known baseline CVD, the adjusted HR became nonsignificant (HR=1.61 (95% CI, 0.79 to 3.28)).[379]

Morbidity

Onset of AF was associated with ln-NT-proBNP in a model including conventional risk factors (adjusted HR=1.45 (95% CI, 1.28 to 1.65)) but not a model that included midregional pro-atrial natriuretic peptide and CRP.[377]

Onset of incident HF was associated with ln-NT-proBNP in the models investigated that included other markers of cardiac risk.[377]

Key Question 6: In patients with HF, does BNP-assisted therapy or intensified therapy improve outcomes compared with usual care?

Design Characteristics of Studies

All studies were RCTs with the objective of determining whether patients treated for HF guided by BNP or NT-proBNP improves outcomes compared to usual care. There were nine studies that fulfilled this objective.[4,5,53,384-389] The term usual care includes the terms standard of care, clinically-guided, symptom-guided, or control group. One study used a congestion score strategy compared to BNP-guided therapy.[387] Another study[4] was a three-arm trial with an additional multidisciplinary group, but only the usual care and NT-proBNP arms are compared for this systematic review.

Inclusion/Exclusion Criteria

Inclusion criteria included age and characteristics of HF patients with regards to severity, therapy, and concentration of BNP or NT-proBNP (Table 35). Age was specified in five studies and included >18 years,[384,388,389] >20 years,[386] and >60 years.[53] All except one study[385] specified the severity of patients with HF by NYHA classification levels II-III,[388] II-IV,[5,53,384,386,389] or III-IV.[4,387] The most frequent LVEF cutpoint used was ≤40 percent,[4,384,386,389] but other studies had values of ≤35 percent,[387] ≤45 percent,[388] <50 percent,[5] and two studies did not require this measure.[53,385] The HF patients were required to be stable in two studies[5,388] and decompensated (or worsening) in five studies.[4,385-387,389] Other criteria included HF diagnosis ≤3 months[384] and previous admission for HF.[53,384] HF therapy was a criteria in four studies and included angiotensin converting enzyme (ACE-I) or angiotensin receptor blocker (ARB),[384,388,389]

aldosterone antagonists (AA),[389] digoxin,[384,388,389] diuretic,[384,388,389] beta-blocker,[388] or be on stable medications[388] or standard therapy,[53,388,389] but without specifically defining the therapy. Elevation of BNP or NT-proBNP was required in four studies.[5,53,385,389]

All studies except one[4] specified exclusion criteria (Table 35). Medical history exclusion criteria included cardiac, hepatic, pulmonary, and renal problems. Cardiac problems included acute coronary syndrome,[53,384,386-389] unstable angina,[53,384] aortic or mitral stenosis,[5,384,386] cardiac transplantation,[5,390] life-threatening arrhythmias,[5,385] cardiac transplantation,[5,390] open heart surgery,[5,389] revascularization,[53,386] revascularization indicated or expected,[53,386,389] surgical or invasive intervention,[385] or valvular disease requiring surgery.[53] Hepatic disease was an exclusion criteria in two studies,[384,389] and hepatic cirrhosis in another study.[388] Pulmonary disorders included asthma,[388] COPD,[385,386,388] pulmonary hypertension,[385] and severely decreased pulmonary function.[389] One study required dyspnea not mainly due to HF as an inclusion criteria.[53] Seven studies excluded patients if the creatinine concentration was above 200 to 309 μmol/L,[5,53,384,386-389] but one study required participants to have renal disease,[385] and another study[4] did not have renal disease as a criteria for inclusion or exclusion. Hemodialysis or peritoneal dialysis were exclusion criteria for two studies.[385,387] Two studies had medications as exclusion criteria. One study excluded patients on beta-blockers or had a contraindication for this medication.[384] Another study[5] excluded patients who were on standard HF therapy.

Other exclusion parameters included BMI >35 kg/m^2,[53] life expectancy for noncardiovascular diseases <1 year[385,386] or 3 years,[53] or limited life expectancy (time not specified).[389] Patients were also excluded if participating in another study or unable to give signed consent,[53,386,389] as well as being unable to follow the study schedule.[389]

Study Characteristics

Table 36 describes baseline characteristics for the BNP/NT-proBNP group. The studies were carried out between 2002 and 2010 for a minimum of 3 months up to a maximum of 18 months. There were seven multicenter studies including three to 45 sites with a minimum of 41 patients up to a maximum of 499 patients. The total number of patients included for all nine studies was 2,104.

Natriuretic Peptides

Four studies measured BNP[384,387-389] and five studies measured NT-proBNP.[4,5,53,385,386] The BNP test was performed on a point-of-care device, whereas all NT-proBNP measurements were performed on an automated clinical analyzer. One study did not blind patients to their NT-proBNP values.[389] All other studies except for one[388] did not explicitly say whether patients were blinded to their BNP or NT-proBNP test result.

Demographics

The study with the youngest patients had a mean age of 59 years (IQR 50 - 70),[387] whereas the study with the oldest patients had a mean age of 71.6 (±12.0) years.[385] Three studies had a low percentage of male participants: 24 percent,[4] 33.3 percent,[384] and 38 percent.[389] The percentage of males in the other studies was 55.0 percent[385] to 88.2 percent[386] with an average of 62.7 percent. Race was reported in only one study (87% Caucasian).[386] Six studies[4,5,53,385,388,389] recruited patients from European countries suggesting race to be mostly Caucasian.

Heart Failure Characteristics

The severity of HF by NYHA class was reported in five of nine studies as the number of patients in each class, and in one study[384] only the mean NYHA class was provided (2.6±0.7). The highest proportion of patients in three studies[5,385,386] was in the NYHA II class, whereas two studies had more NYHA III class patients.[53,389] The mean LVEF was as low as 20 percent[387] to as high as 34.9 percent[391] and reported as preserved, or reduced in one study.[4] The most common cause of HF was ischemic in four studies[4,53,386,388] in about half of the patients. The duration of HF[388] and a congestive score[387] were other criteria recorded.

B-Type Natriuretic Peptide Concentration

The baseline concentration of BNP was not reported in one of the four studies that measured this natriuretic peptide.[388] The mean concentration was higher in one study (808±676 pg/mL)[389] by about 40 percent compared to the other two studies.[384,387] For NT-proBNP, the baseline concentrations were similar, from 2,216 pg/mL to 2,998 pg/mL.

Clinical Measures

Various physiological measures were reported in all but one study[384] and included BMI,[53,386,389] blood pressure,[4,5,385,386] heart rate (all except one[389]), jugular vein distension,[5] lower extremity edema,[5] mitral valve regurgitation,[385] murmur,[5] pulmonary edema,[5] QRS duration,[5,385,388] Third Heart Sound (S3) and Fourth Heart Sound (S4) gallop,[5] and weight.[388]

Table 35. Inclusion and exclusion criteria for heart failure patient selection

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2011	TIME-CHF[53] 2009	UPSTEP[389] 2011
Inclusion (unless otherwise specified)									
Age, years	>18	-	-	>20	-	-	>18	>60	>18
Heart failure characteristics									
NYHA	II-IV	III-IV	-	II-IV	II-IV	III-IV	II-III	II-IV	II-IV
HF diagnosis ≥3 months	Yes	-	-	-	-	-	-	-	-
HF admission, previous	Yes	-	-	-	-	-	-	Yes	-
LVEF	≤40%	≤40% [c]	-	≤40%	<50%	≤35%	≤45%	-	<40%
Stable	-	-	-	-	Yes	-	Yes [h]	-	-
Decompensated	-	Yes	Yes	Yes [j]	-	Yes	-	-	-
Worsening	-	-	-	-	-	-	-	-	Yes [a]
BNP, elevated	-	-	-	-	-	-	-	-	Yes [b]
NT-proBNP, elevated	-	-	Yes [f]	-	Yes [e]	-	-	Yes [d]	-
Heart failure therapy									
ACE or ARB	Yes	-	-	-	-	-	Yes	-	Yes
Aldosterone antagonists	-	-	-	-	-	-	-	-	Yes
Digoxin	Yes	-	-	-	-	-	-	-	Yes
Diuretic	Yes	-	-	-	-	-	Yes	-	Yes
Stable medications ≤1 month	-	-	-	-	-	-	Yes	-	-
Beta-blockers	No	-	-	-	-	-	Yes	-	-
Contraindication for beta-blockers	No	-	-	-	-	-	-	-	-
Standard therapy	-	-	-	-	No	-	Yes	Yes	Yes
Exclusion criteria (unless otherwise specified)									
Medical history									
Cardiac	-	-	-	-	-	-	-	-	-
Acute coronary syndrome, months	<1	-	-	-	<3	No	<3	<0.3	<3
Angina, unstable	<1	-	-	-		-	-	≥ II [g]	-
Aortic or mitral stenosis, months	No [m]	-	-	No [k]	<3	-	-	-	-
Arrhythmias, life-threatening	-	-	No	-	No	-	-	-	-
Revascularization, months	-	-	-	≤3		-	-	<1	-
Revascularization indicated or expected, months	-	-	-	≤6	-	-	-	-	No
Stroke, months	-	-	-	-	<3	-	-	-	-
Cardiac transplantation	-	-	-	No	-	-	-	-	No
Open heart surgery, months	-	-	-	-	<3	-	-	-	No
Surgical or invasive intervention [q]	-	-	No	-	-	-	-	-	-
Valvular disease requiring surgery	-	-	-	-	-	-	-	No	-

Table 35. Inclusion and exclusion criteria for heart failure patient selection (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2011	TIME-CHF[53] 2009	UPSTEP[389] 2011
Hepatic	-	-	-	-	-	-	-	-	-
Hepatic disease[r]	No	-	-	-	-	-	-	-	No
Hepatic cirrhosis	-	-	-	-	-	-	No	-	-
Pulmonary	-	-	-	-	-	-		-	-
Asthma	-	-	-	-	-	-	No	-	-
COPD	-	-	No	No	-	-	No	-	-
Dyspnea not mainly due to HF	-	-	-	-	-	-	-	Yes[p]	-
Pulmonary hypertension	-	-	No	-	-	-	-	-	-
Severely decreased	-	-	-	-	-	-	-	-	No
Renal	-	-	-	-	-	-	-	-	-
Hemodialysis or peritoneal dialysis	-	-	No	-	-	No	-	-	-
Renal disease (creatinine, umol/L)	>200	-	Yes	>220	≥265	>309	>250	>220	>250
Other									
Body mass index, kg/m^2	-	-	-	-	-	-	-	>35	-
Life expectancy for noncardiovascular diseases, years	-	-	<1	<1	-	-	-	<3	-
Limited life expectancy	-	-	-	-	-	-	-		No
Participating in another study	-	-	-	-	-	-	-	No	No
Unable to give signed consent or unable to follow study schedule	-	-	-	No	-	-	-	No	No

[a] Within the last month, requiring hospitalization, and/or intravenous diuretics, metolazone, increased doses of diurectics, and/or need for inotropic support
[b] BNP >150 pg/mL if <75 years and >300 pg/mL if >75 years
[c] Or a cardiothoracic ratio >0.5
[d] NT-proBNP >400 pg/mL if <75 years or >800 pg/mL if >75 years
[e] NT-proBNP >800 pg/mL for males and >1000 pg/mL for females
[f] ≥1,700 pg/mL
[g] Canadian Cardiovascular Society Class
[h] No hospitalization, <1 month
[j] Hospital admission, emergency department visit, outpatient therapy for destabilized HF at least once within 6 months prior to enrollment
[k] Inoperable aortic valve disease
[m] Severe aortic stenosis
[p] Not due to LV systolic dysfunction
[q] Urgent and includes noncardiac surgery
[r] 3 times upper reference limit for transaminases
Abbreviations: ASE = American Society of Echocardiography

Table 36. General study description and baseline patient characteristics in the BNP/NT-proBNP group

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Country	Canada	Austria	Netherlands	United States	Sweden	United States	France	Switzerland and Germany	Sweden and Norway
Year study conducted	2002 to 2003	2003 to 2005	2004 to 2007	2006 to 2010	2009 to 2009	2003 to 2005	NR	2003 to 2008	NR
Centers study conducted, n	1	8	12	1	45	3	17	15	19
Total participants enrolled, n	41	182 [a]	345	151	250	137 [h]	220	499	279
Natriuretic peptide									
Type	BNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	BNP	BNP	NT-proBNP	BNP
Method, instrument	Triage	NR	Elecsys	NR	Immulite 2000	Cardioprofiler	Triage	NR	NR
Method, company	Biosite	Roche	Roche	Roche	Siemens	Biosite	Biosite	Roche	Biosite
Patients blinded to result	NR [b]	NR	NR	No	NR	NR	Yes	NR	No
Concentration, pg/mL	502 (411)	2,216 (355 to 9,649) [g]	2,961(1,383 to 5,144)	2,344 [f]	2,661 (56) [d]	453 (221 to 1,135)	NR	2,998 (2,075 to 7,220)	808.2 (676.1)
Demographics									
Age	64.5 (15.2)	71 (13)	71.6 (12.0)	63 (14.5)	78 (7)	59 (50 to 70)	65 (5)	76 (7)	71.6 (9.7)
Male, n (%)	7 (33.3)	22 (24)	95 (55)	67 (88.2)	96 (76)*	44 (67.7)	65 (59)	171 (68)	107 (38)
Heart failure characteristics									
NYHA	2.6 (0.7)	-	-	-	-	-	2.29 (0.60)	-	-
NYHA I	-	-	20 (11.5)	-	-	-	-	-	-
NYHA II	-	-	113 (64.9)	65 (88.5)[e]	78 (62)	-	-	-	47 (32)
NYHA III	-	-	41 (23.6)	-	48 (38)	-	-	186 (74.1) [j]	76 (52)
NYHA IV	-	-	-	-	-	-	-	-	22 (15)
Congestion score [n]	-	-	-	-	-	0 (0 to 1)	-	-	-
Duration of HF, months	-	-	-	-	-	-	31	-	-
LVEF, %	23.8 (8.8)	NR[b]	34.9 (13.7)	-	31 (9)	20 (15 to 25)	29.9 (7.7)*	29.8 (7.7)	84 (57)[m]
LVEDD, mm	-	-	57.5 (9.6)	-	-	-	67 (12)	-	-
Cause, ischemic	7 (33.3)	61 (66)	40 (23.0)	40 (53.3)	-	23 (37.7)	61 (55)	138 (55.0)	-
Cause, nonischemic	-	25 (27)	26 (14.9)	25 (33.3)	-	38 (62.3)	-	106 (42.2)	-
Cause, other or unknown	-	14 (15)	1 (0.6)	10 (13.3)	-	-	-	7 (2.7)	-

Table 36. General study description and baseline patient characteristics in the BNP / NT-proBNP group (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Physiological measure									
BMI, kg/m^2	-	-	-	28.8 (6.4)	-	-	-	25.4 (4.0)	27.2 (4.6)
BP, diastolic, mmHg	-	72 (13)	68.7 (11.3)	64 (9)*	73 (11)	-	-	-	-
BP, systolic, mmHg	-	119 (19)	116.8 (18.5)	108 (15)*	133 (21)	108 (95 to 121)	-	119 (18)	-
Heart rate, beats/min	-	79 (19)	72.1 (11.4)	73 (13)	71 (14)	80(72.5 to 91)	68 (13)	75 (14)	-
Jugular vein distension	-	-	-	-	24 (31.6)	-	-	-	-
Lower extremity edema	-	-	-	-	26 (34.2)	-	-	-	-
Mitral regurgitation grade ≥II	-	-	84 (48.3)	-	-	-	-	-	-
Murmur	-	-	-	-	51 (67.1)	-	-	-	-
Pulmonary rales	-	-	-	-	8 (10.5)	-	-	-	-
QRS duration, months	-	-	116	-	140 (35)	-	119 (43)	-	-
S4 gallop	-	-	-	-	6 (7.9)	-	-	-	-
S3 gallop	-	-	-	-	20 (26.3)	-	-	-	-
Weight, kg	-	-	-	-	-	-	76 (18)	-	-
Medical history									
Atrial fibrillation, history or current	-	-	-	31 (40.8)	75 (60)	-	-	82 (32.7)	-
Atrial fibrillation, chronic	-	-	29 (16.7)	-	-	-	-	-	-
Atrial fibrillation, paroxysmal	-	-	28 (16.1)	-	-	-	-	-	-
Arthritis	-	-	-	-	-	-	-	63 (25.1)	-
CABG	-	-	32 (18.4)	-	-	-	-		-
Cancer	-	-	-	-	-	-	-	33 (13.1)	-
COPD	-	15 (16)	29 (16.7)	15 (19.7)	17 (13.5)	-	-	60 (23.9)	-
Coronary artery disease	-	-	97 (55.7)	42 (55.3)*	-	-	-	-	-
Diabetes (type not specified)	5 (24)	34 (49)	-	-	-	-	18 (16)	-	-
Diabetes mellitus	-	-	44 (25.3)	30 (39.5)	23 (18.3)	-	-	77 (30.7)	39 (27)
Diabetes, insulin-dependent	-	-	-	-	-	-	-	33 (13.1)	-
Dyslipidemia	-	-	-	-	-	-	51 (46)	-	-
Hypertension	-	65 (71)	83 (47.7)	40 (52.6)	67 (53)	-	27 (30)	175 (69.7)	39 (27)

Table 36. General study description and baseline patient characteristics in the BNP / NT-proBNP group (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Kidney disease	-	-	-	-	-	-	-	140 (55.8)	-
MI	-	42 (46)	65 (37.4)	28 (36.8)	56 (44)	-	-	-	-
PCI	-	-	20 (11.5)	-	-	-	-	-	-
Smoking, current	-	-	37 (21.3)	5 (6.6)	-	-	43 (39)*	-	-
Smoking, history	-	-	56 (32.2)	24 (31.6)	-	-	-	-	-
Smoking, never	-	-	-	47 (61.8)	-	-	-	-	-
Stroke	-	12 (13)	17 (9.8)	-	-	-	-	36 (14.3) [k]	-
Transient ischemic attack	-	-	8 (4.6)*	-	-	-	-	-	-
Valve replacement	-	-	11 (6.3)	-	-	-	-	-	-
Ventricular tachycardia	-	-	-	23 (30.3)	-	-	-	-	-
Heart failure medication									
ACE-I	-	-	-	53 (70.7)	89 (71)	49 (75.4)	-	-	113 (77)
ACE-I or ARB	21 (100)	91(99)	138 (79)	-	-	-	109 (99)	238 (94.8)	-
ACE-I and ARB	-	0 (0)	-	-	-	-	-	-	-
ACE or ARB with beta-blocker	-	-	117 (67)	-	-	57 (87.7)	-	-	-
ACE or ARB with spironolactone	-	7 (8)	-	-	-	-	-	-	-
Aldosterone antagonist	-	-	92 (53)	37 (49.3)	28 (22)	-	-	102 (40.6)	81 (55)
ARB	-	-	-	8 (10.7)	33 (26)	8 (12.7)	-	-	51 (35)
Beta-blocker	-	82 (89)	139 (80)	74 (98.7)	100 (79)	46 (70.8)	109 (99)	191 (76.1)	137 (93)
Digoxin	21 (100)	-	-	22 (29.3)	18 (14)	-	-	-	33 (22)
Diuretic, loop	21 (100)	76 (83)	169 (97)	67 (89.3)	93 (74)	62 (95.4)	110 (100)	232 (92.4)	128 (87)
Diuretic, thiazide	-	-	-	5 (6.7%)	-	-	-	-	-
Hydralazine	-	-	-	4 (5.3)	-	-	-	-	-
Nitrates	-	-	-	8 (10.7)	-	-	-	71 (28.3)	-
Spironolactone	-	45 (49)	-	-	-	-	28 (25)	-	-
Heart failure device									
Biventricular pacemaker	-	-	-	30 (40.0)	-	-	-	-	-
Pacemaker	-	-	11 (6.3)	-	-	-	-	-	-
Implantable cardioverter-defibrillator	-	-	13 (7.5)	52 (69.3)	-	-	-	13 (5.2)	-

Table 36. General study description and baseline patient characteristics in the BNP / NT-proBNP group (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Biochemical test									
Creatinine, umol/L	-	15[c]	121 (98 to 157)	111 (38)	105 (43)	108 (84 to 137)	92 (40)	101 (34)	106.3 (33.3)
eGFR, mL/min/1.73 m^2	-	-	-	-	-	-	-	-	61.4 (20.9)
Hemoglobin, mmol/L	-	-	8.5 (1.2)	-	-	-	-	-	-
Potassium, mmol/L	-	-	4.27 (0.46)	4.3 (0.4)	-	-	-	-	-
Sodium, mmol/L	-	-	139.5 (3.2)	138 (3.5)	-	137 (133 to 139)	137 (13)	-	-
Urea, U/L	-	-	11.5 (8.2 to 16.2)	11.2 (6.0)	-	9.8 (7.5 to 14.3)	-	-	-
Quality of life									
Duke Activity Status Index	-	-	-	-		-	-	-	-
KCCQ frequency score	-	-	-	-	67.9 (23.3)	-	-	-	-
KCCQ symptom stability score	-	-	-	-	50.2 (16.8)	-	-	-	-
KCCQ overall summary score	-	-	-	-	66.0 (20.7)	-	-	-	-
MLHFQ	41 ± 24	-	-	-	-	-	-	40 (20)	-
SF-12, physical	-	-	-	-	-	-	-	34 (10)	-
SF-12, mental	-	-	-	-	-	-	-	46 (11)	-

* Significant difference between usual care group and BNP / NT-proBNP group.
Values are expressed as n (%), mean (SD), or median (IQR).
[a] Does not include third arm of study (nurse lead multi-disciplinary care)
[b] Recorded as preserved (n=2), mild to moderately reduced (n=20), and severely reduced (n=76)
[c] Number of patients with values >177umol/L
[d] SD
[e] NYHA class II and III
[f] Whole group NT-proBNP= 2,118 pg/mL (IQR: 1,122 tp 3,831)
[g] Expressed as mean and 95% CI,
[h] The characteristics were given for the 130 individuals who completed the study (n=65 for each arm)
[j] NYHA class III and IV
[k] Includes transient ischemic attack (TIA)
[m] Number (%) with LVEF <30%
[n] Congestion Score: Patients received 1 point for each of the following criteria: (1) orthopnea; (2) jugular venous pressure ≥10 cm H2O; (3) weight gain ≥pounds from dry weight; (4) the need to increase diuretics during a clinic visit or in the past 48 hours during the index hospitalization; and (5) ≥peripheral edema. The congestion score calculated at the time of discharge served as the target congestion score for each individual patient

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP=blood pressure; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLHF = Minnesota Living with Heart Failure Questionnaire; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SF-12 = 12-item Short Form Health Survey

Medical History

All except one study[387] reported at least one item for medical history. These included AF,[5,53,385,386] arthritis,[385] coronary artery bypass graft,[53] cancer,[4,5,53,385] COPD,[385,386] coronary artery disease,[388] diabetes mellitus (all studies reported this disease), dyslipidemia,[388] hypertension,[4,5,53,385,386,388,389] kidney disease,[53] myocardial infarction,[4,5,385,386] percutaneous coronary intervention,[385] smoking (current, former or never),[385,386,388] stroke or transient ischemic attack,[4,385] valve replacement,[385] or ventricular tachycardia.[386]

Heart Failure Therapy

Medication use was reported in all studies. Comparison of the main HF medications among studies is illustrated in Figure 21. This figure shows that at least 70 percent of the patients in all studies were taking an ACE-I or ARBs, beta-blocker (except in one study where no patients were taking this medication),[384] and diuretic. These included ACE-I,[5,386,387,389] of which close to 75 percent of participants were taking. Almost all patients in studies reporting ACE-I or ARB were taking one or the other medication.[4,53,384,385,392] No patients in any study were taking both ACE-I and ARB. Two studies reported patients taking ACE-I or ARB with a beta-blocker.[385,387] One study reported patients taking ACE-I or ARB with spironolactone.[4] Aldosterone agonists were reported in seven studies and in most studies, about half of the patients were taking this medication.[4,5,53,385,386,388,389] ARB alone was reported in four studies with 10.7 percent to 35 percent of patients taking this medication.[5,386,387,389] Beta-blockers were taken by almost all patients in all except one study[384] where the objective was to titrate beta-blockers using BNP-guided therapy compared to usual care. Beta-blockers were taken by at least 76.1 percent and up to 99 percent of all patients.[388] Digoxin was reported in four studies of which one study[384] had all patients on this medication. In the other studies[5,386,389] the percent of patients taking this medication was 14 percent to 29.3 percent. Loop diuretics were taken by 83 percent to 100 percent of all study patients. Only one study reported patients taking a thiazide diuretic.[386] Hydralazine[386] and nitrates[53,386] were taken by some patients.

HF devices were reported in three studies and included a biventricular pacemaker[386] and implantable cardioverter-defibrillators.[53,385,386]

Quality of Life

Three studies had baseline quality of life (QOL) data based on four types of questionnaires. The questionnaires included the Duke Activity Status Index,[5] Kansas City Cardiomyopathy Questionnaire (KCCQ),[5] Minnesota Living with Heart Failure Questionnaire,[53,384] and the Short Form 12.[53]

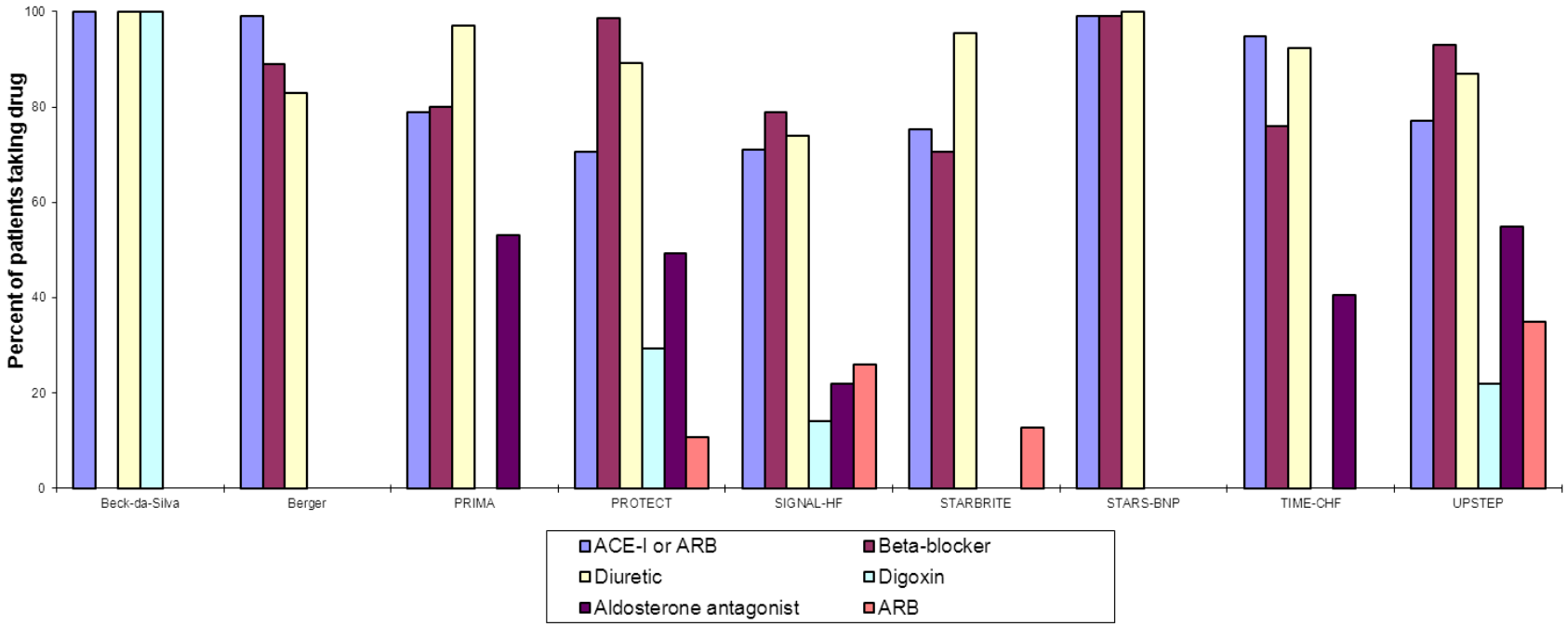
Other Biochemical Tests

Creatinine concentration was reported in all but one study.[384] The concentrations were between 92±34 μmol/L[388] and 121 μmol/L (IQR 98 to 157)[385] with one study reporting the number of patients with a value >177 μmol/L.[4] The eGFR was reported in one study (61.4±20.9 mL/min/1.73 m^2).[389] Hemoglobin,[385] potassium,[385,386] sodium,[385-387,392] and urea[385-387] were the other biochemical tests reported.

Differences Between the Two Treatment Arms

There were few significant differences in the reported characteristics between the usual care group and BNP/NT-proBNP treated group (BNP/NT-proBNP group). They included percent male (76 in BNP/NT-proBNP group and 66 in usual care group),[5] LVEF percent (29.9 in BNP/NT-proBNP group and 31.8 in usual care group),[388] mean (SD) blood pressure (diastolic (mmHg) 64(±9) in BNP/NT-proBNP group and 67(±9) in usual care group; systolic (mmHg) 108(±15) in BNP/NT-proBNP group and 112(±16) in usual care group),[386] percent coronary artery disease (55 in BNP/NT-proBNP group and 67 in usual care group),[386] percent current smoker (39 in BNP/NT-proBNP group and 53 in usual care group),[388] and percent transient ischemic attack (five in BNP/NT-proBNP group and 15 in usual care group).[385]

Figure 21. Proportions of medication use reported at baseline in all studies



Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
ACE-I or ARB	100	99	79	70.7	71	75.4	99	94.8	77
Beta-blocker	-	89	80	98.7	79	70.7	99	76.1	93
Diuretic	100	83	97	89.3	74	95.4	100	92.4	87
Digoxin	100	-	-	29.3	14	-	-	-	22
Aldosterone antagonist	-	-	53	49.3	22	-	-	40.6	55
ARB	-	-	-	10.7	26	12.7	-	-	35

Treatment Protocol

Table 37 outlines the treatment protocols for each study for both the BNP/NT-proBNP group as well as the usual care group. Three studies chose a specific target concentration for the BNP/NT-proBNP group. For the study[388] using BNP, it was 100 pg/mL, which is the cutpoint used for ruling out a diagnosis of HF. For NT-proBNP the target concentrations were 1,000 pg/mL[386] and <2,200 pg/mL.[4] A concentration of 900 pg/mL has been recommended as the cutpoint to rule out HF in patients 50 to 75 years old, but higher in patients >75 years old in an acute setting (1,800 pg/mL). Two studies defined target concentrations according to age. For the study using BNP these values were <150 pg/mL for patients <75 years old and <300 pg/mL for patients ≥75 years old.[389] Similarly, a higher target concentration was required for patients ≥75 years old for NT-proBNP (<800 pg/mL) compared to <75 years old (<400 pg/mL).[53] The remaining four studies expressed target values according to individual patient baseline concentrations. These target values included the NT-proBNP concentration at discharge or 2-week followup after admission (whichever was lower and at minimum 850 pg/mL),[385] and ≤2-fold discharge for BNP[387] or NT-proBNP.[5] In the last study,[384] uptitration was defined specifically if: (1) BNP <baseline and clinical status was unchanged or better; (2) BNP <10 percent of previous value with mild signs of congestion; or, (3) BNP ±10 percent of previous value treatment based on clinical signs alone.

The treatment protocols were the same between study arms in six studies apart from the additional requirement of aiming to achieve the BNP/NT-proBNP target concentration in the BNP/NT-proBNP group. The treatment protocols were those recommended by the European Society of Cardiology (ESC)[391] and American College of Cardiology (ACC),[53] or Swedish HF guidelines.[5] In another study, treatment was based on clinical assessment alone[388] or in combination with a congestion score.[387] The congestion score included one point for each of the following criteria: (1) orthopnea; (2) jugular venous pressure >10 cm H_2O; (3) weight gain ≥2 pounds from dry weight; (4) the need to increase diuretics during a clinic visit or in the past 48 hours during the index hospitalization; and (5) ≥one peripheral edema. Treatment in one study was specific to the uptitration of a beta-blocker dose to 10 mg/d.[384] The three studies with different treatment protocols dependent on study arms included one study that followed a predefined treatment schedule for the BNP/NT-proBNP group compared to ESC guidelines at the discretion of the investigator.[389] In another study, no specific guide to treatment was required for the NT-proBNP group other than drug therapy intensification and/or careful reassessment of medical programs, whereas in the usual care group, ACC/AHA guidelines were followed.[386] In one of the studies, an HF specialist was involved in the care of patients in the NT-proBNP group compared to primary care physicians in the usual care group.[4] In the NT-proBNP group, patients were seen by the HF specialist every two weeks in addition to multidisciplinary care to optimize therapy following a predefined plan. In the usual care group, the primary care physicians followed a management plan but patients had no contact with HF specialists nor did they have a structured followup.

The followup frequency varied among studies. Two studies had monthly followups[384,387] and two studies had 3 month followups after the first visit[5,386,388] or second visit.[385] Two other studies had the first two followups at 3 months and then 6 months after that.[4,53] Another study had 2-, 6-, and 10-week followups and then 4, 6, 9, and then 6 months thereafter.[389]

Table 37. Treatment strategies for the BNP/NT-proBNP group and usual care group

Study Year	BNP / NT-proBNP Group	Usual Care Group	Followup Frequency
Beck-dal-Silva,[384] 2005	1) BNP <baseline and clinical status unchanged or better, or 2) BNP <10% previous value with mild signs of congestion, or 3) BNP ±10% previous value treatment based on clinical signs alone		1, 2, and 3 m
	Increase beta-blocker dose up to 10 mg/d	Clinical status unchanged or better Increase beta-blocker dose up to 10 mg/d	
Berger,[4] 2010	NT-proBNP <2,200 pg/mL		
	Chronic HF specialist visit every 2 weeks, plus multidisciplinary care to optimize therapy following a predefined plan	Primary care physicians followed a management plan; no contact with HF specialists or structured followup	1, 3, 6 and 12 m
Prima,[385] 2010	NT-proBNP <10% individual target level (minimum 850 pg/mL) at discharge or at 2 weeks followup after admission		2 w, 1 m and then every 3 m up to 2 y
	ESC HF guidelines	ESC HF guidelines	
Protect,[386] 2011	NT-proBNP <1,000 pg/mL		
	Drug therapy intensification and/or careful reassessment of medical programs: no algorithm	ACC/AHA guidelines by physicians skilled in HF care	1, 3, 6 m (min), 9 and 12 m (max)
Signal-HF,[5] 2010	NT-proBNP ≤50% baseline		1, 3, 6, and 9 m
	Swedish HF guidelines with a step-wise treatment schedule	Swedish HF guidelines with a step-wise treatment schedule	
Starbrite,[387] 2011	BNP ≤2-fold discharge BNP		1, 2, 3 and 4 m
	Clinical judgement; diuretic therapy adjusted with congestion score	Clinical judgement; diuretic therapy adjusted with congestion score	
Stars-BNP,[388] 2007	BNP <100 pg/mL		3, 6, 9, 12, 15 m
	Clinical assessment	Clinical assessment	
Time-CHF,[53] 2009	NT-proBNP <400 pg/mL <75 yrs or <800 pg/mL ≥75 yrs and NYHA class II or less		1, 3, 6, 12 and 18 m
	ESC and ACC/AHA guidelines with predefined escalation rules and individually adjusted as deemed appropriate by the investigator	NYHA class II or less ESC and ACC/AHA guidelines with predefined escalation rules, individually adjusted as deemed appropriate by the investigator	
Upstep,[389] 2011	BNP <150 pg/mL <75 yrs or <300 pg/mL ≥75 yrs		
	Predefined treatment schedule; patients aware of BNP value	ESC guidelines and discretion of investigator	2, 6, & 10w, 4, 6, & 9m, then every 6 m

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ESC = European Society of Cardiology; HF = heart failure; m = month; max = maximum; min=minimum; NYHA = New York Heart Association; w = week; yr = year

Outcomes

All data collected on the study patients are summarized in Table 38 and includes sections on BNP/NT-proBNP, endpoints, and medications. The reported parameters were described as no difference, decrease, or increase for the BNP/NT-proBNP group compared to the usual care group. Table 39 shows the primary endpoints in these studies.

The outcomes included clinical visits, hospital events, mortality, days alive, and QOL scores. They were recorded in various ways and this heterogeneity made it unsuitable to perform any meta-analyses. For example, admissions to the hospital included all-cause, HF only, and cardiovascular events. The events were captured as number of days admitted, time to first admission, and number of patients admitted.

BNP/NT-proBNP

The final concentration of BNP/NT-proBNP for all patients was reported in all studies except one.[389] Of these studies, two found decreased values of BNP[388] or NT-proBNP.[386] The percent of patients who achieved the target concentration was reported in five studies.[5,386-388,391] One study had 80 percent of patients below the target at the 3-month followup.[391] However, the target was only 10 percent below the patients' baseline value. In the other studies, the percent of patients achieving the target value was between 20 percent and 40 percent.

Primary Endpoint

A composite of endpoints was used in six studies,[4,5,53,386,388,389] two studies used only one endpoint,[385,387] and one study did not define a primary endpoint.[384] Patients in the BNP/NT-proBNP group had fewer events compared to the usual care group in three studies.[4,386,388] The other studies showed no difference in the primary endpoint between treatment groups (Table 39).

Clinic Visits

Clinic visits were reported in only two studies[4,385] of which one reported more visits for the BNP/NT-proBNP group compared to the usual care group.[4]

Hospitalizations

Admissions were considered all-cause unless otherwise specified. All studies except one[53] reported on some parameter related to admissions, most reported on cardiovascular admissions, and three of the four studies[4,386,388] reported fewer admissions in the BNP/NT-proBNP group compared to the usual care group.

Deaths

Deaths were reported as all-cause, cardiovascular, or HF. Two studies did not report deaths.[53,387] Of the seven studies that did report on deaths, six reported all-cause,[4,5,384,385,388,389] four reported a cardiovascular cause,[5,386,388,389] and only two studies reported on death related to HF.[388,389]

Table 38. Outcome data at end of followup for BNP/NT-proBNP group

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Followup duration, months	3	18	24	10 (3)	9	3	15 [g]	18	12
Completed, %	93	63 [b]	90	100	95	95	100	100	97
Natriuretic peptide									
BNP, pg/mL	No	NA	NA	NA	NA	No	Decrease	NA	NR
BNP, total patients below target, %	NA	NA	NA	NA	NA	33	33 [h]	NA	NR
NT-proBNP, pg/mL	NA	No	No	Decrease	No	NA	NA	No/Increase [j]	NA
NT-proBNP, total patients below target, %	NA	NR	80 [h]	40	20	NA	NA	NR	NA
Combined endpoint [m]	NA	Decrease	NA	Decrease	No	NA	Decrease	No	No
Clinic Visits									
All visits (schedule and unscheduled)	-	Increase [a]	-	-	-	-	-	-	-
Scheduled visits	-	-	No	-	-	-	-	-	-
Unscheduled visits	-	-	No	-	-	-	-	-	-
Hospital Events									
Admissions, all-cause	No	-	-	-	-	-	No	-	-
Time to first all-cause hospitalization	-	-	-	-	-	-	-	-	No
Days admitted to the hospital expressed as a percentage of total days alive	-	-	No	-	-	-	-	-	-
Days hospitalized in patients who survived	-	-	-	-	-	No	-	-	-
Admissions, cardiovascular	-	-	No		No	-	-	-	-
Admissions, HF	-	Decrease	No	Decrease [k]	-	-	Decrease	-	-
Time to first HF hospitalization	-	-	-	-	-	-	-	-	No
Mortality									
Death, all-cause	No	-	No	-	No	-	No	-	-
Death rate	-	Decrease	-	-	-	-	-	-	-
Time to all-cause mortality (days to first event)	-	-	-	-	-	-	-	-	No
Death, cardiovascular	-	-	No	No	No	-	-	-	-
Time to cardiovascular mortality	-	-	-	-	-	-	-	-	No
Death, HF	-	-	-	-	-	-	No	-	-
Time to HF mortality	-	-	-	-	-	-	-	-	No

Table 38. Outcome data at end of followup for BNP / NT-proBNP group (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
Days Alive									
Number of days alive outside hospital	-	-	-	-	No	-	-	-	-
Days alive outside hospital as a percentage of the total days of followup	-	-	No	-	-	-	-	-	-
Days alive without LVAD or transplant	-	-	-	-	-	No	-	-	-
Event-free survival	-	-	-	-	-		Increase	-	-
Survival free of hospitalization	-	-	-	-	-	-	-	No	-
Survival free of hospitalization for HF	-	-	-	-	-	-	-	Increase	-
Other									
Acute coronary syndromes	-	-	-	No	-	-	-	-	-
Cerebral ischemia	-	-	-	No	-	-	-	-	-
Congestion score[f]	-	-	-	-	-	No	-	-	-
Significant ventricular arrhythmia	-	-	-	No	-	-	-	-	-
Worsening HF defined as new worsening symptoms and signs of HF requiring unplanned intensification of decongestive therapy	-	-	-	Decrease	-	-	-	-	-
Time to first worsening HF	-	-	-	-	-	-	-	-	No
Time to cardiovascular death or cardiovascular hospitalization	-	-	-	-	No	-	-	-	-
Quality of Life (QOL)									
Duke Activity Status Index	-	-	-	-	-	-	-	No	-
KCCQ score	-	-	-	-	No	-	-	-	-
MLHFQ, score	Increase	-	-	-	-	-	-	No	-
Short Form 12, physical	-	-	-	-	-	-	-	No	-
Short Form 12, mental	-	-	-	-	-	-	-	No	-
Medication final record									
Aldosterone antagonist, number	-	-	No	Increase	-	-	-	-	-
Aldosterone antagonist, target dose	-	-	No	-	-	-	-	-	-
Aldosterone antagonist, dose	-	-	-	-	-	-	-	-	No
ACE-I	-	-	-	No	No	Increase	-	-	-
ACE-I, target dose	-	-	-	No[d]	No	-	-	-	-
ACE-I, dose	-	-	-	-	-	-	-	-	No
ACE-inhibitor, discharge dose	-	-	-	-	-	-	-	-	-
ARB, number of patients	-	-	No	Decrease	No	-	-	-	-
ARB, target dose	-	-	No	No[d]	No	-	-	-	-

Table 38. Outcome data at end of followup for BNP / NT-proBNP group (continued)

Study Year	Beck-da-Silva[384] 2005	Berger[4] 2010	PRIMA[385] 2010	PROTECT[386] 2011	SIGNAL-HF[5] 2010	STARBRITE[387] 2011	STARS-BNP[388] 2007	TIME-CHF[53] 2009	UPSTEP[389] 2011
ARB, dose	-	No	-	-	-	-	-	-	No
ACE-I or ARB, number of patients	-	Increase	Increase	-	No	No	-	-	-
ACE-I or ARB, target dose	-	Increase	No [d]	-	-	Increase	-	Increase	-
ACE-I + ARB, number of patients	-	-	-	-	No	-	-	-	-
ACE-I + AA	-	-	-	-	No	-	-	-	-
ACE-I + ARB + AA	-	-	-	-	No	-	-	-	-
ACE-I or ARB and beta-blocker, number	-	-	Increase	-	-	Increase	-	-	-
ACE-I or ARB and beta-blocker, target dose	-	No	No [d]	-	-	-	-	-	-
Beta-blocker, number of patients	No	Increase	No	No	No	-	-	-	-
Beta-blocker, target dose	No	-	No	No [d]	No	-	-	Increase	-
Beta-blocker, dose	-	-	-	[d]	-	-	-	-	No
Digoxin	-	No	-	-	No	-	-	-	-
Diuretic, number [c]	-	Decrease	No	Decrease [e]	No	No	-	-	-
Diuretic, dose [c]	-	-	No	No [e]	No	-	-	-	No
Nitrates	-	No	-	No	-	-	-	-	-
Spironolactone, number of patients	-	No	-	-	-	No	-	Increase	-
Spironolactone, dose	-	-	-	-	-	-	-	-	-

[a] Difference in groups for scheduled visits if NT-proBNP >2,200 pg/mL but not if <2,200 pg/mL or unscheduled visits
[b] The median followup time for the 37% that did not complete median was 15 months (IQR13 to 16)
[c] Loop diuretic unless otherwise specified
[d] ≥50% target dose
[e] Only for loop diuretics
[f] Congestion Score: Patients received 1 point for each of the following criteria: (1) orthopnea; (2) jugular venous pressure ≥10 cm H2O; (3) weight gain ≥ pounds from dry weight; (4) the need to increase diuretics during a clinic visit or in the past 48 hours during the index hospitalization; and (5) ≥peripheral edema. The congestion score calculated at the time of discharge served as the target congestion score for each individual patient
[g] Median followup time (minimum 6 months)
[h] At 3-month followup. At 1-year followup
[j] Patients ≤75 years improved vs. ≥75 years for NYHA (p=0.05) and NT-proBNP (lower concentration; p=0.04)
[k] Includes treatment with intravenous diuretic agent in the emergency department setting without hospitalization
[m] Refer to Table Q6.5 for study specific endpoints
Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AA = aldosterone agonist; ARB = angiotensin-receptor blocker; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVAD = ; MLHFQ = Minnesota Living With Heart Failure Questionnaire; QOL = quality of life; NA = not applicable; NR = not recorded.

Table 39. Primary endpoints of the nine BNP/NT-proBNP-guided therapy studies

Study Year	Beck-da-Silva[384] 2005*	Berger[4] 2010†	PRIMA[385] 2010	PROTECT[386] 2011†	SIGNAL-HF[5] 2010†	STARBRITE[387] 2011	STARS-BNP[388] 2007†	TIME-CHF[53] 2009	UPSTEP[389] 2011†
Death									
Duration of time to death	-	-	-	-	-	-	-	-	-
Death due to any cause	-	-	-	-	-	-	-	-	x
Death related to HF	-	-	-	-	-	-	x	-	-
Cardiovascular death	-	-	-	x	-	-	-	-	-
Hospitalization									
Need for hospitalization	-	-	-	-	-	-	-	-	x
Duration of time to HF rehospitalization	-	-	-	-	-	-	-	-	-
Unplanned hospital stays for HF	-	-	-	-	-	-	x	-	-
HF hospitalization	-	-	-	x	-	-	-	-	-
Out of hospital									
Difference in total number of days alive and outside hospital between treatment groups	-	-	x	-	-	-	-	-	-
Number of days alive outside hospital	-	-	-	-	x	x	-	-	-
Days out of hospital for cardiovascular reasons	-	-	-	-	x	-	-	-	-
Survival free of any hospitalization*	-	-	-	-	-	-	-	x	-
Quality of Life									
KCCQ symptom score	-	-	-	-	x	-	x	x	-
MLHFQ	-	-	-	-	-	-	x	-	-
SF12	-	-	-	-	-	-	x	-	-
Other									
Acute coronary syndrome	-	-	-	x	-	-	-	-	-
Cerebral ischemia	-	-	-	x	-	-	-	-	-
Significant ventricular arrhythmias	-	-	-	x	-	-	-	-	-
Worsening HF	-	-	-	x	-	-	-	-	x

* No primary endpoint defined.

†Composite endpoint of all endpoints listed in the column.

Abbreviations: HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living With Heart Failure Questionnaire; SF12 = Short Form 12

Days Alive

Opposite to death data, days alive data were captured in five studies.[5,53,385,387,388] Two studies[53,388] showed that patients in the BNP/NT-proBNP group had more days of survival outside the hospital compared to the usual care group.

Quality of Life

Three studies include a QOL questionnaire.[5,53,384] One study[384] using the Kansas City Cardiomyopathy Questionnaire (KCCQ) showed improvement in score in the BNP/NT-proBNP group compared to the usual care group.

Other Parameters

Studies also reported on acute coronary syndrome,[386] cerebral ischemia,[386] significant ventricular arrhythmia,[386] a combined endpoint of time to cardiovascular death or cardiovascular hospitalization,[5] congestion score,[5] and worsening of HF.[386,393] Only one parameter, worsening HF (i.e., new, worsening symptoms and signs of HF requiring unplanned intensification of decongestive therapy) was different in the BNP/NT-proBNP group compared to the usual care group. The study showed fewer events in the BNP/NT-proBNP group.[386]

Medications

Medication (type, dosage, and titrations) was recorded in all but one study.[388] The information was usually percent of patients taking the medication, but some studies also reported on the dose or percent of patients achieving the target dose or a percentage of the target dose.

Three studies reported no changes in medications[5,384,389] and one study did not report final medical use.[388] Five studies reported significant change in some medication use between the BNP/NT-proBNP group and the usual care group.[4,53,385-387] The direction of change was consistent in all studies reporting on that medication. Of the eight medications (or group of medications), six (AA, ACE-I, ACE-I or ARB, ACE-1 or ARB and beta-blocker, beta-blocker, spironolactone) were increased and two (ARB, diuretic) were decreased.

No differences between the BNP/NT-proBNP group and usual care groups were found for ACE-I and AA,[5] ACE-I plus ARB and AA,[5] digoxin,[4,5] or nitrates.[4,386] Table 38 provides further details.

Risk of Bias

Methodological quality was assessed using the modified Jadad scale with four additional questions (Table 40). The risk for the nine studies[4,5,53,384-389] was low. The SOE was assessed using the single outcome of mortality (Table 41). It was an outcome that all nine studies reported, although one study reported this as days only,[387] and it was not clear if the study reporting only cardiovascular death included all deaths.[386] Therefore, the RR and CI was calculated on seven studies.[4,5,53,384,385,388,389] The effect sizes were variable and dispersion of the effect size was low in three studies[4,53,385] but high in four,[5,384,388,389] resulting in the precision domain being scored as imprecise. The studies were rated as inconsistent; two studies[5,388] reported fewer deaths in the BNP/NT-proBNP group compared to the usual care group, whereas five[4,53,384,385,389] did not report a difference. Based on these data, the SOE for this outcome was rated as low. This means there is limited confidence that the estimate of the effect is close to the true effect. The studies were heterogeneous in design and further evidence is needed to conclude whether the effect (outcome) is stable.

Table 40. Methodological quality (Modified Jadad scale) of randomized controlled trials assessing BNP/NT-proBNP

Author Year	Double Blinding Stated	Double Blinding Method Described	Randomi-zation Stated	Randomi-zation Method Described	Description of Withdrawals/ Dropouts	Assess Adverse Event	Statistical Analysis	Include/ Exclude Criteria	Allocation Adequately Concealed	Analysis Based on Intention To Treat	Sample Size Justified	Outliers Reported	Role of the Study Sponsor/ Funder
Jourdain[388] 2007	√	X	√	?	X	X	√	√	?	√	X	?	√
Beck-da-Silva,[384] 2005	X	?	√	?	X	X	√	√	?	?	√	?	?
BoldaXva,[4] 2010	X	?	√	√	√	X	√	√	√	√	X	?	?
Pfisterer,[53] 2009	X	?	√	√	X	√	√	√	?	√	√	?	√
Persson,[5] 2010	X	?	√	?	√	X	√	√	?	√	√	?	√
Eurlings,[385] 2010	X	?	√	?	√	X	√	√	X	√	√	?	X
Januzzi,[386] 2011	X	?	√	?	X	√	√	√	?	√	√	?	√
Karlstrom,[389] 2011	X	?	√	?	√	X	√	√	?	√	√	?	?
Shah,C.[387] 2011	X	?	√	√	X	√	√	√	√	?	√	?	?

√ = low risk of bias; X = high risk of bias; ? unclear

Table 41. Strength of evidence for studies evaluating the benefit of BNP and NT-proBNP-guided therapy compared to usual care for HF

Design	Risk of Bias*	Consistency	Directness	Precision	Effect Size, RR (95% CI)	Strength of Evidence
RCT	Low	Inconsistent (5 studies with no effect and 2 studies with a lower RR)	Direct	Imprecise (Unable to assess if the studies were adequately powered and the overall event rates were variable because of length of followup	Beck daSilva[167] 2005: 0.48 (0.05,4.85) Berger[168] 2010: 0.56 (0.35,0.89) PRIMA[169] 2001: 0.79 (0.57,1.10) STARS-BNP[173] 2011: 0.64 (0.26,1.58) UPSTEP[175] 2007: 0.96 (0.61,1.50) SIGNAL-HF[171] 2010: 0.98 (0.36,2.72) TIME-CHF[174] 2009: 0.65 (0.52,0.81)	The strength of evidence was rated as Low. BNP/NT-proBNP guided therapy, when compared with usual care, reduced all-cause mortality. Future research is likely to change the magnitude and direction of the effects for the outcome of all-cause mortality

*Modified Jadad scale

Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

Key Question 7: What is the biological variation of BNP and NT-proBNP in patients with HF and without HF?

Design Characteristics of Studies

Seven studies[37,38,394-398] included data on biological variation for BNP and NT-proBNP (Table 42). Of these, the population consisted of patients with stable HF for five studies,[37,38,394-396] one study that also included healthy individuals,[397] and one study that had only healthy individuals.[398] No study reported on race but six[37,38,394-396,398] of the seven studies were done in Europe suggesting individuals were mostly Caucasian. All study designs were prospective cohort studies, except for one which was a retrospective chart review.[38] The diagnosis of HF was described in only three studies,[394,395,397] but one did not refer to a standard guideline although criteria were appropriate for a clinical diagnosis of HF.[397] Patients with HF were primarily selected from HF clinics, but also from a cardiologist's practice,[394] and an unknown source.[397] Patients were considered as having stable HF by various physical parameters (e.g, weight, blood pressure, heart rate, waist circumference), clinical status (e.g., heart function, NYHA class, AF, edema, palpitations, renal function) medications, and no hospitalization or death in all but one study[397] where no description was provided. The criteria used to assess stability varied across studies and also when the assessment of HF stability was made. Two studies[394,396] assessed this before study inclusion at 1 month,[396] 2 months,[394] and since last clinic visit.[37] Four studies assessed stability during the collection period[37,38,395,397] and one study also considered stability 6 months after the study period.[37] The severity of HF was assessed by NYHA classification as mostly level II (58 to 79 percent).

Study duration varied in length from as short as 1 day to as long as 2 years. Overall, the number of patients or participants sampled was small (mean=32, range 5 to 78), as were the samples obtained to calculate biological variation (median=4, range 2 to 15). There were more males than females in the studies. The average of participants was over 60 years except in the two studies[397,398] that determined biological variation in younger healthy individuals, which is not representative of the same age range as individuals who have HF.

Blood collection parameters and analytical protocols varied among studies and were inconsistently reported. Some studies considered diurnal rhythm of BNP and NT-proBNP and collected samples at specific times.[37,394,395,397,398] Two studies required patients to fast overnight.[38,398] A few studies also specified rest time before collection,[37,395,396] as BNP and NT-proBNP are known to increase after exercise. Two studies sampled blood from an indwelling catheter.[395,396] All studies but two[38,396] stored aliquots of separated blood in the freezer prior to their analysis. Storage temperature was from –80°C to –20°C. The studies that did not store samples analyzed samples within 10 min,[37] or 2 hours after collection.[38] Attention was paid to how the samples were analyzed to reduce analytical variation. Samples were analyzed on the same day or in a batch on a different day; however, two studies did not report this information.[396,397] Three assay methods were used for BNP and included Biosite Triage,[396,397] Bayer Centaur,[37] and Abbott (instrument type not specified).[394] The Roche instruments were used for all NT-proBNP assays (Elecsys 1010 and 2010), and all studies assayed samples by this method.

Table 42. Study characteristics and blood collection parameters

Study	Bruins,[394] 2004	Frankenstein,[395] 2009	Melzi d'Eril,[398] 2003	O'Hanlon,[396] 2007	Shou,[37] 2007	Shou,[38] 2007	Wu,[397] 2003
Country	The Netherlands Antilles	Germany	Italy	Ireland	Denmark	Denmark	United States
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort[d]	Cohort
Population	Heart failure patients	Heart failure patients	Healthy participants	Heart failure patients	Heart failure patients	Heart failure patients	Healthy participants / Heart failure patients
Patient/Participant Source	Cardiologist's practice	Heart failure study, NT-proBNP arm	Hospital laboratory	Heart failure unit	Heart failure clinic	Heart failure clinic	NS
HF diagnosis	ACC/AHA	ESC	NA	NS	NS	NS	Physical exam, history, LVEF<35%
Patients in each NYHA class I-IV	3/30/10/0	9/29/3/0	NA	10/26/9/0	1/12/7/0	8/62/8/0	I to III[j]
Study length	6 weeks	12 weeks	17 days	1 week	1 week	2 years	1 week / 1 day
Number of participants	43[a]	41	16	45	20	78	8 / 5[f]
Number of samples per participant	15[b]	4	5	2	4	2	4 / 2
Sex, M/F	22 / 21	33 / 8	5 / 11	29 / 16	15 / 5	50 / 28	3 / 5[g]
Age, years	63 (20 to 86)[i]	61 ± 10	43 to 62	69.6 ± 12.1	69.3 (51 to 82)	74 (50 to 91)	21 to 45[g]
Fasting	None	NS	Overnight	NS	No	Overnight	NS
Time of collection	0800-1000[c]	1400 to 1600	0800-0900	NS	same time/day	NS	same time/day
Collection position	NS	NS	Seated	Supine	Seated	NS	NS
Rest time	NS	30 min	NS	30 min	at least 10 min	NS	NS
Tube type	EDTA (aprotinin added)	EDTA	NS	EDTA	Heparin (NT-proBNP) / EDTA (BNP)	Heparin	EDTA
Collection mode	Venipuncture	Indwelling catheter	Venipuncture	Indwelling catheter	Venipuncture	Venipuncture	NS
Storage temperature	-80°C	-20°C	-70°C	-20°C[e]	-80°C	None	-70°C
Storage time	6 months	NS	Study end	NS	Study end	NA	NS

Table 42. Study characteristics and blood collection parameters (continued)

Study	Bruins,[394] 2004	Frankenstein,[395] 2009	Melzi d'Eril,[398] 2003	O'Hanlon,[396] 2007	Shou,[37] 2007	Shou,[38] 2007	Wu,[397] 2003
BNP method	Abbott	None	None	Biosite Triage	Bayer Centaur	None	Biosite Triage/Bayer Centaur[h]
NT-proBNP method	Roche	Roche 2010	Roche 2010	Roche 1010	Roche 2010	Roche 2010	Roche 2010
Analysis protocol	Single series per patient, analyzed within 2 days	Single run	Single run	NS	2 h after collection (NT-proBNP) and 1 day at study end (BNP)	Same day	NS
Number of replicates per sample	1	NS	1	NS	2	NS	1

[a]Within-day (n=41), day-today (n=35), week-to-week (n=43)
[b]Within-day (n=6), day-to-day (n=5), week-to-week (n=6)
[c]Collected in patient's home during regular visits. Within-day samples collected 2h apart.
[d]Retrospective, chart review
[e]BNP was analyzed by the Biosite Triage method within 10 min of collection
[f]There were 12 participants, but data from 3 were below the lowest limit of detect for the BNP method and one was a statistical outlier (Reed and Cochran test)
[g]No age or sex specified for HF patients
[h]Only the Biosite Triage method was used for the HF patients
[i]Median age
[j]Number or patients in each class
Abbreviations: BNP = B-type natriuretic peptide; EDTA = Ethylenediaminetetraacetic acid; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NS = not specified

Biological Variation Data

Tables 43 and 44 provide the biological variation data for patients with HF and healthy controls, respectively. The mean concentrations of BNP and NT-proBNP for the group of patients or participants were reported for all except one study.[397] Five of the six studies with HF measured NT-proBNP and showed a wide range of concentrations. Three of these studies[37,38,396] had mean or median NT-proBNP values which were more than double the other two studies.[394,395]

The analytical coefficient of variation (CV_a) values were calculated by repeat analysis of patient or participant samples,[37,396-398] a combination of patient samples and quality control material,[395] or quality control material alone.[394,396] One study did not specify the type of sample used and provided only an estimate of CV_a.[38] Of those that used patient or participant samples, two used data from all samples. There were differences in when these samples were tested: some performed the analyses in one run while others did analyses at different time points. The CV_a values for BNP were lowest for the Bayer Centaur method (1.8%, 4%) and highest for the Biosite Triage (8.6%, 13.7%), reflecting the higher imprecision for point-of-care devices. Similar CV_a values were obtained for NT-proBNP (1.4% to 3.0%). The study with the lowest CV_a[37] also had the highest number of samples for this estimate (n=80). Analytical variance may vary with analyte concentration, but in the study by Bruins et al.[394] no relationship between CV_a and BNP or NT-proBNP concentration was found.

Total variation (CV_t) is the variance of differences between repeat measurements and is the combination of analytical and biological variation. This relationship provides the basis for calculating the biological variation values for within-individual (CV_i), where $CV_i = (CV_t^2 - CV_a^2)^{1/2}$.

All studies except for two reported this parameter.[397,398] CV_i were reported for all studies, but between-individual (CV_g) was reported in only three studies.[37,397,398] Since CV_g is also a derived value, calculated by nested analysis of variance (ANOVA) of the repeated measurement data, it is unclear why it was missing in most studies. Absence of CV_g does not permit calculation of the index of individuality (IOI), which is a useful parameter to assess the degree of individuality for a biomarker. Review of the CV_i values for BNP and NT-proBNP in patients with HF or healthy controls showed lower values (about one-half) for within-hour[396] and within-day[394] compared with within-week up to 12 weeks. The CV_i values in studies of patients with HF for longer than 1 day were very similar and did not differ between BNP and NT-proBNP (mostly around 20%) except for one study.[394] This study did not provide information on how patients were assessed for stability at each time point and therefore it is unknown if they were indeed stable. The patients were also recruited from a single cardiologist practice in a population of mostly Afro-Caribbeans. The ethnicity of the patients in the other five studies was not provided but in four it was a European country and one study was done in the United States.

Figure 22 compares the CV_a and CV_i values for BNP, and Figure 23 compares CV_a and CV_i values for NT-proBNP in all studies. These figures show that analytical variation values are much lower than intra-individual values, except for BNP at 1 hour and 10 hours where the opposite occurs. Also, the ratios of CV_i/CV_a are higher for NT-proBNP compared with BNP (Figures 24 and 25). This means CV_a constitutes a larger portion of the total variation for BNP measurements compared with NT-proBNP. These differences were independent of the type of BNP method used, which included a point-of-care method with the highest CV_a (Biosite Triage) and two automated methods (Abbott and Bayer Centaur). These data also suggest that variation increases over time. When the data were limited to only NT-proBNP from patients with HF, a

plateau appeared at 1 week. There were two data points for the 1-week measurement, which were quite different from each other, but this is most likely a function of the higher CV_a for the study using the point-of-care method.[396] The smaller CVi at shorter time intervals is likely a function of autocorrelation in repeated measures.[399]

The relative change value (RCV) is a parameter derived from CV_a and CV_i values, which constitutes a clinically meaningful change in serial results.

The formula is $RCV=Z \times 2^{1/2} (CV_a^2 + CV_i^2)^{1/2}$, where Z is typically set at 1.96 for a probability of 0.05 for statistical significance. Four of the six studies that reported RCV used the Z value of 1.96, however, two studies did not report this value.[37,398] The largest RCV values were found for healthy individuals for BNP (123% and 139% for two different methods) and NT-proBNP (92%).[397] The only other study with RCV values on healthy individuals measured NT-proBNP and found a much lower value (26%).[398] The large difference between RCV values for NT-proBNP is due in part to the log transformation of NT-proBNP data in one[398] but not the other study.[397] Other reasons for a smaller RCV include more participants (16 vs. 8), more samples (5 vs. 2), and overnight fast and early morning collection (lowest concentration is morning). For patients with HF, the RCV values were overall higher for BNP (32% to 113%) compared with NT-proBNP (16% to 55%). This span of values and pattern reflect the CV_i values, as the CV_a values were similar since the same method of measurement for NT-proBNP was used.

Four studies reported IOI values.[37,395,397,398] This value is a ratio of CV_i to CV_g and the lower the ratio the greater the difference is between individual variances; the higher the ratio, the more similar individual variances are to each other. The implication is on the applicability of the RCV to individuals. The IOI for NT-proBNP in healthy individuals (0.64 and 0.90) was higher than for patients with HF (0.03 and 0.12). Similarly, the IOI for BNP was lower (0.14) for patients with HF than for healthy individuals (1.1 and 1.8; same patients but different methods). This means there is more individuality for BNP and NT-proBNP for patients with HF compared with healthy individuals.

Sources of Variation

Several studies investigated the sources of the variation using linear[38] or multivariate regression analysis.[37,395,396] In the study by Frankenstein et al.,[396] the authors examined known confounders, including NYHA class, sex, age, weight, waist circumference, heart rate, hemoglobin, and ejection fraction, but none was significant. In another study,[396] multivariate analysis controlled for age and sex, did not identify any independent predictors of variance at any time interval. Variation was also not explained by mean arterial pressure, eGFR, plasma volume, weight, or heart rate.[37]

Table 43. BNP and NT-proBNP analytical and biological variation in chronic heart failure patients according to time interval

	Time	1 Hour	10 Hour	1 Day	5 Day	1 Week	1 Week	2 Week	4 Week	6 Week	12 Week	2 Year
BNP	**Method**	Biosite Triage	Abbott	Biosite Triage	Abbott	Biosite Triage	Bayer Centaur			Abbott		
	Mean (SD) pg/mL	219.4 ±210.3	134 (0-1,630)[f]	NR	134 (0-1,630)[f]	219.4±210.3	127 (11-387)			134 (0-1,630)[f]		
	CV_a	13.7[a]	8.4[d]	8.6[g]	8.4[d]	13.7	4			8.4[d]		
	CV_i	5.0	8.2	24	25	24.8	18			40		
	CV_g	NR	NR	NR	NR	NS	77[f]			NR		
	CV_t	14.6	12	NR	27	28.4	19			41		
	RCV	34.0	32	77	74	66.2	53			113		
	IOI	NR	NR	NR	NR	NR	0.14			NR		
NT-proBNP	**Method**	Roche 1010	Roche		Roche	Roche 1010	Roche 2010	Roche 2010	Roche 2010	Roche	Roche 2010	Roche 2010
	Mean (SD) pg/mL	1,385 ±1,912	570 (17-5,048)[f]		570 (17-5,048)[f]	1385 ±1,912	1036 (44-3777)	582 (272-1,538)	590 (286-1,193)	570 (17-5,048)[f]	520 (215-1,494)	1421 (29-6,849)
	CV_a	2.8[b]	3.0[c]		3.0[c]	2.8[b]	1	1.4[e]	1.4[e]	3.0[c]	1.4[e]	<3%
	CV_i	6.3	8.6		20	20.9	15	18.4 (9.5-29.2)	18.9 (9.1-28.7)	35	16.2 (7.1-36.9)	NR
	CV_g	NR	NR		NR	NR	102	NR	NR	NR	NR	NR
	CV_t	6.9	9.1		20	21.1	15	18.5 (9.6-29.2)	19.0 (9.2-28.7)	35	16.3 (7.2-36.9)	35
	RCV	16.1	25		55	49.2	42	51.1	52.5	98	45.0	NR
	IOI	NR	NR		NR	NR	0.03	0.11	0.12	NR	0.10	NR
Study, Year		O'Hanlon[396] 2007	Bruins[394] 2004	Wu[397] 2003	Bruins[394] 2004	O'Hanlon[396] 2007	Shou[37] 2007	Frankenstein[395] 2009	Frankenstein[395] 2009	Bruins[394] 2004	Frankenstein[395] 2009	Shou[38] 2007

[a] Duplicate measurements of 23 patient samples
[b] Two control samples assayed in two separate runs (n=20)
[c] Five control samples assayed once after every 20 patient samples
[d] Three control samples assayed once after every 20 patient samples
[e] Four samples from study patients and controls in one run (n=21) – not used in this table
[f] Median values. Sample information was not specified
[g] Duplicate measurements from 36 healthy individuals
Abbreviations: CV_a = analytical coefficient of variation; CV_g = between-person (or interindividual) coefficient of variation; CV_i = within-person (or intraindividual) coefficient of variation; CV_t = total coefficient of variation; IOI = index of individuality; RCV = reference change value; NR = not reported

Table 44. BNP and NT-proBNP analytical and biological variation in healthy subjects according to time interval

	Time	17 Days	8 Weeks	8 Weeks
BNP	**Method**		Biosite Triage	Bayer Centaur
	Mean, pg/mL		NR	29.0
	CV_a		8.6*	1.8*
	CV_i		43.6	50.3
	CV_g		39.4	27.9
	CV_t		NR	NR
	RCV		123	139
	IOI		1.1	1.8
NT-proBNP	**Method**	Roche 2010	Roche 2010	
	Mean, pg/mL	29.0	NR	
	CV_a	2.7†	1.6*	
	CV_i	9.1†	33.3	
	CV_g	14†	36.5	
	CV_t	NR	NR	
	RCV	26.33†	92	
	IOI	0.64	0.9	
Study, Year		Melzi d'Eril[398] 2003	Wu[397] 2003	Wu[397] 2003

* Duplicate measurements from 36 healthy subjects
† Log transformation of data
Abbreviations: CV_a = analytical coefficient of variation; CV_g = between-person (or interindividual) coefficient of variation; CV_i = within-person (or intraindividual) coefficient of variation; CV_t = total coefficient of variation; IOI = index of individuality; RCV = reference change value; NR = not reported

Figure 22. Analytical (CV_a) and intra-individual variation (CV_i) for BNP according to time frame

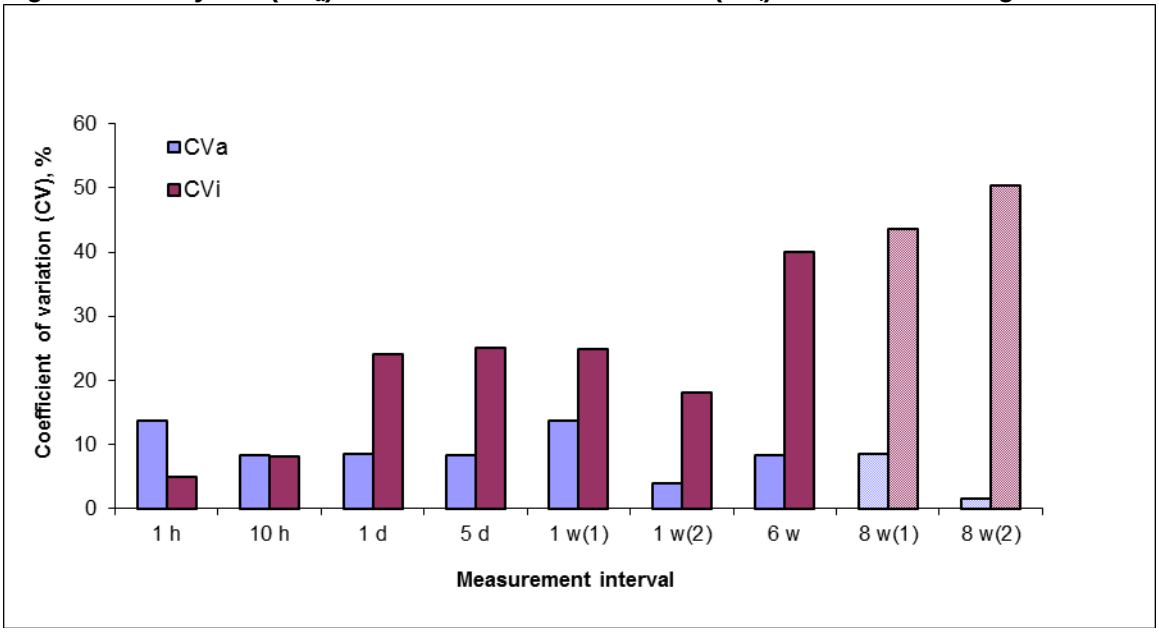
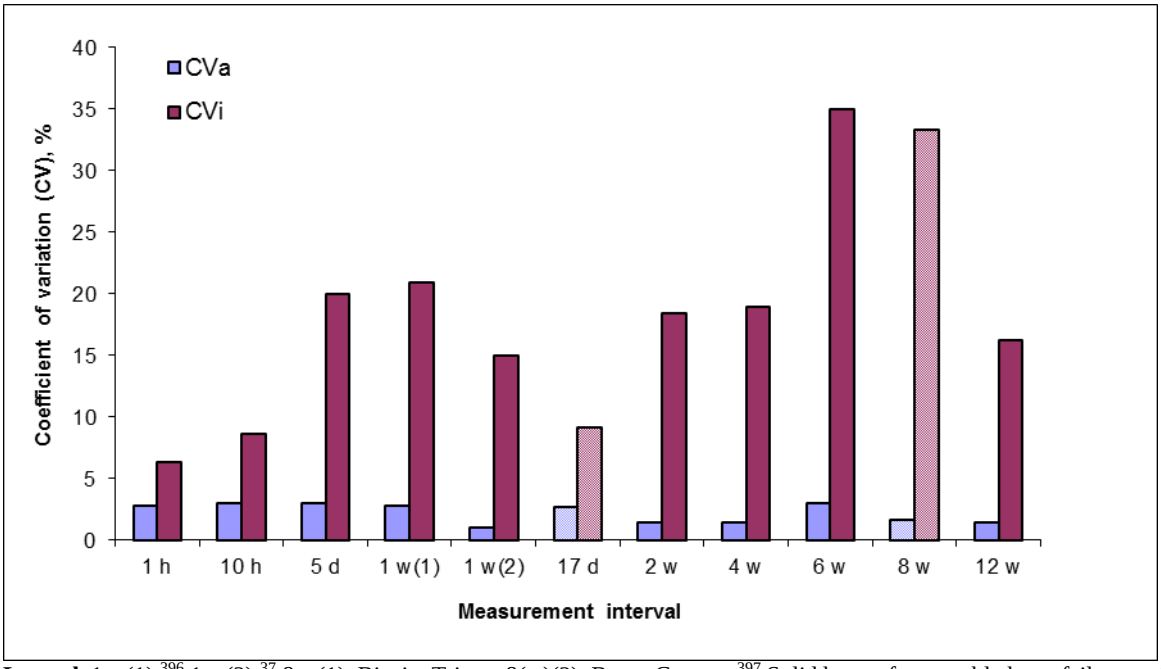
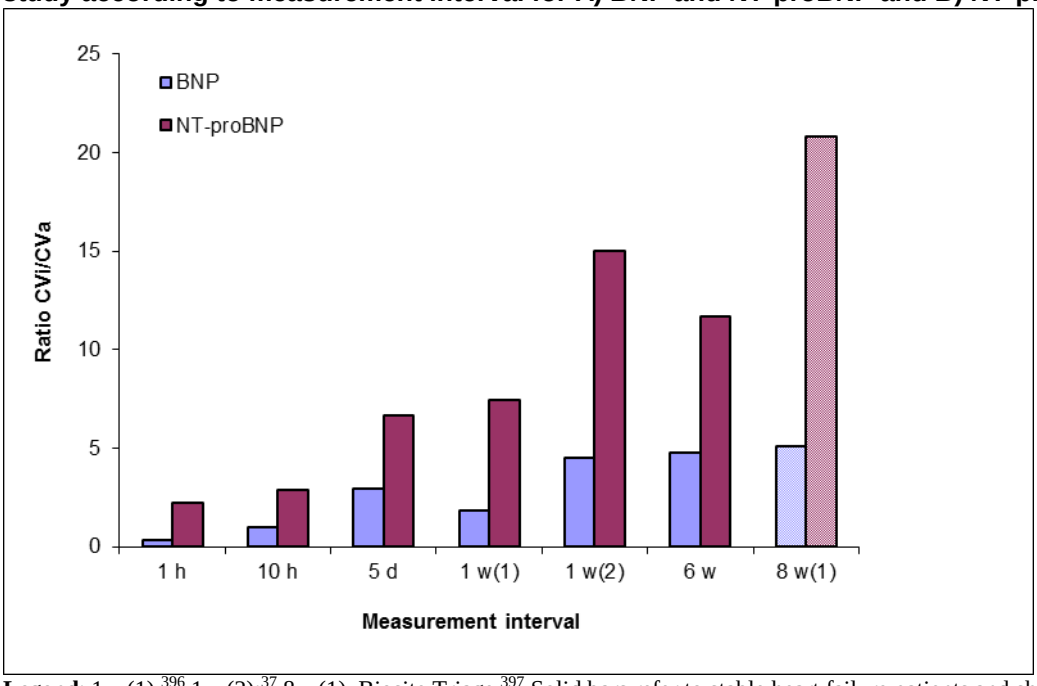


Figure 23. Analytical (CV_a) and intra-individual variation (CV_i) for NT-proBNP according to time frame



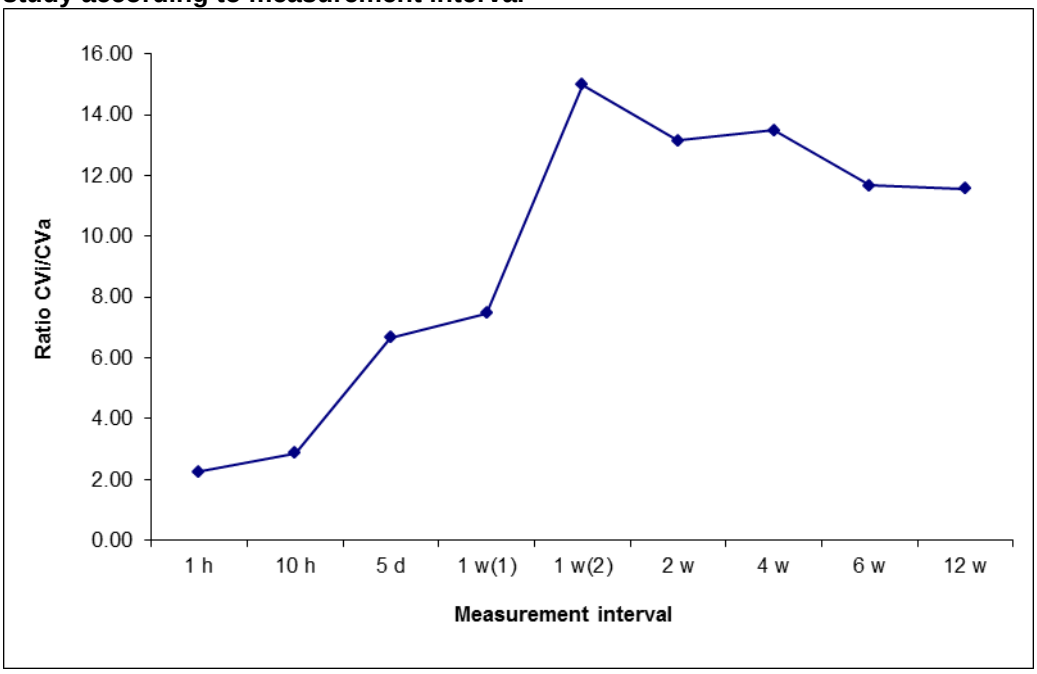
Legend: 1 w(1),[396] 1 w(2);[37] 8 w(1), Biosite Triage, 8(w)(2), Bayer Centaur.[397] Solid bars refer to stable heart failure patients and shaded bars refer to healthy individuals. The 17 d data has been log-transformed.

Figure 24. Ratio of intra-individual variation (CV_i) and analytical variation (CV_a) within the same study according to measurement interval for A) BNP and NT-proBNP and B) NT-proBNP only



Legend: 1 w(1),[396] 1 w(2);[37] 8 w(1), Biosite Triage.[397] Solid bars refer to stable heart failure patients and shaded bars refer to healthy individuals.

Figure 25. Ratio of intra-individual variation (CV_i) and analytical variation (CV_a) within the same study according to measurement interval



Discussion

A comparative effectiveness review (CER) was undertaken to assess the state of the evidence for diagnosis, prognosis, treatment, and biological variation of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) in patients with heart failure (HF). HF is a major concern for health care systems because of its chronic nature and resource implications. BNP and NT-proBNP have emerged as promising markers for HF diagnosis, prognosis, and treatment; use of these markers has been recommended in guidelines.[400]

The search strategy for this CER uncovered a very large volume of literature and the inclusion/exclusion criteria ensured the selection of the most relevant evidence for each of the seven Key Questions (KQs). Given the complexity of these questions and the volume of literature, we partitioned the discussion to reflect the four major areas evaluated in this review. Issues relevant to diagnosis, prognosis, treatment, and biological variation are detailed below in the context of the relevant KQ.

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

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

Overview: Key Question 1

There were 51 publications that met the criteria for KQ1 and examined BNP,[3,72-121] and 39 articles that met the criteria for KQ1 and examined NT-proBNP.[1,2,26,88,108-122,124-143] In patients with signs and symptoms suggestive of HF presenting to an emergency department or urgent care center, measurement of BNP or NT-proBNP is a useful tool to rule out HF as a cause of the symptoms. Irrespective of the cutpoint chosen, which could be the lowest in each study, the manufacturers' suggested cutpoint, or the optimal cutpoint selected by a study's authors, the sensitivity is high and the negative likelihood ratio (LR^-) is low. On the other hand, both BNP and NT-proBNP displayed lesser ability to rule in HF as to the cause of patients' symptoms.

The selection of an "optimal" cutpoint was evaluated in order to rule out and rule in HF in this population. Low cutpoints, either the lowest cutpoint reported, or the manufacturers' suggested cutpoint, resulted in high sensitivity and low LR-. To evaluate the rule-in capability of the tests, higher cutpoints proposed by the studies were examined. For BNP, 100 pg/mL is suggested by all manufacturers as the diagnostic cutpoint. All BNP studies that presented diagnostic performance data examined this cutpoint. This cutpoint provides excellent rule-out capability and moderate rule-in capability. For NT-proBNP, attempts to increase the value of these tests to rule in HF by using an optimal cutpoint (often set as the best combination of sensitivity and specificity) resulted in an increase in specificity and LR+, with a small loss of sensitivity and LR-. There was no agreement among the studies as to which optimal cutpoint(s) to choose. One study[2] reported on a consensus amongst four studies where the analysis was pooled for 1,256 patients in 3 continents. They reported an age stratified "rule-in" strategy of

450, 900, and 800 pg/mL for ages <50, 50 to75, and >75 respectively, and an age independent "rule-out" cutpoint of 300 pg/mL. The European Society of Cardiology guidelines[391] recommends a rule out cutpoint of 300 pg/mL, and further investigation (echocardiogram) above this.

BNP concentrations increase with age. Three[101,111,119] of four studies examining diagnostic performance propose increased cutpoints with age, but no consensus was reached. NT-proBNP concentrations also increase with age. Three studies[2,138,141] proposed consistent cutpoints of 450 pg/mL for patients <50 years, 900 pg/mL for patients 50 to 74 years, and 1,800 pg/mL for patients ≥75years.

Both BNP and NT-proBNP concentrations increase as renal function (as measured by estimated glomerular filtration rate (eGFR)) decreases. Four authors[109,113,114,120] suggested increasing the diagnostic threshold with declining renal function, but the studies differ in the proposed cutpoints. For NT-proBNP, one author[113] suggested increased cutpoints for patients with reduced renal function.

Not enough evidence exists to make firm conclusions with respect to the effects of sex, ethnicity, BMI, or the presence of diabetes on the diagnostic performance of BNP or NT-proBNP.

Applicability in Diagnostic Studies

The diagnosis of HF in patients presenting to emergency departments is difficult.[401] The differential diagnosis for patients presenting with the chief complaint of dyspnea is large, including cardiac causes, pulmonary causes, combined cardiac and pulmonary causes, and neither cardiac nor pulmonary causes.[401]

In KQ1 of this review, the focus was on studies that enrolled patients presenting to the emergency department with the clinical symptoms of HF as the chief complaint, regardless of comorbidities, to create a summary of the evidence with maximum generalizability. Studies that required the presence of a specific disease or condition as a criterion for enrollment were excluded.

For BNP, we present data on the common cutpoint of 100 pg/mL as proposed by all manufacturers of FDA-approved BNP assays. This should provide users of the test with robust information on the applicability of the test to patients in the emergency department with appropriate symptoms. For NT-proBNP, few studies commented on the diagnostic performance of the test using the manufacturers' recommended cutpoints of 125 pg/mL for those less than 75 years and 450 pg/mL for those older. Researchers proposed various cutpoints based on age. This lack of uniformity for NT-proBNP suggests clinicians should apply the findings of this report cautiously to their practices in emergency departments and urgent care centers.

Conclusions for Diagnostic Studies

Diagnostic Studies From Emergency Settings

For patients presenting to emergency departments or urgent care settings with signs and symptoms suggestive of HF, BNP and NT-proBNP have good diagnostic performance to rule out, but lesser performance to rule in, the diagnosis of HF compared with the reference standard of overall global assessment of the patient's medical record. The strength of evidence (SOE) was as high for sensitivity and moderate for specificity for both BNP and NT-proBNP at all cutpoints examined. Nevertheless, we rated the overall SOE as high. Further studies are unlikely to change

the conclusions presented here. Comorbidities, including age, renal function, and BMI (BMI for BNP only) have important effects on the performance of these tests. There is, however, no agreement amongst the studies regarding the appropriate cutpoints that should be applied, dependent on the test, age and renal function of the patient.

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

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

Overview: Key Question 2

There were 12 articles that met the criteria for KQ2 that examined BNP,[148-159] and 20 articles that met the criteria for KQ2 examining NT-proBNP.[154,156-159,161-175]

In primary care settings, patients often present with risk factors but have mild or no obvious symptoms of HF. Thus, diagnosis can be challenging. BNP or NT-proBNP tests are often used with these patients as the first step in the diagnostic algorithm. Those with low BNP or NT-proBNP values can be safely ruled out, whereas those with increased values can be diagnosed directly, or referred for further confirmatory testing.

This review indicates that BNP and NT-proBNP are useful diagnostic tools to identify patients with HF in primary care settings. The results obtained from this review are in agreement with a recent systematic review using individual patient data meta-analysis where both BNP and NT-proBNP had high sensitivities for diagnosis of HF.[402] When separating the sensitivities of the studies into the optimum cutpoint as defined by the authors of included studies, the lowest cutpoint, or the manufacturers' cutpoint all provided similar pooled sensitivities. However, the pooled specificities for diagnosis of HF were substantially lower.

In the case of BNP, studies that reported results for the manufacturers' suggested cutpoint of 100 pg/mL were pooled, since this is likely the cutpoint that the majority of laboratories would use. The study by Barrios et al.[153] had a substantially lower sensitivity and a high specificity for identifying patients with HF. Predominantly elderly patients were enrolled in this study and HF was defined according to the Framingham criteria. Sixty percent of patients had diastolic dysfunction and only 2.8 percent had a reduced left ventricular ejection fraction (LVEF). The authors suggested that the reduced sensitivity for diagnosis of HF found in this study, relative to the other studies, is due to the high proportion of diastolic HF.

Only two studies[159,168] looked at the manufacturers' suggested cutpoints for NT-proBNP. The sensitivities were somewhat different; however, the specificities were similar. Gustafsson et al.[168] used an LVEF of <40 percent to identify patients with HF, while Christenson et al.[159] used cardiologist adjudication, including an LVEF <40 percent as well as other signs, symptoms, and other objective markers. This may account for the lower sensitivity in the Christenson report.

When the effect of various determinants on BNP and NT-proBNP were examined, we found that values for both peptides increased with age and declining renal function, and decreased as BMI increased.

A single study looked at the age effect on BNP and demonstrated that a higher cutpoint is required in patients greater than 65 years to maintain an optimal sensitivity compared with patients less than 65 years.[158] A similar age-related increase in NT-proBNP is seen in the same study, with higher cutpoint required to maintain an optimal sensitivity.[158] A pooled analysis performed by Hildebrandt et al. showed similar results by demonstrating that higher cutpoints are required to maintain equivalent diagnostic accuracy as age increases.[403]

In terms of sex, two studies investigated the effect on BNP. Both Fuat et al.[156]and Park et al.[158] did not identify any significant effects. Five studies[156,158,162,166,170] examined the effect of sex on NT-proBNP, and although the authors identified different optimal cutpoints for males and females, no clear conclusions could be drawn regarding optimal cutpoints.

The effect of BMI on BNP and NT-proBNP was investigated by several studies. Most studies showed a negative correlation of BMI with BNP or NT-proBNP, with decreasing sensitivities for diagnosing HF. However, no BMI-specific cutpoints were suggested in the included articles.

Decreased renal function, measured by creatinine clearance (concentration <60 mL/min), was determined by Park et al.[158] to increase the levels of both BNP and NT-proBNP; however, the effect was more significant with NT-proBNP. The differential effect is likely due to the fact that NT-proBNP is cleared by the kidneys,[404] while BNP is not.[405]

Applicability in Diagnostic Studies

In primary care settings the majority of patients do not present to general practitioners with obvious serious symptoms of HF. Many of the patients may present with limited symptoms or subclinical disease. Identification of patients at risk of developing HF or those with subclinical or limited symptoms is critical, as there are effective treatments for HF and in undiagnosed patients, the condition will progress without treatment, increasing the cost to the health care system and decreasing the quality of life of the patient.

BNP, using either the optimal or manufacturers' suggested cutpoint, is effective at identifying patients at risk of HF or patients with few or no symptoms of HF. NT-proBNP is effective at identifying patients at risk of HF using the optimal cutpoint; however, limited evidence exists for using the manufacturers' suggested cutpoint. Goode et al.[173] performed a cost-benefit analysis of using NT-proBNP to identify patients at high-risk of developing HF. In their population, 7.5 percent had undiagnosed left ventricular systolic dysfunction and use of NT-proBNP was effective for identifying patients at risk and provided a significant cost benefit.

Conclusions for Diagnostic Studies

Diagnostic Studies From Primary Care Settings

Both BNP and NT-proBNP have good diagnostic performance in primary care settings for identifying patients who are either at risk of developing HF, or have fewer symptoms and/or less severe signs suggestive of HF. Using the manufacturers' suggested cutpoint, BNP can effectively be used to rule out the presence of HF in primary care settings. In the case of NT-proBNP, limited evidence is available to determine if the manufacturers' suggested cutpoint is as effective. We rated the SOE for sensitivity as high and specificity as moderate. We rated the overall SOE as high. Further studies are unlikely to change the conclusion presented here.

Limitations of the Review of Diagnostic Studies in KQ1 and KQ2

This review examined the evidence for the use of the BNP and NT-proBNP in the diagnosis of HF, without examining this test in combination with other diagnostic tools. The effect of BNP and NT-proBNP as part of "test panels" or in combination with other diagnostic algorithms was not investigated.

The effect of heterogeneity among the studies on the overall estimates of diagnostic performance was not investigated. Mastandrea et al.[406] examined factors that can contribute to heterogeneity of meta-analyses of studies using BNP and NT-proBNP. He examined 98 samples from 67 studies (52 samples/41 studies of BNP, 46 samples/24 studies of NT-proBNP) and found that disease severity, disease prevalence, and the reference test were factors that contributed to heterogeneity for BNP. Whereas disease severity is an intrinsic factor in the pathology of the disease, the disease prevalence and the reference test were considered to be true elements of interference. For NT-proBNP, Mastandrea et al. were unable to identify factors contributing to heterogeneity.

One study[86] for BNP used the echocardiogram as the sole criterion for the reference test in the diagnosis of HF. All others used a combination of signs, symptoms, and objective criteria (e.g., X-ray, electrocardiogram, echocardiogram) and diagnostic scorecards (e.g., Framingham, Boston, National Health And Nutritional Examination Survey (NHANES)). Similarly, for NT-proBNP, one study[137] used echocardiogram as the sole diagnostic criterion. All others used the same global criteria as BNP. The lack of a single "gold standard" for the diagnosis of HF necessitates the use of the clinical diagnosis.

Future Research Recommendations in Diagnostic Studies in KQ1 and KQ2

1. More studies are needed to determine the effect of age on the diagnostic cutpoints, especially for NT-proBNP. Common cutpoints that can be used in all situations would increase the applicability of this test.
2. More studies are needed to determine the effect of declining renal function on the diagnostic performance of both BNP and NT-proBNP, and to establish cutpoints in situations of reduced renal function.
3. More studies are needed to determine the effect of sex, ethnicity, and BMI on BNP and NT-proBNP concentrations and ultimately on the cutpoints for diagnosis.
4. There is a need to examine the evidence for the value of BNP and NT-proBNP in multi-marker panels for the diagnosis of HF.
5. A more detailed study of the effects of heterogeneity amongst the studies would allow a clearer understanding of the effects of various confounders, including comorbidities.

Key Question 3: In heart failure populations, is BNP or NT-proBNP measured at admission, discharge, or change between admission and discharge an independent predictor of morbidity and mortality outcomes?

Overview: Key Question 3

Overview of Issues in Studies Evaluating Decompensated Heart Failure Subjects

The majority of studies were not designed with the primary objective to evaluate the prognostic ability of BNP /NT-proBNP nor were higher level model validation computations undertaken. Almost all of the studies with large sample cohorts were designed for another purpose (usually intervention assessment) and were primarily aimed at "predictor finding" analyses showing some association between BNP/NT-proBNP and the outcomes of interest.

Seventy-nine studies evaluated levels of BNP (n=38), NT-proBNP (n=35), or both (n=6) as predictors of mortality and morbidity outcomes in subjects with decompensated HF, ranging over time intervals from 14 days to over 6 years. When considering single outcomes, most publications (n=55) evaluated mortality outcomes, predominately all-cause; morbidity outcomes were inconsistently defined and assessed as endpoints less frequently (n=8). The majority of studies assessing single outcomes, evaluated admission BNP levels with fewer studies evaluating serial measurements (while hospitalized), change from admission levels, or discharge levels prior to leaving the hospital as potential prognostic factors. Composite outcomes were reported as frequently as all-cause mortality outcomes and within these, all-cause mortality and morbidity were most frequently assessed. Studies with composite outcomes had relatively equal numbers of studies assessing admission and discharge or change levels as predictors.

In general, higher levels of admission BNP and NT-proBNP incurred greater risk for the outcomes of mortality, morbidity, or a combination of both. A decrease in BNP levels was also predictive of decreased rates of mortality and morbidity. The range of thresholds for high or higher levels was markedly varied across studies. Similarly, for the studies evaluating pre-hospital discharge BNP/NT-proBNP levels as a predictor, or a change relative to baseline, the thresholds or percent change varied markedly across studies. Comparison of BNP study results relative to NT-proBNP levels were limited to six studies and were inconsistent across studies; the findings of these studies would not indicate superiority of one test relative to the other.

When considering threats to internal validity of the studies evaluating levels in patients with decompensated HF as a whole, many studies were rated as problematic for establishing the validity and reliability of the methods used to ascertain the outcome. Similarly, a minimum of four key confounder domains identified in the 2006 report for the Agency for Healthcare Research and Quality (AHRQ)[20] (age, sex, BMI, and renal function) were established a priori as confounders that the clinical experts judged to be important, and therefore studies were downgraded if they did not include or consider these covariates in their analyses. Many studies did not consider all of these factors concurrently. Finally, when applying the Hayden[58] criteria to assess appropriate statistical analyses, our evaluations were relatively less stringent than those proposed elsewhere[407] and, as such, most studies rated well; however, problems with reporting sufficient information to replicate the statistical analyses were noted across these studies. This issue decreases the confidence in the approaches that these studies used to estimate the prognostic strength of BNP and NT-proBNP. This group of studies is at high risk of bias for validity of outcome measurement and for confounding; however, considering all other criteria

within the Hayden checklist, the overall risk of bias was judged as moderate because of the uncertainty with these two criteria.

An important factor influencing the interpretation of the study findings is the length of followup. Study findings were presented as a function of intervals for followup and in the context of decompensated HF patients, this was short term (up to 31 days, 2 to 3 months) and longer term (6 to 11 months, 12 to 23 months, 24 months and greater). We observed the fewest number of studies for the shortest (up to 31 days) and longest time intervals (24 months or greater); within these studies the levels of BNP used, the thresholds for determining high and low risk, and the prognostic models differed. As such, the consistency of the direction of effect and the magnitude varied. The most frequently evaluated interval was the medium range time interval (6 to 12 months), and these studies consistently showed that BNP or NT-proBNP concentrations are independent predictors of all-cause and cardiovascular mortality, some morbidity outcomes, and composite outcomes. This was shown across studies despite the variations in the factors included within the statistical models. These factors included: different cutpoints when used as a dichotomous data, other potential prognostic factors in the statistical models, and the time intervals. It would be important for the clinical community to reach a consensus on what are the most clinically relevant short-term time intervals for predicting specific outcomes; these intervals could reflect optimal timepoints when additional or different interventions may assist in minimizing risk of morbidity and mortality (both for the shorter and longer term) following an acute episode of decompensation. Conversely, it may be equally important to provide a rationale for the longest interval that would be meaningful for clinicians to expect that BNP/NT-proBNP levels from admission or discharge of a current episode are relevant.

The challenge with these differing study factors is in interpreting the magnitude of the predictive values across studies. As noted previously, with differing prognostic models, it is problematic to assume a hazard ratio (HR) equal to two in one study is in fact comparable to that same estimate from another study. Within the decompensated HF studies there was the added problem of when the BNP/NT-proBNP levels were measured. Levels measured at admission would suggest that the subjects had not had significant intervention to manage the acute episode. Serial measurements during the course of hospitalization reflects a short-term response (or lack of response) to treatment that was commenced following admission. Pre-discharge values reflect that the patient is considered to be sufficiently stable that hospitalization is no longer required; it also reflects a degree of response to treatment. From a methodological perspective, treatment intervention associated with the decompensation episode is a confounder (associated with changing BNP/NT-proBNP levels and with the outcomes of mortality and morbidity). The timing of receiving treatment relative to when the BNP/NT-proBNP levels were measured is important to consider when interpreting the magnitude for risk.

Overview: Populations With Chronic Stable Heart Failure

Fifteen publications evaluating BNP levels, 88 publications for NT-proBNP, and one study evaluating both assays considered these tests as predictors of mortality and morbidity in patients with chronic stable HF. For BNP levels in patients with chronic stable HF, there is an association between BNP and the outcome of all-cause mortality. The other mortality outcomes (i.e., cardiac and sudden cardiac) demonstrated less convincing association, which did not remain statistically significant in all of the reviewed studies after multivariable adjustment. The importance of BNP as an independent predictor appears to depend on severity of the HF and possibly the length of

followup. Severity is suggested as an important factor. A study that selected New York Heart Association (NHYA) level III or IV subjects, found a significant HR for BNP >1,000 pg/mL,[261] while three other studeis that used more general HF populations did not find a significant relationship to all-cause mortality at 24 months.[268,269,271] The studies that extended beyond 24 months in more general HF populations also found a significant relationship to all-cause mortality.[274,275] The other mortality outcomes (i.e., other than all-cause mortality) were less frequently reported and thus consistency in the findings is not generalizable to this group.

The outcome of hospitalization for HF also demonstrated an association with BNP using a natural log (ln) transformed BNP (lnBNP), but this was only reported in one study.[274]

The composite outcome of all-cause mortality and cardiovascular morbidity demonstrated a significant independent association for BNP with the outcomes selected by the investigators. This was consistent for six of the seven papers in this subsection. The HRs reported here were often a little higher than the ones for all-cause mortality alone.

The use of cutpoints for determining risk is problematic considering the range of cutpoints reported in this review: 250 pg/mL to 1,000 pg/mL for BNP in all-cause mortality and 55 pg/mL to 590 pg/mL for BNP in the combination of all-cause mortality and cardiovascular morbidity. Most often the studies determined the cutpoint from their own population using receiver operating characteristic (ROC) analysis, median, or mean values. Predetermined cutpoints are required for any study aiming to assess the prognostic ability of a test used in a dichotomous fashion. Similar comments would apply to tertiles, quartiles, or quintiles and these values should be selected based on previous studies rather than determined in the study population. Cutpoints are attractive to the clinician because they are easy to remember, but they are likely to lose valuable information from the continuous variable. The use of log transformed BNP seems to hold as much predictive value as that not transformed; an alternative to a predetermined cutpoint could be lnBNP.

The negative association of BMI with BNP has been demonstrated in the paper by Horwich et al.,[262] as well as in a paper that was excluded from this review because the authors did not use BNP to diagnose or prognose HF.[408] Studies should include either BMI or another measure of body fat, such as waist circumference or waist-to-hip ratio, in their variables. Other variables such as age, sex, and renal function are included in the papers reviewed; these are also known to have strong associations with BNP. Measured parameters, such as LVEF and the NYHA stages, also have strong associations with BNP and should be included in predictive models to prove that BNP holds independent predictive ability. In addition, common factors used in the prediction of cardiovascular disease (CVD) outcome such as hypertension, diabetes, total cholesterol to HDL-cholesterol ratio, and smoking, should be included in predictive models as these have been shown to be associated with mortality from CVD and should thus be accounted for in all-cause mortality and cardiovascular specific mortality assessment.

While the independent association with all-cause mortality and hospitalization for HF is suggested, it is not always found. The applicability of these findings to patient care is not demonstrated in the papers reviewed, as there are no transferable common cutpoints and there is no risk stratification model that has been studied that uses BNP in the risk score. Some of these findings will be discussed under KQ4 where the direct comparison between other prognostic markers is considered in more detail.

Eighty-eight publications evaluated NT-proBNP levels as predictors of mortality and morbidity in patients with chronic stable HF. Overall, the evidence consistently supports the trend that NT-proBNP is an independent predictor of mortality and morbidity outcomes in

people with chronic stable HF. The applicability of the aforementioned results rests largely in middle-aged or elderly males. The included studies did not explore whether the prognostic effects of NT-proBNP would differ by age, sex, or time period. Also, the studies did not suggest a single cutpoint to optimize the prognostic ability of the peptide. In general, the studies were problematic with respect to measuring the outcome and including a predefined set of confounders.

The largest number of studies, and the strongest evidence, concerns the outcome of all-cause mortality. Fifty-two publications included all-cause mortality as an outcome and all of the point estimated measures of association, whether statistically significant or not, indicated positive associations between NT-proBNP and all-cause mortality. This conclusion applies across all periods of followup, from 12 months to 44 months.

For cardiovascular mortality, the evidence in 17 publications also suggests a positive association with NT-proBNP. However, this conclusion largely applies to studies with followups that are longer than 24 months.

Twelve studies examined the prognostic value of NT-proBNP for morbidity in persons with stable HF. Overall, higher NT-proBNP levels were shown to be associated with greater hospitalization in eight studies. Twenty-six publications evaluated composite outcomes and showed that NT-proBNP is an independent predictor; the results also suggest that higher levels of NT-proBNP predict greater numbers of composite events.

Overview: Populations With Heart Failure Following Cardiac Surgery

There were eight studies that evaluated BNP/NT-proBNP levels in HF patients who underwent cardiac surgery. Five studies evaluated the effect of resynchronization therapy on BNP levels (n=3) and NT-proBNP levels (n=2) and one study evaluated the effect of cardiac resynchronization defibrillator therapy on BNP. Both assays were shown to be independent predictors of all-cause and cardiovascular mortality and morbidity. The remaining three studies evaluated surgical interventions of intracoronary infusion of bone marrow-derived mononuclear progenitor cells, noncardiac surgery (e.g., abdominal, orthopedic), and peritoneal dialysis. All showed that BNP or NT-proBNP were independent predictors of all-cause and cardiovascular mortality and morbidity, with the exception of the peritoneal dialysis study.

General Issues With Prognosis Studies Evaluating BNP and NT-proBNP as Predictors of Mortality and Morbidity

This systematic review netted a large number of studies (198 publications) and would have been larger still, had the criteria included studies using non-FDA approved BNP/NT-proBNP assays. Despite this large study base, consistent issues with research methodology were observed. These issues, with respect to definitions of HF populations, selection of cutpoints for determining high risk groups, defining and validating outcomes, study design, and statistical modeling approaches, are detailed below.

Defining the Heart Failure Population: Classification Systems for Heart Failure Are Problematic for Establishing Levels of Prognostic Risk

One of the important issues in evaluating any potential prognostic factor in patients with HF is the current classification system for this cardiovascular disorder. HF is considered to be a

syndrome rather than a primary diagnosis.[15] HF has many different causes and variations in clinical features and exists with a number of comorbidities. In this systematic review, all definitions of HF (i.e., as provided by the study authors) were considered; however, it could not be certain that the patients within the studies were clearly patients with HF or were similar across studies, and it was therefore assumed that findings could be compared across studies with respect to this clinical syndrome classification. This assumption does, however, reflect clinical practice and thus this limitation does not negate the findings. It would, however, be helpful if investigators defined explicitly which categories of HF were included in their populations.

A division among the studies was established to distinguish those patients who were recruited with acute episodes and those who were stable but chronic. This is an important clinical division as the required clinical response is often different in these two settings.[12] It was assumed that the level of acuity was adequately categorized by the site of recruitment and that patients who were recruited from emergency or hospital admissions were acute and likely decompensated. Patients recruited from outpatient settings were assumed to be stable and chronic. It would be helpful if authors defined the acuity of their subjects in the methods or results of the study. The case has been made that there is inconsistency in defining the subtypes of acute HF, decompensated HF, or exacerbation of HF.[16] The European Society of Cardiology divides acute HF syndromes into six clinical profiles (worsening or decompensated chronic, pulmonary edema, hypertensive HF, cardiogenic shock, isolated right HF, acute coronary syndrome, and HF).[13] The American College of Cardiology Foundation (ACCF)/American Heart Association(AHA) has a four stage classification system for acute HF.[10] It is not clear that the eligibility criteria of studies included in the acute decompensated category of this review made these distinctions; nor is it clear which of these definitions or subgroups may likely influence the predictive ability of BNP/NT-proBNP for the outcomes of interest.

Defining the Heart Failure Population: Influence of Comorbid Conditions

As patients age, the incidence and prevalence of HF increases[409] as do the comorbid conditions of patients. Comorbidity was not consistently considered within the prognostic models, and the degree to which such conditions can confound the estimates of the predictive ability of BNP/NT-proBNP levels needs to be considered appropriately in the analysis of the study.

BNP/NT-proBNP Transformations in Statistical Models and Selection of Thresholds or Cutpoints

When undertaking statistical computations for outcomes that are dichotomous, logistic regression is undertaken and study authors must decide whether to model BNP/NT-proBNP as a continuous or categorical covariate. BNP and NT-proBNP are continuous measures, and typically the distributions are heavily skewed. When they are included as continuous variables, it is recommended that markers that are skewed should be log transformed to “normalize” the distribution in subsequent computations.[48] In the presence of such skewing, if the distribution of the BNP or NT-proBNP marker is not transformed, then there is a great risk that results will be misleading. It was observed that the minority of studies log transformed the BNP or NT-proBNP distribution. The practical implication is that one must transform the results back to the previous scale and as such, the HR estimate as reported is not intuitively understood. It is recognized that

some study authors may be reluctant to log transform the BNP or NT-proBNP data because of issues with interpretation (which would require a back translation of the log HR). However, it is necessary that the assumptions used in logistic regression are not violated. A tool that calculated risk based on the log transformed test result would be a simple practical way for clinicians to use BNP/NT-proBNP in the clinical setting. An alternative approach is to categorize the BNP or NT-proBNP covariate, typically into quartiles. This option is preferred when the relationship between the BNP or NT-proBNP and the outcome is nonlinear;[48] if a continuous covariate were used in this instance, then error is introduced in the estimate of predictive strength. However, if a linear relationship exists between BNP and NT-proBNP, then not analyzing this covariate as a continuous variable will decrease the ability for the model to accurately evaluate the prognostic value. In general, the justification for either approach was not always well reported, which serves to decrease our confidence in the magnitude of the HR.

Another challenge with interpreting results from statistical models was the widely varying thresholds to determine who was or was not at greater risk for future adverse events. Many studies provided a rationale for selecting cutpoints (typically based on ROC analysis or use of mean, median, or tertiles); however, this choice of threshold may in effect select the point producing the largest difference in outcome between categories. If this is the case, then the models would likely overestimate the predictive ability of BNP/NT-proBNP. Finally, interpretation of estimates of predictive strength are problematic from a pragmatic perspective. It is not clear what thresholds to suggest to clinicians, because most studies have overlapping cutpoints. This essentially makes these tests of little use in the clinical setting.

Unspecified Interventions for Patients With Heart Failure in Prognosis Studies

Although the intervention is not often described in prognostic studies, from a methodological perspective it can be considered an important confounder, particularly if patients receive different treatments based on perceived prognostic risks. Interventions were not always well described in the majority of studies reviewed, and it is not clear to what extent diverse treatments have comparable effects on BNP/NT-proBNP concentrations. Often the results of both treatment groups were put together for the purposes of the secondary paper that described prognosis and it was difficult to work from the primary paper which group may have influenced the results. Although in theory the effect of interventions may be less important than other intrinsic prognostic factors (e.g., age, sex, disease stage), it is entirely possible that these studies are at risk of bias for confounding by indication (a variant of selection bias in observational studies).[410] Typically, in observational studies, the indication for treatment or the way in which treatment is administered to subjects is poorly reported. Thus if patients differ at baseline with respect to perceived prognostic risk, then either these patients will not receive adequate treatment or will receive more aggressive or different treatment. This bias can result in over- or underestimation of the predictive ability of the factor of interest. Additionally, if an explanatory variable representing treatment is included in the model, then a clear definition (standardized and reproducible description) would be required.[411]

Selection and Definition of Other Prognostic Factors Within the Prognostic Models

It is important to clearly define all variables included in the prognostic risk models. Within this systematic review, the definitions of prognostic factors included in the predictive models were generally not clearly defined to the level that would allow reproducibility or facilitate comparison across models. Difficulties arise when common and accepted predictors are operationalized differently across studies, particularly those that dichotomize or categorize continuous variable (e.g., age and BMI). Additionally, reporting standards with respect to how factors were selected and included in models were inconsistently reported. Hayden et al.[412] present some convincing arguments that much of the prognostic research lacks explicit theoretical frameworks to establish the potential relationship among variables within prognostic models. This would imply the need to hypothesize the potential for intermediary or mediating pathways among prognostic factors. This may involve the use of multilevel or structural equation modeling the aim of which is to evaluate the strength of relationships among the variables.

Study Designs and Phased Hierarchical Approach To Establishing Predictive Value of BNP and NT-proBNP

Several attempts have been made to develop frameworks for establishing sequential or hierarchical phases of prognostic research in order to establish convincing evidence of the value of a predictive marker (prognostic indicator). Table 45 shows four such attempts, with one framework specifically developed for cardiovascular markers.[44] Appendices E & F detail the explanation for these phases of development for prognostic research. These frameworks, showing a phased sequential approach to prognostic research, can be paralleled to grading systems for the SOE with respect to credible validation of predictive strength of BNP or NT-proBNP concentrations.

In our judgment, irrespective of the prognostic model used, the majority of BNP and NT-proBNP studies reviewed within this evidence synthesis, fall into the earliest phases of prognostic study development. At the lowest level of prediction, prognosis studies are designed to identify potential associations of the factors of interest and are termed "exploration"[412] or "predictor finding studies".[43] From 198 studies eligible for KQ3, only 41 undertook statistical procedures related to discrimination, calibration, or reclassification of risk; from these, 15 did not report the results of these computations. As such, we would classify the majority of studies in KQ3 as having the aim of establishing or exploring the independent contribution of BNP/NT-proBNP, but these studies did not attempt to evaluate the predictive performance of the model and therefore, represent the early phases of multivariable prognostic research (predictor variable studies). Clearly, this reflects that, as a whole, the evidence for prognostic ability of BNP/NT-proBNP evaluated within this systematic review is based on early and less convincing statistical evidence for predictive strength.

Table 45. Frameworks for sequential development of prediction models that assess the contribution of potential prognostic factors

Framework of an Explanatory Approach to Studying Prognosis Hayden et al. 2008[412]	Consecutive Phases of Multivariable Prognostic Research Moons et al. 2009[411]	Types of Multivariable Prediction Research Bouwmeester et al. 2012[43]	Phases of Evaluation of Novel Risk Markers for Cardiovascular Risk Hlatky et al. 2009[44]
Phase 1: Identifying associations		Predictor Finding Studies (Majority)	Phase 1: Proof of Concept
Phase 2: Testing independent associations (majority)	Developmental Studies: (Least)	Model Development studies without external validation (Least)	Phase 2: Prospective Validation (Majority)
Phase 3: Understanding Prognostic Pathways	Validation Studies (External)	Model Development studies with external validation	Phase 3: Incremental Value (Least)
		External validation with or without model updating.	
	Impact Studies	Model Impact Studies	Phase 4: Clinical Utility
			Phase 5: Clinical Outcomes and Cost Effectiveness.
			Phase 6: Cost-effectiveness

Ideally, prognostic studies would employ prospective cohort or RCT designs.[411] In addition to the study design, establishing the predictive value of a marker can be considered to be phased or hierarchical in nature (see Table 45). Specifically, a six-phase model has been proposed for the development and evaluation of cardiovascular risk markers.[44] In this systematic review, the majority of studies can only be viewed as meeting the earliest phases of development, irrespective of the particular framework used; most studies were aimed at establishing that BNP and NT-proBNP were independent predictors but did not seek to establish incremental value (relative to base model and other markers) or attempt validation (internal or external) of the predictive model.

Although prospective designs are ideal, we observed that retrospective cohort designs were frequently used in the eligible prognosis studies; retrospective designs may contain bias or omit information critical to the subsequent model used to establish the relative importance of predictors. Additionally, some of the prospective studies were not originally designed to establish the prognostic predictive strength of BNP/NT-proBNP but were secondary analyses from intervention trials, which may also be prone to the same issues as observational retrospective studies. Studies were not restricted by their design type in this review. A few studies addressed the more advanced phases of the evaluation of BNP and NT-proBNP as predictors, attempting internal or external validation (see KQ4 and validation of models).[251,353,357] This review found very few studies that addressed the impact of the prediction models on clinical practice (final phases). Although this represents a significant gap in the literature, it is problematic to undertake such studies unless there is clear evidence from high quality predictive models that BNP/NT-proBNP are important predictors of the outcomes of interest.

Development of Statistical Models To Establish Predictive Strength

The multivariable nature of prognostic research can pose some challenges with respect to estimating adequate sample sizes.[411] The issue of sample size is particularly important when one considers the number of explanatory variables within statistical models (model development or validation) used to predict HR relative to the number of outcome events. The rule of thumb is that there should be a minimum of 10 events for every prognostic factor included within the multivariate model;[411,413] this suggests that some studies included in this review did not have adequate sample sizes with respect to the statistical analyses related to the number of prognostic factors. Conversely, because of the limited sample sizes some studies may have been limited in the number of possible confounders or covariates to include in their prognostic models. The result of this is that the HR will be overestimated. The studies eligible for this review undertook multivariate or multivariable analyses. However, it was difficult to assess the validity of these computations because of the lack of detail in the reporting of the computation methods. Had we evaluated the studies for adequate reporting criteria for multivariate analyses, we suspect that the studies would not have performed well. Additionally, the evaluation of statistical models for use within patient care should take into account the intended purpose of the model. The purpose of prognostic models may be more complex than those of other clinical aims (e.g., diagnostic accuracy). Although multivariable models can predict future events, the issue of discrimination (accurate classification of those with or without the outcome or disease), calibration (estimating probabilities or predictive values for future risk), and reclassification methods are key aspects that need to be taken into account.[45,46] Similarly, there is a need to identify the intended aims of the study with respect to the prognostic factor. We have described the phased nature of prognostic research in Table 45. In this systematic review, the majority of studies did not specify the main aim of the research in the context of these frameworks and, as such, we surmised their aim based on the statistical analyses that were attempted and presented. We also note that many of the included studies did not specify that the primary purpose of the study was to evaluate BNP/NT-proBNP; in these studies, BNP/NT-proBNP was one of many predictor variables that were being evaluated.

Some studies in KQ3 could be classified as developmental studies, undertaking discrimination and calibration statistics to establish the model performance. These were the studies that we then included for KQ4, as they provided some information about the incremental added value of BNP/NT-proBNP. Some of the studies in KQ4 provided validation of the model, using internal validation approaches; in this review, only two studies[251,375] attempted external validation. This systematic review identified very few impact studies[176,414] that attempted to evaluate the clinical impact of the prognostic model on decisionmaking and patient outcomes. Future research studies also need to move toward developing impact studies.

Future research should consider undertaking consensus exercises to establish a minimum set of prognostic factors to be consistently evaluated (or potentially included) in the base statistical models in these prognostic studies. In the best case scenario, the base model contains prognostic factors that have already been established. Unfortunately, this is not clear or consistent in the literature we evaluated. This makes comparison across studies or evaluation of incremental value of adding BNP or NT-proBNP problematic. In this systematic review, we established a priori a minimum set of confounders that were felt to be important for this population and these included age, sex, BMI (or some other metric of body mass), and any measure of renal function which we used to assess risk of bias criteria for confounding; the rationale was based primarily on theoretical biological grounds but none have been definitely established.

Defining Outcomes in Prognostic Studies of BNP and NT-proBNP

The use of composite outcomes is prevalent in the prognosis literature dealing with CVDs. Approximately one half of the studies in the decompensated and stable BNP and NT-proBNP studies eligible in this review used composite outcomes and about one third reported combined outcomes only. The interpretation of these combined outcomes is problematic for clinicians and for patients and could result in misinterpretation of study findings. Although composite endpoints are common in cardiovascular studies because they are used by clinicians or because they increase the event rates and assist in statistical analyses, they can be misleading as the combined outcomes have widely varying importance to patients. Clearly, mortality and morbidity are likely to be valued differently by patients; similarly, even combined outcomes within one category (i.e., morbidity: hospital re-admission combined with reduced quality of life) can be valued differently by patients. For example, patients might place higher value on improved quality of life rather than hospital-free survival. In addition, mixing of a hard outcome, such as cardiac death, with a soft outcome, such as clinical symptoms of angina or HF, is not ideal, as the soft outcomes are more subjective.[44] There are also data to suggest that clinicians may overestimate the impact of treatments on preventing adverse events that matter most to patients when considering composite outcomes.[415] The events that are often combined within composite endpoints tend to have widely differing frequencies and therefore, different relative risk reductions.[416]

In the context of prognosis or establishing BNP/NT-proBNP as predictors of composite outcomes, the interpretation for patients and clinicians can be equally challenging. If composite outcomes are to be presented, we recommend that they be presented in conjunction with noncomposite outcomes. Further, study authors should justify why they are combining outcomes (i.e., with similar biological factors and hence similar frequencies or risk). Alternatively, a suitable combined cardiovascular outcome could be defined by cardiology societies. When large variation among the individual components of combined outcomes exist, likely the best choice is to avoid combined outcomes.[416] Even if combined estimates were to be used in studies, there is a need for consistency in how these are combined. For example, consider the composite endpoint of cardiovascular death and re-admission to hospital. It is not clear how these events are counted within the same patient, where re-admissions can occur in more than one instance for the same patient. It is not clear if the combined outcome considers these events once per subject or as multiple events per subject; this is further compounded by the use of “and” in some studies and “or” in other studies. Greater clarity in this would be helpful.

Applicability in Prognosis Studies

When one considers the applicability of the BNP and NT-proBNP findings to clinical situations, note that the majority of papers pertained to populations aged 60 years or older, although we could not find specific evidence to suggest that the predictive value of BNP or NT-proBNP varies by the age of the study population. The majority of studies included samples whose composition was over 50 percent, and sometimes over 80 percent, male. Thus, we cannot conclude that the results are equally applicable to males and females.

In these articles we reported on the variety of cutpoints used for developing the prognostic models. It is not clear if these thresholds are truly generalizable because there is such wide variation in practice.

Limitations of This Review for Prognosis Studies in Both Decompensated and Chronic Stable Heart Failure Populations

In studies with decompensated HF patients, it was necessary to assume that the level of acuity was adequately categorized by the studies and so any study that recruited subjects from emergency or hospital admissions was classified as being acute; conversely, subjects not recruited from these settings were considered to be non-acute or stable and chronic. We contacted seven authors to clarify the acuity levels of their studies. From these, five replied but two did not. A judgment call was then made to classify all seven as chronic stable populations. In general, most studies did not provide sample size calculations for either the decompensated or chronic stable HF populations. This is particularly important when one considers the number of explanatory variables within the statistical modeling (model development or validation). Studies were not restricted to those that used appropriate statistical methods (or reported these adequately). However, studies with univariate analyses (including univariate ROC analyses) alone were excluded; for studies that reported univariate and multivariable or multivariate analyses, only the latter were reported and considered in our review synthesis.

We also found a few studies that reported negative BNP and NT-proBNP results, but these studies were most often reporting primarily on alternative markers. The potential bias for not reporting negative BNP and NT-proBNP association is very high and may suggest the risk of publication bias and selective outcome reporting bias. It is expected that publication bias may be particularly problematic for prognostic studies that employ nonrandomized or observational study designs, especially retrospective analyses of existing databases.[417] We did not formally assess publication bias for prognosis studies using statistical computations such as funnel plots. Currently, no registry for protocols of prognostic prediction studies exists. As such, it is difficult to assess the potential for selective outcome reporting and the Hayden criteria do not address this specific bias.

Conclusions for Prognosis Studies

The findings demonstrate that there is an association between BNP and NT-proBNP predominately for the outcomes of all-cause mortality and composite outcomes in both decompensated and stable populations. The other mortality outcomes (cardiac and sudden cardiac) demonstrated a less convincing association in chronic stable populations, and were less often evaluated in populations with decompensated HF. In studies with decompensated HF patients, admission and discharge levels and change from admission were all shown to be predictors. The majority of studies were characterized as early phases of prognostic research attempting to establish the independent association of BNP or NT-proBNP with the outcomes of interest. Far fewer studies attempted to undertake model validation methods either in internal or external samples. Very few studies evaluated the impact of using BNP or NT-proBNP on clinical decisionmaking or cost-benefit analyses. Six studies evaluated the prognostic ability of BNP/NT-proBNP in patients undergoing resynchronization therapy and were shown to be independent predictors of all-cause and cardiovascular mortality and morbidity.

The conclusions regarding the evidence must be considered in light of the risk of bias. Many of the papers did adjust for multiple confounders and most included the important covariates of age and sex in the regression models. Our moderate risk of bias rating for this domain can thus be considered more of a caution than a reason to impugn the results. The same could be said of the moderate risk of bias that was assigned to the domain for the measurement of outcomes.

We do not believe that the potential for a moderate risk of bias in these two domains mitigates the overall conclusion that BNP and NT-proBNP are independent predictors of mortality and morbidity outcomes in persons with decompensated and chronic stable HF. However, it is difficult to provide useful, clinically applicable information from these data because there are neither established cutpoints nor simple means of interpreting the test in the different clinical situations.

Future Research Recommendations for Prognosis Studies in Decompensated and Chronic Stable HF Populations

A number of recommendations for future research in assessing the prognostic strength of BNP/NT-proBNP in decompensated acute and chronic stable HF patients are listed.

Population:

1. Include more women and subjects of different races when assessing the predictive value of BNP/NT-proBNP in both decompensated and chronic stable HF patients. Reporting the racial composition of study participants would also be important.
2. Evaluate the impact of different age tertiles on the predictive value of BNP and NT-proBNP.
3. Identify clearly if the study subjects are acutely ill (decompensated) or chronic and stable HF patients; this should be specified irrespective of the setting in which treatment is administered.
4. Improve clarity (better reporting) with regard to the different classifications of decompensated HF subjects. This will minimize misclassification of subjects, improve comparability across studies, and assess potential differences in risk prediction for the HF disease subgroups (that may vary with the different disease taxonomy categorizations).

Intervention (Measurement and Analysis of BNP/NT-proBNP):

1. For studies of decompensated HF patients, greater clarity in reporting when BNP/NT-proBNP levels were measured relative to the commencement of treatment (e.g., BNP levels were taken within 2 hours of admission prior to pharmacological treatment, etc.).
2. Report if BNP/NT-proBNP levels were normally distributed and if skewed, the method of adjustment (e.g., log transformation) for subsequent inclusion in the prognostic model.
3. Consider assessing the same sets of cutpoints in different age groups to examine whether the predictive value of BNP or NT-proBNP changes with age.
4. Consider prognostic study design to include predetermined cutpoints (based on the literature).
5. For populations with decompensated HF, there is the need for studies to consistently evaluate potential differences between admission and discharge levels of BNP/NT-proBNP with respect to their predictive ability for both short-term and long-term outcomes.
6. Future research should adhere to transparent and reproducible methods when defining and selecting all prognostic factors included within the model.[407]

Study Design:

1. Aim to increase the number of studies that employ prospective designs with a primary aim to establish developmental and external validation models (prospective second-phase

studies). This review showed a large number of retrospective studies not primarily designed to assess BNP/NT-proBNP as an independent predictor; there is a need to move away from these retrospective designs.
2. Increase the number of studies designed to assess the impact (including cost-effectiveness) of BNP/NP-proBNP that demonstrate how decisionmaking and patient outcomes are affected.
3. Provide a sample size calculation. Consider the number of potential predictors relative to the number of events to prevent overestimation of the predictive ability of BNP/NT-proBNP or other markers (as the number of predictors is larger than the number of outcome events).

Comparators/Covariates in Prognostic Model:

1. Adherence to transparent and reproducible methods when defining and selecting all prognostic factors included within the model.[407]
2. Consensus on using a minimum standard set of covariates to account for potential confounding; age, sex, BMI, and renal function is what was suggested by the clinical experts in this systematic review.
3. Comorbidities are important confounders and attempts should be made to assess and report these within study subjects and possibly adjust for these in the prognostic model.
4. Clarification of method used to adjust for age, BMI (i.e., another measure of body mass such as waist circumference or waist-to-hip ratio) in the predictive model.

Statistical Prognostic Models:

1. Adherence to reporting standards[407] that allow for adequate assessment of the validity of the methods undertaken to develop the predictive model and estimate the prognostic risk. All covariates placed into the model and tested should be reported.
2. Do not limit statistical analyses to univariate methods (even for ROC analyses). The assumption that BNP/NT-proBNP levels are not mediated by other prognostic factors or that time does not change their predictive ability[412] is problematic.

Outcomes:

1. Consensus on defining key outcomes is needed. Outcome assessment should be standardized, both in terms of the types of outcomes investigated and the ways in which these outcomes are defined and measured. This standardization will improve the uniformity of research in this domain and enhance the comparability of results across different studies. The outcomes should be predefined and the investigators should only report on the predefined outcomes,
2. Report negative as well as positive findings from multivariate or multivariable analyses (even if negative findings are shown). Most authors will run all the possible variables through logistic regression but only report those that demonstrate a significant relationship.
3. Report findings of single outcomes when composite outcomes are reported.

Timing:

1. For subjects with decompensated HF, consensus on what are the most clinically relevant time intervals (shorter and longer term) for predicting outcome.

Key Question 4: In HF populations, does BNP measured at admission, discharge, or change between admission and discharge add incremental predictive information to established risk factors for morbidity and mortality outcomes?

Overview: Key Question 4

From the 198 publications that evaluated prognosis in KQ3, we examined a subset of 41 studies specifying that their intent was to assess incremental value. From these 41 studies, 17 were not extracted as they did not provide data[2,247] or included BNP in the base prognostic model,[106,196,210,212,273] in the NT-proBNP predictive model,[282,303,316,339,343,348,352,362,375] or both assays were included in the model.[217] In all these circumstances, the incremental value could not be extracted.

Incremental Value of BNP and NT-proBNP in Patients With Decompensated Heart Failure

Seven publications evaluated incremental value of BNP/NT-proBNP in decompensated HF subjects for admission BNP[3,187,193,198,205] and admission NT-proBNP.[251,256] Within the BNP publications incremental value was consistently shown to predict all-cause mortality for short-term (3 and 6 months) and longer-term (9 and 12 months). Two studies compared the incremental value of BNP to other cardiac markers (carbohydrate antigen125 (CA125),[205] C-reactive protein (CRP),[193] and cardiac troponin-T (cTnT)[193]) and did not show superiority. Within the two NT-proBNP publications, both studies[251,256] showed incremental value at 22 months and 6.8 years for predicting all-cause mortality. In those studies that considered other cardiac markers and all-cause mortality, the highest incremental predictive value was achieved when BNP/NT-proBNP was combined with these other markers. Only two studies evaluated predicting cardiovascular mortality in the short term (31 days) and longer term (9 months) and showed BNP did add incremental value; NT-proBNP studies did not evaluate cardiovascular mortality.

Only mortality related outcomes were evaluated in these studies and none evaluated outcomes of morbidity or composite outcomes. All studies evaluated admission BNP levels and none evaluated discharge or change in BNP/NT-proBNP levels. Future research in patients with decompensated HF should endeavor to evaluate incremental predictive value for morbidity and composite outcomes and also to evaluate BNP/NT-proBNP levels at discharge from acute care centers or change relative to baseline but before discharge.

The majority of studies were predictor finding or developmental with respect to phased development of prognostic validation. None of the BNP publications included in KQ4 undertook internal or external model validation computations. Only one of the NT-proBNP studies[251] evaluated incremental value and presented internal model validation computations. Future research in the incremental value of BNP/NT-proBNP should endeavor to undertake internal and external validation computations consistently to better assess the role of these assays.

Overall, despite the differences in the base models, cutpoints, and lengths of followup, evidence from lower hierarchical statistical approaches and early phase prognostic development studies suggest that BNP or NT-proBNP adds incremental predictive value in patients with decompensated HF.

Incremental Value of BNP and NT-proBNP in Patients With Stable HF

No eligible studies evaluated the incremental value of adding BNP in patients with stable chronic HF. Fifteen publications[283,286,301,306,309,320,329,340,344,349,353,357,360,373,376] evaluating chronic stable HF patients considered the prognostic value of NT-proBNP.

When considering all-cause mortality, all but one study[344] showed incremental value of adding NT-proBNP to the base models. The findings from four publications (with relatively large sample sizes) show consistent trend for incremental value to predict all-cause mortality at approximately 2 years. Similarly, four publications that evaluated the incremental value predicting mortality at 30 and 34 months were consistent in showing the added value of NT-proBNP. When incremental predictive value of NT-proBNP is compared to midregional pro-atrial natriuretic peptide (MR-proANP), hs-cTnT, or ST2, the relative contribution appears similar but the greatest increment was shown when NT-proBNP is combined with the other markers. When considering cardiovascular mortality, three studies consistently reported on the incremental value of NT-proBNP in patients with stable chronic HF for predicting from 12 to 24 months. Six publications that evaluated five different composite outcomes that combined mortality and morbidity events all suggest that NT-proBNP adds incremental value in predicting these outcomes from 22 to 37 months.

All but two publications, which evaluated the same cohort, undertook validation approaches, and the remaining studies were predictor finding or developmental with respect to phased development of prognostic research. Overall, despite the differences in the base models, cutpoints, and lengths of followup, these studies consistently show that NT-proBNP adds incremental predictive value for predicting mortality, morbidity and composite outcomes in patients with stable HF.

Applicability Issues in Prognosis Studies Evaluating Incremental Value

When considering the applicability of the BNP and NT-proBNP studies for KQ4, note that they do not differ from those that were identified for KQ3. Studies for KQ4 were derived from those eligible for KQ3; however, a much smaller pool of studies is considered. Of particular note is that the base models (covariates included), cutpoints, and lengths of followup varied widely across studies; it is not clear how these might impact applicability. Time intervals were heterogeneous for both studies of decompensated HF (from 31 days to 6.8 years) and stable chronic HF (from 12 to 37 months), making comparisons across studies problematic.

Conclusions for Prognosis Studies Adding Incremental Value

There is limited but consistent evidence that BNP or NT-proBNP adds incremental value for patients with decompensated HF for all-cause mortality and cardiovascular mortality in the short (3 and 6 months) and longer term (22 months to 6.8 years); outcomes of morbidity or composite outcomes have not been evaluated. There were no studies assessing the incremental value of BNP in populations with stable chronic HF. There is a consistent trend showing that NT-proBNP adds incremental value to predicting outcomes of all-cause mortality, cardiovascular mortality, and composite outcomes from 1 to 3 years when considered with other prognostic factors. Clinical utility of using multi-factor prognostic scoring need to be designed and evaluated before this becomes an established clinical tool.

Future Research Recommendations for Adding Incremental Value

1. There is a need to evaluate outcomes of morbidity and composite outcomes in subjects with decompensated HF respect to the incremental value of BNP and NT-proBNP.
2. There is a need to evaluate BNP in stable chronic populations with respect to incremental predictive value using appropriate computations.
3. There is a need to move to higher level hierarchical approaches (internal and external validation) when selecting statistical evaluations (i.e., reclassification methods), as well as designing impact studies.
4. Future research recommendations for KQ3 are also applicable for KQ4 for both decompensated and chronic stable populations.

Key Question 5: Is BNP or NT-proBNP measured in the community setting an independent predictor of morbidity and mortality outcomes in general populations?

Overview: Key Question 5

The use of markers to predict adverse outcomes in the general population has become fairly well established in the field of cardiology, especially with the advent of risk stratification tables for predicting CVD outcomes using variable such as age, sex, smoking, diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein (HDL)-cholesterol. These scoring systems have limitations and unfortunately are based on combined mortality and morbidity outcomes. The use of BNP or NT-proBNP in a community setting to add to these prediction scores would be valuable. The findings demonstrate clearly that an association exists between NT-proBNP and the outcomes of morbidity (HF and atrial fibrillation (AF)), as well as mortality (all-cause, cardiovascular, and sudden cardiac). No studies reported on the use of BNP in a community setting.

The adjusted HR demonstrates the log-linear relationship between baseline NT-proBNP and cardiovascular death, as well as all-cause mortality, taking into consideration age, sex, BMI, and renal function. The loss of independence in the prediction of cardiovascular death when baseline CVD is documented requires further assessment. The loss of independence may be a result of the smaller number of events (92) compared with 220 events in the whole population.[379]

For outcomes that are associated with cardiac disease (incident HF and AF), there appears to be a log linear relationship between NT-proBNP and the outcome, taking into consideration age, sex, BMI, and renal function. In addition, NT-proBNP seems to perform well, even when adjusted for other conventional risk markers and some of the more recently investigated biomarkers.

The prediction of AF became nonsignificant when all the other factors were used in a backward elimination adjustment.[377] This suggests that when all the factors are considered, NT-proBNP may not provide independent prediction of future AF. It should be noted that this reference did measure another natriuretic peptide (MR-proANP) that showed significance in the model.

Applicability for Prognostic Studies From the General Population

While the association is clear, the directness of these findings to patient care is not demonstrated well in the papers reviewed. The statistical approaches to considering discrimination of prediction risk, Harrels c-statistic, the integrated discrimination of

improvement (IDI), and net reclassification improvement (NRI), were evaluated in a number of papers.[377,379-381] All of these demonstrated statistical benefit in including NT-proBNP in the prediction models (using other traditional risk factors) for incident HF,[377] all-cause mortality,[379] cardiovascular death,[380,381] and combined cardiovascular outcomes.[381] In these studies, the addition of NT-proBNP made a significant change to the c-statistic when added to conventional risk markers (similar but not identical in the papers).[377,379-381] The reclassification data in these papers are presented using the best fit models that include NT-proBNP along with other biomarkers.[377,380] One paper reported IDI and NRI.[377]

To translate this into clinical practice will require the development of specific risk calculators that take into consideration the confounders for NT-proBNP/BNP (renal function and BMI) and any other established risk markers (age, diabetes, hypertension, total cholesterol, HDL-cholesterol, smoking, and high sensitivity C-reactive protein). Such models will require testing in population cohorts before the use of NT-proBNP/BNP can be validated for use as a prognostic marker in community settings. These studies will have to demonstrate that measurement of NT-proBNP/BNP and any other biomarkers will clearly add to the predictive power of the risk calculation and change patient outcomes (all-cause mortality or cardiovascular mortality). In addition, to demonstrate economic benefit, the impact on actual outcomes is essential for the public to understand the benefit of the test in addition to all the other measurements that are usually required.

The term general population was strictly applied to this review. One study[418] had selected subjects based on urine albumin excretion but claimed that they weighted their participants to model a general population. A companion paper[419] was excluded because of the exclusion criteria reported in the study (type 1 diabetes mellitus) and the fact that they selected subjects based on urinary albumin excretion. This study had recruited 8,592 individuals and had data for 7,819 available for analysis.[418] It is interesting to note that the reclassification statistics (HR, Harrell c-statistic, and IDI) reported in this paper largely confirm the findings of other reports and suggest that the weighting applied in the paper is a reasonable simulation of a general population.[418] For all-cause mortality, HR=1.28 (95% CI, 1.11 to 1.47); Harrel c-statistic 0.84 (95% CI, 0.83 to 0.86); IDI 1.86 (95% CI, 1.26 to 2.45), are similar to the summarized results in Appendix L Table L-1. Similarly, for cardiovascular mortality, HR=1.40 (95% CI, 1.03 to 1.87); Harrel c-statistic 0.92 (95% CI, 0.89 to 0.95); IDI 2.06 (95% CI, 1.10 to 3.02); and cardiovascular events (HR=1.23 (95% CI, 1.11 to 1.38); Harrel c-statistic 0.83 (95% CI, 0.81 to 0.85); IDI 1.07 (95% CI, 0.73 to 1.40) are comparable.

Conclusions for Prognosis in Studies From the General Population

The findings demonstrate clearly that there is an association between NT-proBNP and the outcomes of morbidity (HF and AF), as well as mortality (all-cause, cardiovascular, and sudden cardiac) in the general population. The use of discrimination of risk statistics has shown that NT-proBNP adds statistical significance to the models of risk prediction. The development of a risk model for direct comparison against a standard risk model has not yet been reported.

Future Research Recommendations for Prognosis in Studies From the General Population

Future research should develop specific risk calculators that take into consideration the confounders and any other established risk markers. BNP has not been evaluated in the general population. The findings of the other sections of this report suggest that these would be similar

and thus we would recommend that future studies consider measuring both NT-proBNP and BNP in the general population.

Such models will require testing in population cohorts before the use of NT-proBNP or BNP can be validated for use as a prognostic marker in community settings. It would also be helpful to have studies designed to help us understand which parameters in cardiac and renal function can be changed based on NT-proBNP or BNP measurement to improve clinical outcome.

Key Question 6: In patients with HF, does BNP-assisted therapy or intensified therapy, compared with usual care, improve outcomes?

Overview: Key Question 6

This systematic review question on BNP-guided therapy falls under the overarching question of how best to manage patients with HF. There were nine RCTs that addressed this question. Variation in study design, patient selection, baseline characteristics of patients, therapy goals, BNP/NT-proBNP cutpoint, outcome types, and how they were reported limited the option of performing any meta-analyses to derive summary estimates. Four studies reported at least one outcome that was better in the BNP/NT-proBNP group compared with the usual care group.[4,53,386,388]

The studies were carried out primarily in settings of cardiologists, which may attenuate the advantage of using BNP/NT-proBNP. Patients who are seen by a cardiologist will likely get less benefit from BNP-guided therapy, compared with those who are seen by a community physician who does not have the same expertise. Studies may also have been underpowered as few provided sample size calculations. In two studies, the followup time was only 3 months.[384,387] All but two studies[384,386] were done in multiple sites, but randomization was still patient-based. Maisel[420] suggests that randomization should be based on site rather than on patient as this can reduce the "learning biases" in single-center randomizations.

The type of patients selected in these studies varied as there were different inclusion and exclusion criteria used. These studies were also limited to patients with systolic HF, as preserved ventricular function was only considered in the "Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?" (PRIMA) trial.[385] The severity (or disease burden) of patients enrolled is therefore inconsistent across studies. Some studies specifically chose patients who were recently diagnosed with HF and therefore early in their time-point of the syndrome. There was a broad spectrum of patients with HF, including the very elderly and those with multiple comorbidities. Therapy at baseline was also variable. For example, NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting (PROTECT) patients were receiving optimal therapy as 99 percent of the patients received angiotensin converting enzyme I (ACE-I) or angiotensin receptor blockers (ARB) and 94 percent of these patients had the recommended dose. Beta-blockers were taken by 99 percent of the patients and 59 percent of these were taking the recommended dose. Similarly, a high percentage of patients in the Trial of Intensified vs. standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) were receiving the recommended HF therapy.[53] Strategies for Tailoring Advanced Heart Failure Regimens in the outpatient setting (STARBRITE) optimized therapy before the start of the trial.

The goals of therapy for the BNP/NT-proBNP group compared with the usual care group were different mainly in the target concentration set. A higher target means concentration did not need to decrease too much and were therefore, less likely to change symptoms or outcomes. A

lower target runs the risk of adverse events outweighing the benefits. There was no consistency in trials with lower compared with higher BNP/NT-proBNP concentrations. In a subanalysis of data from the PRIMA study,[385] patients who achieved their target concentration did better than those who did not. This provides some support to using individualized target concentrations rather than population-based targets. Furthermore, the application of biological variation data (see Results KQ7), specifically the reference change value (RCV), may be enhanced when therapy is altered (e.g., titration of medications or addition of medications). We know that patients can vary widely between serial BNP/NT-proBNP measurements, some to a larger degree and others to a smaller degree, but sporadic increases could also occur. A predefined BNP/NT-proBNP cutpoint that is seen with the most stable patients with HF (e.g., <200 pg/mL for BNP and <1,000 pg/mL for NT-proBNP) may be a reasonable choice.[3] The frequency of measurements is another aspect that has not been assessed in BNP/NT-proBNP therapy studies. Another consideration is whether BNP/NT-proBNP measured using point-of-care devices (e.g., Triage BNP), has a higher analytical variation and therefore contributes to a higher RCV, and is less sensitive to detecting a change in HF status. There are also different forms of BNP/NT-proBNP that may vary depending on worsening symptoms and other comorbidities and the assays may measure these species differently. Making patients and caregivers aware of the BNP or NT-proBNP test result may encourage patients to stay on treatment but evidence is limited. Two studies used this approach, one with a positive outcome[386] and one with a negative outcome.[389]

The aggressiveness of therapy among the studies appeared to vary, but this was difficult to assess as not all studies reported drug titrations in the same way. The timing was not always reported, nor the change in dose or when additional medications were given. A structured approach would be difficult, as patient care is individualized, but the data need to be captured to compare interventions. The recommendation for therapy suggested by Maisel[420] is to establish predefined treatment goals, at least to recommended guideline doses, and to use clinical judgment to individualize medications according to the patient's response. That is, mirror what is normally done. In the BNP/NT-proBNP group, Maisel suggests to increase followups and increase doses as long as there are no adverse events (e.g., decreased blood pressure or worsening kidney function). Also, have additional followups if the condition is worsening. Furthermore, ensure there is documentation that the clinician has responded to an elevated BNP/NT-proBNP concentration for the BNP/NT-proBNP-guided group. Another suggestion is to enhance data collected from these studies to consider measuring other biomarkers that reflect HF pathology, including more heart-specific and renal biomarkers. A multi-marker panel may offer greater value than a single marker in guiding therapy by adding greater precision to the estimate of pathology.

A successful BNP/NT-proBNP-guided therapy study is one in which hospital admissions are reduced, clinicians and physicians adhere to HF therapy guidelines, renal function is preserved, and quality of life is improved.[420] All studies captured information on hospital events and most measured kidney function, but only four had quality of life data. No studies reported on how well physicians followed therapy guidelines.

There were six studies that used composite endpoints, but because the combination of outcomes were different it was difficult to compare studies. There was no relationship between the number of individual endpoints within the composite and overall effect. Combining endpoints into a composite helps to reduce the number of patients required to achieve adequate power. However, it can also obscure the component in the composite that had the most events

causing a misinterpretation of the positive or negative outcome achieved. For example, the PROTECT trial[386] had the combined outcome of cardiovascular death, HF hospitalizations, acute coronary syndrome, cerebral ischemia, significant ventricular arrhythmias, and worsening HF. However, the only difference between the two treatment arms was for the individual endpoints of HF hospitalizations and worsening HF. Mortality was no different between treatment arms, and only two studies[4,53] that included this endpoint in the composite found a difference (lower in the BNP/NT-proBNP arm) and happened to be the two of three studies with the longest followup. Endpoints such as mortality would occur less frequently and therefore there are fewer events to capture in shorter trials, but these trials can achieve sufficient power by recording more frequent events like hospitalizations. In addition, in trials where adverse events were collected, BNP/NT-proBNP-guided therapy differed between treatment groups. This finding suggests that clinicians used other information in addition to the BNP/NT-proBNP results to make decisions on therapy.

Five studies reported negative results, three (Beck-da-Silva,[384] SIGNAL-HF,[5] STARBRITE[387]) had short followups (3 to 9 months), which would have limited the number of outcomes that would have occurred over a longer period of time. In the other two studies, one[385] only required a 10 percent reduction in BNP/NT-proBNP from baseline, and in the other study[389] patients had the most type of medications, 35 percent of which were taking an ARB. Studies have shown that ARB use decreases mortality, and in one study cardiovascular mortality was decreased in patients with HF and reduced LVEF.

Data interpreted based on age may also be important. In the TIME-CHF study,[421] younger patients (≤75 years) benefited more than older patients (>75 years), but there was no difference between these age groups in the Use of Peptides in Tailoring hEart failure Project (UPSTEP).[389] Younger patients may seem to do better, but this may depend on how care is given, as older patients need a more careful, gradual approach.

One limitation to this systematic review was the exclusion of two trials, the first trial assessing BNP/NT-proBNP-guided therapy in 2000,[422] and a more recent study in 2010 done by the same research group.[423] They were not included because the method for NT-proBNP measurement is not a commercially available one, but an in-house method. The data from these trials would have strengthened the results of this systematic review but not altered the conclusions. Also, meta-analyses were not performed because of the heterogeneity among the studies, and therefore no quantitative summary estimates could be made. Two previously published studies did conduct meta-analysis and reported reduced mortality in the BNP/NT-proBNP guided group.[35,424]

Applicability for BNP-Guided Therapy

Understanding the usefulness of BNP or NT-proBNP measurement in the assessment of HF status will allow for better management of patients with HF. It may or may not be useful. If it is useful, it would essentially serve as a barometer for disease improvement or deterioration. Currently, the data from the studies that have evaluated BNP or NT-proBNP for this purpose are inconclusive.

Conclusions for Intervention Studies

Over the last 10 years, few studies have been undertaken to assess whether BNP/NT-proBNP-guided therapy has benefits over usual care. The conclusions from these studies are varied in part because of the difference in study design and outcomes. Differences among studies

provide greater understanding on how BNP/NT-proBNP-guided therapy can be used, regardless of whether trials succeeded or failed. The SOE for all-cause mortality was low.

Future Research Recommendations for Intervention Studies

The data reported from the nine studies evaluating the utility of BNP or NT-proBNP for guiding therapy in patients with HF provides a rich basis of information to draw upon to design further RCTs. Based on the information gathered, future trials should consider the following design features:

1. Therapy optimized at baseline according to clinical guidelines.
2. BNP or NT-proBNP target near the median value for patients with stable HF.
3. Consider using the RCV when considering a change in therapy.
4. Followup of 2 years or more.
5. Include all relevant endpoints: cardiovascular mortality, total mortality, days alive and not hospitalized for HF, number of HF hospitalizations, number of HF events not requiring hospitalization, surrogate measures of renal function (e.g., creatinine) and ischemia (e.g., troponin), number of patients who have achieved target BNP/NT-pro-BNP concentration, and number of patients who have achieved recommended medication doses. Also, include as part of medication information the number of patients who are taking additional medications or doses above the recommended amounts. Quality of life questionnaires would be of additional value.
6. Provide sample size calculations to demonstrate adequate study power for the outcomes selected.
7. Consider age in the statistical analyses to determine how age affects outcome (treatment effect).
8. Consider regression analyses to test for interactions between intervention and characteristics such as age, sex, NHYA class, and disease.
9. Provide confidence intervals for all statistical measures to allow meta-analyses to be performed as recommended by the CONSORT Statement.[425]
10. Consider evaluating other biomarkers in establish a panel that can be used to assess disease improvement or deterioration.

Key Question 7: What is the biological variation of BNP and NT-proBNP in patients with HFand without HF?

Overview: Key Question 7

It is important to know biological variation for BNP and NT-proBNP in order to be able to effectively use these measurements for managing patients with HF. Specifically, what constitutes a significant change in serial measurements or RCV? In other words, this information provides knowledge about the reproducibility of the test result in patients with no change in clinical status, deterioration, or improvement. This systematic review found six studies that contained biological variation data in patients with stable HF. The requirement for stable HF was made so as to eliminate variation from individuals who were not optimized on medical therapy and thus could have a change in their HF status or who had experienced a recent event such as hospitalization or myocardial infarction. The value in doing this is to be able to apply the biological variation data to the group of patients where they would be used as biological variation maybe different in other patient groups. From this systematic review, the two studies where healthy individuals

were evaluated, the RCV values were higher than those in the studies of patients with stable HF. However, this difference may also reflect the difference in age as the healthy groups were younger than the HF groups. The age dependence of within-individual variation is known for other analytes, that is, lower variation compared to younger individuals.[426]

Within-individual variation was similar for BNP (median=25%) compared with NT-proBNP (median=20%), but lower in short measurement intervals (hours, days) compared to longer measurement intervals (weeks, year). Although the circulating half-life of BNP is much shorter (21 min) compared with NT-proBNP (60 to 120 min), this did not seem to affect the biological variation values for within-individual (CV_i) values by much.[427] Another factor to consider when interpreting the CV_i values is that they are calculated from the difference in variance between total variation (CV_t) and analytical coefficient of variation (CV_a). Thus, a lower CV_a will provide a more accurate and higher CV_i. The highest CV_a values were obtained from the point-of-care instrument (Triage BNP) and correspondingly resulted in higher RCV values. Reduction of CV_a is possible by using automated instruments and measuring samples in duplicate.

Accuracy of biological variation estimates is a function of study design, including the selection of participants, preanalytical factors such as participant preparation (e.g., fasting, posture, and stress), and time of collection (to minimize diurnal variation; NT-proBNP, and more so BNP, increase during the day and stabilize in the afternoon). Further precision can be gained by increasing the number of samples collected within the measurement interval (study time frame), number of replicates for each sample (e.g., duplicate), and statistical methods. The number of replicates becomes more important when variation (analytical or biological) is high. In the study by Schou et al.[37] the number of determinations of a sample on the biological variation estimates was explored, with small changes seen between single and double determinations. This was explained by the very low analytical variation for both BNP and NT-proBNP.

Most studies included in this systematic review considered at least some known pre-analytical factors and tried to minimize or address them. However, the determinants of within-person biological variation have not been well explored; more is known about between-person variation, such as sex, age, exercise, and comorbidity.[428] The biological variations are likely due to subclinical changes in hemodynamics, hormonal regulation, clearance, and perhaps even differences in the type of circulating forms of BNP, as well as whether the measurement method detects them.[427]

Calculations for biological variations should also consider the distribution of the data. It is well known that the distribution of NT-proBNP data is skewed to the right and log transformation of data is appropriate for statistical analysis. The reason for this skewness is not known but may indicate the population is heterogeneous or nonbiological variation factors are present. If Gaussian distribution is assumed, then all data (99.7%) will fall within ±3 SD of the mean. Therefore, in an RCV calculation, the CV_i cannot be greater than 33.3% without including negative values. There is a linear relationship between CV_i and NT-proBNP concentration, but after log transformation, CV_i is reduced and the association with concentration is removed. Shou[38] examined the difference in CV_i values using year-to-year NT-proBNP normal and log data and found the mean CV_i to drop from 35 percent to 5.4 percent. The log CV_i suggests the variation in NT-proBNP to be fairly stable. However, monitoring on a log scale is difficult because it carries a risk that small changes reflecting a true biological change are missed. Therefore, biological variation data should be interpreted on a non-log scale.

No meta-analysis could be done to compute summary estimates for CV_i or RCV as confidence limits were not provided for variance data in any study. Recently, Roraas[429] described how experimental design greatly influences the confidence interval and reliability of the biological variation estimate.

The index of individuality (IOI) for BNP and NT-proBNP was between 0.03 and 0.14, which is lower than any of the common biochemistry analytes.[430] For example, the IOI for creatinine is 0.24 and for cholesterol it is 0.33. This means patients are not like each other and reference intervals or decision limits are not as useful. A low IOI (<0.48) is considered to reflect strong individuality, which in turn indicates that an individual patient should be assessed with respect to his or her individual hormonal level. In contrast, a high IOI (>1.4) indicates this patient should be assessed with respect to population-derived reference intervals (or decision points). In practice, serial monitoring of patients using the RCV provides the best assessment of change. However, this information is rarely provided on laboratory reports to assist clinicians in interpreting test results.

Applicability Issues in Biological Variation

The applicability of the RCV values calculated from patients with stable HF is to assess instability in patients with HF. Although the inclusion criteria of patients with stable HF varied among studies, some stricter than others, this did not seem to influence the RCV values by a large degree. The time frame of collection for the biological variation data seemed to influence the RCV. The within-hour and within-day values were much lower, yet there was no discernible difference beyond this time period (up to 2 years). Interestingly, the RCV values for BNP were about double those for NT-proBNP. This information, in addition to the shorter half-live of BNP (minutes) compared to NT-proBNP (hours), raises the possibility that NT-proBNP may have an advantage over BNP to detect the same clinical change. Since NT-proBNP has a longer half-life it can be regarded as an averaging effect of the biologically active BNP. An analogy to BNP and NT-proBNP in HF could be drawn from fructosamine and glycated hemoglobin (HbA1c) in diabetes. Both tests measure glycation but fructosamine has a higher RCV and shorter half-life compared to HbA1c (10.2% and 2 to 3 weeks compared to 7.6% and 8 to 12 weeks, respectively).[431] Current practice recommends HbA1c for monitoring diabetic control because it correlates better with diabetic complications compared to fructosamine.

Conclusions for Biological Variation

The data on biological variation for BNP and NT-proBNP offer insight into the changes that can be expected in patients with stable HF and in healthy individuals. The difference in serial results, expressed as RCV, was higher for BNP compared with NT-proBNP. Furthermore, the IOI for BNP and NT-proBNP was very low, thereby highlighting the individuality of this hormone and suggesting serial measurements need to be interpreted carefully.

Future Research Recommendations for Biological Variation Studies

1. Additional studies would provide supporting evidence of the biological variation parameters. These studies should be designed to capture sources of biological variation determinants by multivariable regression analysis requiring large sample sizes. These analyses may also provide clues as to why the data distributions for BNP and NT-proBNP are right-skewed.

2. Preanalytical and analytical variation should be minimized by collection of samples in the early morning when BNP and NT-proBNP are at their nadir, increasing the frequency of collection and duplicating determinations to increase accuracy of the measure.
3. Statistics used should be clearly described, include all biological variation components, and provide confidence intervals to show reliability and allow meta-analyses to be done.

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Abbreviations

°C	Degrees Celsius
ACC	American College of Cardiology
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin Converting Enzyme
ACEI/ARB	angiotensin receptor blocker
aCHF	Acute congestive heart failure
ACID	Automatic Implantable Cardiac Defibrillator
ACS	Acute Coronary Syndrome
ADHF	Acute decompensated heart failure
ADM	admission mean
AF	atrial fibrillation
AHA	American Heart Association
AHF	acute heart failure
AHRQ	Agency for Healthcare Research Quality
AMED	Allied and Complementary Medicine
AMI	Acute myocardial infarction
ANP	A-Type Natriuretic Peptide
AR	Aortic Regurgitation
ARB	Angiotensin receptor blockers
AS	Aortic Stenosis
AUC	Area Under the Curve
AVLD	Asymptomatic Left Ventricular Dysfunction
BACH	Biomarkers in Acute Heart Failure
BASEL	B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation
BMI	body mass index
BMod	Behavior modification
BNP	B-Type Natriuretic Peptide
BP	Blood pressure
BUN	blood urea nitrogen
CA125	carbohydrate antigen 125
CABG	Coronary Artery Bypass Graft
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CES-D	Center for Epidemiologic Studies Depression
cGMP	Cyclic guanosine mononucleotide phosphate
CHD	Chronic heart disease
CHF	congestive heart failure
CI	Confidence Interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CP	cutpoint
CPE	Cardiogenic pulmonary edema
CRF	Chronic renal failure
CRP	C-reactive protein
CRT	Cardiac Resynchronization Therapy

CT	Computerized Tomography
cTnT	cardiac troponin T
CT-proET-1	C-terminal pro-endothelin-1 precursor fragment
CV	Cardiovascular
CVD	Cardiovascular Disease
CXR	Chest radiograph
d	days
D/C	discharge mean
DD	diastolic dysfunction
DIAST-CHF	Diastolic congestive heart failure
DM	diabetes mellitus
DOR	Diagnostic Odds Ratio
Dx	diagnosis
E/A	Early to late (atrial) echocardiographic phases of ventricular filling
ECG	Electrocardiogram
ECHO	Echocardiogram/echocardiography
ECHOES	Echocardiographic Heart of England Screening
ECP	Enhanced Counterpulsation
ED	emergency department
EDTA	Ethylenediaminetetraacetic acid
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme Linked ImmunoSorbent Assay
EPIDASA	Epidemiological study of acute dyspnea in elderly patients
ER	Emergency room
ESC	European Society of Cardiology
F/U	followup
FDA	Food and Drug Administration
FN	False Negative
FPR	False-Positive Rates
g/dl	grams per deciliter
G-CSF	granulocyte colony-stimulating factor
G-CSF	granulocyte colony-stimulating factor
GDF-15	Growth differentiation factor 15
glow	Lower gray zone
GP	General practitioner
gup	Upper gray zone
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HD	heart disease
HEARD-IT	Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment
HF	heart failure
HFnEFESC	Heart failure with normal ejection fraction recommended by European Society of Cardiology
HFrEF Grp	Heart failure with reduced ejection fraction group

HGF	hepatocyte growth factor
HID	Heart ischemic disease
HO	History of
HO HF	history of heart failure
HO of MI	history of myocardial infraction
HR	Hazard ratio
HR	heart rate
hsCRP	high-sensitivity c-reactive protein LVEF
HT	hypertension
IABP	Intra-Aortic Balloon Pump
ICON	International Collaboration of NT-proBNP
ICU	intensive care unit
IDD	Isolated diastolic dysfunction
IDI	integrated risk improvement
IHD	Idiopathic Heart Disease
IL-6	interleukin-6
IMPROVE-CHF	Improved Management of Patients with Congestive Heart Failure
IQR	Interquartile range
JVP	Jugular Venous Pressure
KCCQ	Kansas City Cardiomyopathy Questionnaire
KD	Kidney disease
kg/m2	kilograms per meter squared
LAD	Left Anterior Descending
LR	Likelihood Ratio
LR-	negative likelihood ratio
LR+	positive likelihood ratio
LV	Left ventricle
LVD	Left Ventricular Dysfunction
LVDD	Left ventricular diastolic dysfunction
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	left ventricular ejection fraction
LVESD	Left Ventricular End Systolic Dimension
LVSD	Left ventricular systolic dysfunction
LVSF	left ventricular systolic function
m	months
M/F	Male or female
MANPRO	Mannheim NT-proBNP Study
MCP-1	monocyte chemoattractant protein 1
M-CSF	macrophage colony-stimulating factor
MEIA	Microparticle enzyme immunoassay
mg/dL	Milligram per deciliter
MI	Myocardial Infarction
MIBG 123	I-metaiodobenzylguanidine
Min	Minutes
ml/min	millimeter per minute
mmol/L	milli mol per Liter

mol/L	mol per Liter
MPO	myeloperoxidase
MRI	Magnetic Resonance Imaging
MRNA	Myocardial Radionuclide Angiogram
MR-proADM	midregional proad- renomedullin
MRproANP	Midregional Pro-A-Type Natriuretic Peptide
MS	Mitral Stenosis
MSHD	Major structural heart disease
MSHD-AF	Major structural heart disease atrial fibrillation
MSHD-SR	Major structural heart disease sinus rhythm
n	number
NA	not applicable
ng/L	Nanogram per liter
NHANES	National Health and Nutrition Examination Survey
NPV	Negative Predictive Value
NR	Not reported
NS	Not stated
NSTEMI	Non ST-Elevation Myocardial Infarction
NT	N-Terminal
NTproBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
PANAMA	Patients with suspected heart failure in primary care
PCI	Percutaneous coronary intervention
PCWP	Pulmocapillary wedge pressure
PEDF	pigment epithelium-derived factor
pg/ml	Picograms per milliliter
pmol/L	Picomol per liter
PPV	Positive predictive value
PRIDE	Pro-BNP investigation of dyspnea in the emergency department
PRIMA	PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality
PROTECT	NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting
PTCA	Percutaneous Transluminal Coronary Angioplasty
pts	patients
PVB	Premature Ventricular Beat
QoL	quality of life
QRS	Quick release system
QUADS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
RDW	Red blood cell distribution width
RNA	Radionuclide Angiogram
ROC	rate of change
ROC	Receiver operating characteristic
RR	Relative Risk

RV	right ventricular
RVD	Right ventricular dysplasia
S3 gallop	heart sounds, rhythm
SBP	Systolic blood pressure
SD	Standard deviation
Serum TC	serum total cholesterol
sFAS	soluble apoptosis-stimulating fragment
SIGNAL-HF	Swedish Intervention study –Guidelines and NT-proBNP Analysis in Heart Failure
SR	Sinus rhythm
SROC	Summary Receiver Operator Characteristic
SRS	Systematic Review Software
ST2	a gene product
STARBRITE	Strategies for Tailoring Advanced Heart Failure Regimens in the outpatient setting
STEMI	ST-Elevation Myocardial Infarction
sTweak	soluble tumour necrosis factor-like weak inducer of apoptosis
TC	Tetracycline
TDI	tissue Doppler imaging
TEP	Technical Expert Panel
TGF beta	Transforming growth factor beta
TIA	Transient ischemic attack
TIME-CHF	Trial of Intensified vs standard Medical therapy in Elderly patients with Congestive Heart Failure
TN	True Negative
TOO	Task Order Officer
TP	True Positive
TPR	True-Positive Rates
Type D	type-D personality
UHFO-IA	Utrecht Heart Failure Organisation – Initial Assessment
UKNPS	United Kingdom Natriuretic Peptide Study
umol/L	Micromol per liter
UPSTEP	Use of PeptideS in Tailoring hEart failure Project
USA	United States of America
VAD	Ventricular Assist Device
VHD	Valvular heart disease
vs	versus
y	years

Appendix A. Search Strategies

Medline-OVID

June 25 2012

1 natriuretic peptide, brain/
2 bnp.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
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 14 to ed=19890101-20110309
17 human/
18 animal/
19 17 and 18
20 18 not 19
21 16 not 20
22 16 and 17
23 21 not 22
24 limit 23 to english language

EMBASE

June 25 2012

1 Brain Natriuretic Peptide/ct, ec, an, dv [Clinical Trial, Endogenous Compound, Drug Analysis, Drug Development]
2 bnp.tw.
3 nt-probnp.tw.
4 brain-type natriuretic peptide.tw.
5 bnp 1-32.tw.
6 bnp1-32.tw.
7 bnp-32.tw.
8 bnp77-108.tw.
9 bnp 77-108.tw.
10 probnp.tw.
11 nt-probnp1-76.tw.
12 nt-probnp 1-76.tw.

13 natriuretic factor-32.tw.
14 natriuretic peptide type-b.tw.
15 type-b natriuretic peptide.tw.
16 ventricular natriuretic peptide.tw.
17 or/1-16
18 (“1989$” or “1990$” or “1991$” or “1992$” or “1993$” or “1994$” or “1995$” or “1996$” or “1997$” or “1998$” or “1999$” or “2000$” or “2001$” or “2002$” or “2003$” or “2004$” or “2005$” or “2006$” or “2007$” or “2008$” or “2009$” or “2010$” or “2011$”).ew.
19 17 and 18
20 limit 19 to (human and english language)
21 limit 20 to “review”
22 20 not 21
23 Brain Natriuretic Peptide/ct, ec, an, dv [Clinical Trial, Endogenous Compound, Drug Analysis, Drug Development]
24 bnp.tw.
25 nt-probnp.tw.
26 brain-type natriuretic peptide.tw.
27 bnp 1-32.tw.
28 bnp1-32.tw.
29 bnp-32.tw.
30 bnp77-108.tw.
31 bnp 77-108.tw.
32 probnp.tw.
33 nt-probnp1-76.tw.
34 nt-probnp 1-76.tw.
35 natriuretic factor-32.tw.
36 natriuretic peptide type-b.tw.
37 type-b natriuretic peptide.tw.
38 ventricular natriuretic peptide.tw.
39 or/23-38
40 (“1989$” or “1990$” or “1991$” or “1992$” or “1993$” or “1994$” or “1995$” or “1996$” or “1997$” or “1998$” or “1999$” or “2000$” or “2001$” or “2002$” or “2003$” or “2004$” or “2005$” or “2006$” or “2007$” or “2008$” or “2009$” or “2010$” or “2011$”).ew.
41 39 and 40
42 human/
43 animal/
44 animal experiment/
45 43 or 44
46 42 and 45
47 45 not 46
48 41 and 47
49 41 not 48
50 49 not 22
51 limit 50 to english language

Cochrane-EBM Reviews

(Cochrane Central Register of Controlled Trials (CCRT), Cochrane Database of Systematic Reviews (CDSR)

June 25, 2012
1 Natriuretic Peptide, Brain/me, bi, bl, se, du [Metabolism, Biosynthesis, Blood, Secretion, Diagnostic Use]
2 bnp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 nt-probnp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 brain-type natriuretic peptide.tw.
5 bnp1-32.tw.
6 bnp-32.tw.
7 bnp77-108.tw.
8 probnp.tw.
9 nt-probnp1-76.tw.
10 natriuretic factor-32.tw.
11 natriuretic peptide type-b.tw.
12 type-b natriuretic peptide.tw.
13 ventricular natriuretic peptide.tw.
14 or/1-13
15 limit 14 to yr=1989-Current

AMED

June 25, 2012
1 exp peptides/
2 bnp.tw.
3 nt-probnp.tw.
4 brain-type natriuretic peptide.tw.
5 bnp 1-32.tw.
6 bnp-32.tw.
7 bnp77-108.tw.
8 probnp.tw.
9 nt-probnp1-76.tw.
10 natriuretic factor-32.tw.
11 natriuretic peptide type-b.tw.
12 type-b natriuretic peptide.tw.
13 ventricular natriuretic peptide.tw.
14 or/1-13
15 limit 14 to yr=1989-Current

CINAHL

June 25, 2012
1 exp Peptides/an, me, bl, ph, st, df, du, ur [Analysis, Metabolism, Blood, Physiology, Standards, Deficiency, Diagnostic Use, Urine]
2 nt-probnp.tw.

3 brain-type natriuretic peptide.tw.
4 bnp 1-32.tw.
5 bnp-32.tw.
6 bnp77-108.tw.
7 probnp.tw.
8 nt-probnp1-76.tw.
9 natriuretic factor-32.tw.
10 natriuretic peptide type-b.tw.
11 type-b natriuretic peptide.tw.
12 ventricular natriuretic peptide.tw.
13 or/1-12
14 limit 13 to yr=1989-2011

Appendix B. FDA Cleared Devices

Table B-1. Details of FDA approved BNP tests characteristics

Test/Instrument Name	Company Name	510(k) Number
Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA)	Axis-Shield Diagnostics	k033606
ADVIA Centaur® B -Type Natriuretic Peptide (BNP) Assay	Bayer HealthCare LLC	k031038
Bayer Diagnostics ADVIA® Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay	Bayer HealthCare LLC	k043228 k040425
B-type Natriuretic Peptide (BNP) Assay for the ADVIA IMS	Bayer HealthCare LLC	k051265
Triage® B-Type Natriuretic Peptide (BNP) Test	Biosite Incorporated	k051787 k032235 k021317 k010266 k003475
Triage® B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems	Biosite Incorporated	k052789 k033383
Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method	Dade Behring, Inc.	k071767 k042347 k041417
ARCHITECT BNP Reagent Kit	Fujirebio Diagnostics, Inc.	k060964
i-STAT BNP test	i-STAT Corporation	k053597
StatusFirst™ CHF NT-proBNP	Nanogen, Inc.	k051596
Triage® CardioProfilER® Panel	Biosite Incorporated	k080269 k030286
Triage® Profiler S.O.B. ™ (Shortness of Breath Panel)	Biosite Incorporated	k080269 k042723 k040437

Table B-2. Details of FDA approved NT-proBNP tests characteristics

Test/Instrument Name	Company Name	510(k) Number
VIDAS® NT-proBNP	bioMerieux, Inc	k073091
Dimension® Vista™ NT-proBNP (PBNP) Flex® reagent cartridge method (K6423)	Dade Behring, Inc.	k061795
Stratus CS® Acute Care™ NT-proBNP (pBNP) TestPak assay	Dade Behring, Inc.	k071834 k060548 k043476
PATHFAST NTproBNP test	Mitsubishi Kagaku Iatron Inc. c/o Polymedco Inc.	k072189
VITROS Immunodiagnostic NT-proBNP Reagent Pack	Ortho-Clinical Diagnostics, Inc.	k060632
RAMP NT-proBNP Assay	Response Biomedical Corporation	k063662
Elecsys® proBNP II Immunoassay	Roche Diagnostics Corporation	k072437
Elecsys® proBNP II STAT Immunoassay	Roche Diagnostics Corporation	k092649
Elecsys® proBNP Immunoassay	Roche Diagnostics Corporation	k051382 k032646 k022516
Dimension® EXLTm N-termninal Pro-Brain Natriuretic Peptide (NTP) Flex® Reagent Cartridge (RF623)	Siemens Healthcare Diagnostics Inc.	k082645
Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Flex® Reagent Cartridge (K6423A)	Siemens Healthcare Diagnostics, Inc.	k080578

Appendix C. Study Selection and Criteria Forms

Title & Abstract level 1

1. Does citation evaluate BNP in any way? (using any related term: BNP, NTproBNP, 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)
Yes
No

Title & Abstract Level 2

1. Is this study published in English?
Yes (unsure)
No (stop)

2. Does this study involve humans aged 18 years or older?
Yes/unsure
No (non-human) (Stop)
No (under 18 years) (stop)

3. Does this report describe a primary study?
Yes (unsure)
No (stop)
No, systematic review (stop)

4. Is this a case report n=1?
Yes (stop)
No/unsure (submit)

Title & Abstract level 3 - keyword screen

1. Does this citation contain the word “variation”?
Yes
No

2. Does this citation contain any of the following words “heart failure” OR “dyspnea” OR “shortness of breath” OR “cardiac failure” OR “systolic failure” OR “diastolic failure” OR “congestive failure” OR “high-output failure” OR “high output failure” OR “low-output failure” OR “low output failure” OR “right-sided failure” OR “right sided failure” OR “left-sided failure” OR “left sided failure” OR “ventricular failure” OR “auricular failure” OR “atrial failure” OR “myocardial failure” OR “cardiac decompensation” OR “heart decompensation” OR “cardiac insufficiency” OR “myocardial insufficiency” OR CHF OR “cardiac edema” OR “paroxysmal dyspnea”?
Yes
No

3. Does this citation contain any of the following words: “general population” or “unselected” or “cohort”?
Yes
No

4. Does NOT contain any of the words above
Exclude

Full Text Screen Level 4
1. Is this paper available for viewing?
Yes No, please gives reasons

2. Is this study published in English?
Yes
No (stop)

3. Does this study involve humans aged 18 years or older?
Yes
No(non-human)(Stop)
No (under 18 years only)(stop)

4. Does this report describe a primary study?
Yes
No (stop)
No, systematic review (stop)

5. Is this a case report or case series?
Yes case report (n=1) (stop)
Yes, case series (specify number of subjects(s))
No (continue)

6. Was BNP or NT-proBNP measured in serum, plasma or whole blood using an FDA approved method? (please consult FDA approved list)
Yes
No (stop)
Unsure (to be viewed by principal investigators) (continue, and please give reasons for uncertainty)

Note: The following questions (7, 8, 9, 10, & 11) will determine inclusion/exclusion of this article and the Key Question(s) it will be assigned to.

7. Does this study report test accuracy data for the diagnosis of heart failure? Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.
Yes, in Emergency Department /Urgent Care setting
Yes, in Primary Care setting
Yes, reports diagnostic accuracy but not one of the above populations
No, not a diagnostic study

8. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.
Yes, in a heart failure population
Yes, in general population not selected for disease
Yes, prognosis but not any of the above populations
No, not a prognosis study

9. Is this an RCT comparing treatment guided by BNP or NT-proBNP to usual care?
Yes, in an outpatient setting (patients with chronic HP)
Yes, but in other setting
No, not a therapy study

10. Is biological variation of BNP or NT-proBNP reported? *Look for terms such as biological variation, intra-individual variation, and inter-individual variation used to describe this data.*
Yes No

11. Does this study have ALL of the following options ticked: 7c or 7d, 8c or 8d, 9c, and 10b (options in CAPS above)?
Yes No

KQ 1 & 2 Investigators Screening
1. Which location did the study take place?
Emergency Department or Urgent Care Settings or Both
Primary Care Setting (i.e. community or family practice or equivalent)
Both Primary Care setting and Emergency Department/Urgent Care settings (STOP)
None of the above (STOP)
Unclear (continue)

2. Did patients have prior diagnosis of HF?
(Note: We are excluding subject with already known diagnosis of heart failure, which includes acute HF or known exacerbation of stable chronic HF.)
No/ Unclear (continue)
Yes (STOP)

3. Did the study only include patients with one or more of the following conditions: Heart Transplant, Hypertrophic Cardiomyopathy, and Valvular Lesions?
No/ Unclear (continue)
Yes (STOP)

4. Did the study describe patients who are recruited as having signs and symptoms suggestive of HF or at risk of HF?
(Note: only including studies that recruit patients who arrive to emergency or urgent care department with signs or symptoms consistent with HF, and excluding studies that recruit patients already diagnosed with acute HF or known exacerbation of stable chronic HF.)
Yes/ Unclear (continue)
No (STOP)

5. Was this a case report or a case series study?
No/Unclear (continue)
Yes (STOP)

6. Does this study report test accuracy data for the diagnosis of heart failure? Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.
Yes/ Unclear (continue)
No (STOP)

7. Does this paper belong in the Diagnosis section?
Yes (continue)
No, not a diagnosis study
Reports diagnostic accuracy but not one of the above populations
Unsure (to be viewed by another investigator)

8. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 7.
Diagnosis and RCT
Diagnosis and Case Control
Diagnosis and Cohort
Diagnosis and Cross-Sectional Design
Not a diagnosis study
Unclear

9. (OPTIONAL) Would you recommend this paper be considered for another section?
No
Yes (which one?)

10. (OPTIONAL) Comments:

KQ 3 & 4 Investigators Screening

1. Which location did the study take place?
Outpatient Clinic or Ambulatory Care or Family Practice
Admitted to hospital
None of the above (STOP)
Unclear (continue)

2. Were participants patients with Heart Failure (HF), with or without co-morbidities?
Yes/ Unclear (continue)
No (STOP)

3. Is this study an RCT/CCT, cohort, before-after or time series?
Yes/ Unclear (continue)
No (STOP)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome?
Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.
Yes/ Unclear (continue)
No (STOP)

5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study
Prognosis, but not any of the above populations for KQ3,4; does not have the outcome of interest
Unsure (to be viewed by another investigator)

6. What type of study is this?
*Only complete this question if you have answered "Yes (continue)" to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear

7. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)

8. (OPTIONAL) Comments:

KQ 5 Investigators Screening

1. Is the study population drawn from the general population? (e.g. community-based, primary care, family practice, or equivalent)
Yes/ Unclear (continue)
No (stop)

2. Did this study use a specific disease to include or exclude subjects (i.e. acute coronary syndrome (ACS), CAD, Diabetes, Renal Failure, etc.)? (Note: We are only looking for studies that recruit the general population (i.e. population with a mixture of conditions), not a population with a specific disease as inclusion or exclusion criteria).
No/ Unclear (continue)
Yes (stop)

3. Is the study an RCT/CCT, cohort, before-after or time series?
Yes
No (stop)
Unclear (continue)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome?
Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.
Yes/ Unclear (continue)
No (stop)

5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study at all
Prognosis, but not any of the above populations for KQ5; does not have the outcome of interest
Unsure (to be viewed by another investigator)

6. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear

7. (OPTIONAL) Would you recommend this paper for consideration in another section?
No Yes (which one?)

8. (OPTIONAL) Comments:

KQ 6 Investigators Screening
1. Are the study patients being treated for chronic HF (exclude if patients are admitted or are known HF patients with acute HF)?
Yes, patients are treated for chronic HF
No (EXCLUDE)(STOP)

2. Was this an RCT where medical therapy was based on BNP/NT-proBNP OR usual care for HF patients (there is no restriction on usual care; only needs to be defined)?
Yes, RCT
No (EXCLUDE)

KQ 7 Investigators Screening
1. Does this study report biological variation data?
Yes
No

KQ 1B & 2B Investigators Screening
1. Which location did the study take place?
Emergency Department or Urgent Care Settings or Both
Primary Care Setting (i.e. community or family practice or equivalent)
Both Primary Care setting and Emergency Department/Urgent Care settings (STOP)
None of the above (STOP)
Unclear (continue)

2. Did patients have prior diagnosis of HF? (Note: We are excluding subject with already known diagnosis of heart failure, which includes acute HF or known exacerbation of stable chronic HF.)
No/ Unclear (continue)
Yes (STOP)

3. Did the study only include patients with one or more of the following conditions: Heart Transplant, Hypertrophic Cardiomyopathy, and Valvular Lesions?
No/ Unclear (continue)
Yes (STOP)

4. Did the study describe patients who are recruited as having signs and symptoms suggestive of HF or at risk of HF? (Note: We are only including studies that recruit patients who arrive to emergency or urgent care department with signs or symptoms consistent with HF, and excluding studies that recruit patients already diagnosed with acute HF or known exacerbation of stable chronic HF.)
Yes/ Unclear (continue)
No (STOP)

5. Was this a case report or a case series study?
No/ Unclear (continue)
Yes (STOP)

6. Does this study report test accuracy data for the diagnosis of heart failure? Look for terms such as: sensitivity/specificity, +/- predictive value, ROC curves, likelihood ratios, and test accuracy.
Yes/ Unclear (continue)
No (STOP)

7. Does this paper belong in the Diagnosis section?
Yes (continue)
No, not a diagnosis study
Reports diagnostic accuracy but not one of the above populations

8. What type of study is this? *Only complete this question if you have answered "Yes (continue)" to question # 7.
Diagnosis and RCT
Diagnosis and Case Control
Diagnosis and Cohort
Diagnosis and Cross-Sectional Design
Not a Diagnosis study
Unclear

9. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)

10. (OPTIONAL) Comments:

KQ 3B & 4B Investigators Screening
1. Which location did the study take place?
Outpatient Clinic or Ambulatory Care or Family Practice
Admitted to hospital
None of the above (STOP)

2. Were participants patients with Heart Failure (HF), with or without co-morbidities?
Yes
No (STOP)

3. Is this study an RCT/CCT, cohort, before-after or time series?
Yes
No (STOP)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? (Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.)
Yes
No (STOP)

5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study (STOP)
Prognosis but not any of the above populations (STOP)

6. What type of study is this? (*Only complete this question if you have answered "Yes (continue)" to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design

7. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)

8. (OPTIONAL) Comments:

KQ 5B Investigators Screening
1. Is the study population drawn from the general population? (e.g. community-based, primary care, family practice, or equivalent)
Yes/ Unclear (continue)
No (STOP)

2. Did this study use a specific disease to include or exclude subjects (i.e. acute coronary syndrome (ACS), CAD, Diabetes, Renal Failure, etc.)? *(Note: We are only looking for studies that recruit the general population (i.e. population with a mixture of conditions), not a population with a specific disease as inclusion or exclusion criteria).*
No/ Unclear (continue)
Yes (STOP)

3. Is the study an RCT/CCT, cohort, before-after or time series?
Yes/ Unclear (continue)
No (STOP)

4. Does this study provide a statistical measure of prognosis demonstrating BNP or NT-proBNP as an independent predictor of outcome? (Look for terms such as: multivariate or adjusted odds ratio, adjusted risk ratio, hazards ratio, and Kaplan-Meier curves.)
Yes/ Unclear (continue)
No (STOP)

5. Does this paper belong in the Prognosis section?
Yes (continue)
No, not a prognosis study
Prognosis but not any of the above populations

6. What type of study is this?
*Only complete this question if you have answered “Yes (continue)” to question # 5.
Prognosis and RCT
Prognosis and Case Control
Prognosis and Cohort
Prognosis and Cross-Sectional Design
Not a prognosis study
Unclear

7. (OPTIONAL) Would you recommend this paper to another section?
No
Yes (which one?)

8. (OPTIONAL) Comments:

Appendix D. Extraction Forms

General Data Extraction Form

1. Which peptide was assessed?

- e.g. BNP
- e.g. NT-proBNP
- e.g. Both

2. In what country was the study conducted or administrated?

Please specify the country where the study was conducted. Note that in some papers only the city/province will be reported, e.g. Copenhagen. In such case, please choose "Others" and report the city's name. For countries not listed in the drop-down option, please choose "Others" and specify.

3. What was the study type?

Please specify study type. Note that the provided list may not contain all the study types, but these are the most common. You may also refer to "Study Design Descriptions" for definition.

4. What is the total number of patients included in the study?

Please report all that apply.

Total # enrolled (n) = *Total number of subjects who meet the inclusion criteria of the study/randomized.*

Total treatment (n) (e.g. "n" of index group) = *Total number of patients in each group who are randomized into the BNP/NT-proBNP or clinical intervention.*

Total control (n) (e.g. "n" of reference group) = *Total number of patient who are receiving receiving usual care/standard care/clinical group.*

- Example = 500 patients are enrolled in the study, but only 450 meets the inclusion criteria. After randomization, 225 receives BNP-guided treatment, while 225 receives usual-care. Therefore:

Total # enrolled (n) = 450
Total treatment (n) (e.g. "n" of index group) = 225
Total control (n) (e.g. "n" of reference group) = 225

5. Please report the AGE CHARACTERISTICS for:

Please record as reported.

6. Please report the AGE GROUPS, if applicable:
If the study reported the group age as, e.g. ≤50 yrs or ≥50yrs, please report the sign as <=50 yrs or >=50 yrs.

7. Please report GENDER:
Please record as reported.

8. Please report Race/Ethnicity:
Please record as reported.

9. Please describe the population included in the study:
Please record as reported the population characteristics.

10. Please describe the following outcomes/end-points:

Primary outcome/end-points: *The primary outcome that is measured to see if a given treatment worked (e.g., the number of all-cause mortality, number of hospitalization).*

Secondary outcome/end-points: *Other outcomes reported in the study.*

11. What other medical conditions (co-morbidities) did the patients have? (Check and record all that apply)
Please record as reported.

12. Which test was used to measure BNP or/and NT-proBNP
Please record as reported.

13. List and report (n,%) the adverse events associated with BNP/NT-proBNP testing reported?
Please record as reported. E.g. Hypotension, renal failure, etc.

<u>Key Question: 1 & 2 Data Extraction Form</u>

RefID:

Author:
Please record first author's last name and the year of the publication.

Setting:

- Emergency Department/Urgent Care
- Primary Care (community/family practice or equivalent)

Test

Please specify either BNP or NT-proBNP or both that was tested, and specify unit(s) (e.g. pg/ml; pmol/l).

- BNP
- NT-proBNP

Prevalence

Please report % of prevalence.
(Definition of Prevalence: The proportion of people in a defined group who have a disease, condition or injury. In the context of diagnosis, this is also called "pre-test probability.")

Mean BNP/NT-proBNP

Provide mean of BNP/NT-proBNP and corresponding SD (in brackets) for study samples; Specify units (pg/ml, pmol/l)

Decision Cut Point

For studies that report decision cut points, provide all the cut points in this column with the units (pg/ml, pmol/l). Remember to report all corresponding test performance measures (sens, spec, etc.) in their appropriate columns.

Population

Report all population characteristics: Comorbidities, Age Categories, Gender, and Race Groups. If studies provided results of test performances by these populations (commorbidities, age categories, gender, and race groups), remember to report all test performance measures in their appropriate column).

- Overall
- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)
- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)

Sens (sensitivity)

Please express sensitivity in proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).

Confidence level

Where reported, specify level of confidence (e.g. 95%, 90%)

Sens.lower/upper (sensitivity lower/upper)
Please express sensitivity's confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).

Spec. (specificity)
Please express specificity as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)

Spec. lower/upper (specificity lower/upper)
Please express specificity confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)

PLR (positive likelihood ratio) *Please record as reported.*

Plr.lower/upper (lower/upper confidence interval for positive likelihood ratio)
Please record as reported.

Negative LR (negative likelihood ratio) *Please record as reported.*

Nlr.lower/upper (lower/upper confidence interval for negative likelihood ratio)
Please record as reported.

TP (true positive) *Please record as reported.*

FP (false positive) *Please record as reported.*

FN (false positive) *Please record as reported.*

TN (true negative) *Please record as reported.*

n (sample size for study) *Please record as reported.*

PPV (positive predictive value) *Please record as reported.*
PPV lower(Positive predictive value lower confidence interval *Please record as reported.*

PPV Upper (Positive predictive value upper confidence interval *Please record as reported.*

NPV (negative predictive value) *Please record as reported.*

NPV lower(Negative predictive value lower confidence interval *Please record as reported.*

NPV Upper (Negative predictive value upper confidence interval *Please record as reported.*

Diagnostic Accuracy *Please record as reported*

AUC (area under the curve) *Please record as reported.*

AUC lower(Area under curve lower confidence interval *Please record as reported.*

AUC upper(Area under curve upper confidence interval *Please record as reported.*

Pre-test Probability *Please record as reported.*
(Definition of Pre-test Probability: The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence).)

Pre-test Odds *Please record as reported.*
(Definition of Pre-test Odds: The odds that the patient has the target disorder before the test is carried out.)

Post-test Probability *Please record as reported.*
(Definition of Post-test Probability: The proportion of patients with that particular test result who have the target disorder.)

Post-test Odds *Please record as reported.*
(Definition of Post-test Odds: The odds that the patient has the target disorder after the test is carried out.)

Key Question: 3, 4, & 5 Data Extraction Form

RefID:

Screener: *Please record your name.*

Author, Year: *Please record first author's last name and the year of the publication.*

Setting:

- Hospital
- Outpatient Clinic/Ambulatory care
- Family practice

Study Design *Please refer to* ***Study Design Descriptions*** *if needed.*

- Randomized Controlled Trials (RCTs)
- Controlled Clinical Trials (CCTs)
- Cohort
- Before/After/Time-series

n (overall sample size for study and specific populations) *Please record as reported.*

Population

Report all population characteristics: Comorbidities, Age Categories, Gender, Race Groups, Population Sub-types, BNP cut-points, and Prognostic Tools used. If studies provided results or information of outcomes, time-points, admissions/discharge/change, statistical measures (e.g. HR, OR), etc. for specific populations, please remember to report all in their appropriate column).

- Overall
- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)
- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)
- Population Sub-types Types (e.g. survivors/non-survivors, with/without readmission or death, acute/chronic or chronic with acute, etc.)
- BNP/NT-proBNP cut-points (e.g. BNP >= 541, BNP < 541)
- Prognostic measures (e.g. NYHA, ejection fraction, electrocardiographic measures, etc.).
- Doubling of NT-proBNP
- Quintile 1
- Quintile 2
- Tertile 1

***Please note that population characteristics will vary across studies. Please capture all that is reported. The above list is only an example.**

Specify Population Units

Specify units (pg/ml, pmol/l) for corresponding population characteristics.

Sub-population

Utilize this column for sub-population descriptions. For instance, if study tested a group of survivors (population) within a BNP level or >=541 (sub-population).

- Age categories (e.g. age>50, age<50)
- Gender (Female/Male)
- Comorbidities (e.g. Non-Dysponea/Dysponea/Diabetes/)
- Race/ethnicity (e.g. White/Hispanic/Caucasian/Asians)
- Population Sub-types Types (e.g. survivors/non-survivors, with/without readmission or death, acute/chronic or chronic with acute, etc.)
- BNP/NT-proBNP cut-points (e.g. BNP >= 541, BNP < 541)
- Prognostic Tools (e.g. NYHA, ejection fraction, electrocardiographic measures, etc.).

*__Please note that population characteristics will vary across studies. Please capture all that is reported. The above list is only an example.__

Kaplan-Meier
Please specify if the number of events and timepoints of outcome assessments were extracted from Kaplan-Meier Curve. Please record a "Yes" or "No."

Timepoint of Outcome Assessments
Report all the different times of outcome assessments (e.g. 6 months, during hospital stay). Time of assessments will differ across studies, could be days, weeks, months or years.

Outcome Type
Please report all types of outcomes.

- All-Cause Mortality
- Heart Failure Mortality
- All-Cause Hospitalization
- Number of Hospitalization
- Heart Failure Hospitalization
- Planned Hospitalization
- Unplanned Hospitalization

# of Events *Please record number of events according to the outcomes, as reported in Outcome Type column.*

 # at Risk *Please record number of risk according to the total number of patients in each group.*

BNP/NT-proBNP Admission Levels (Mean)
Report all Mean levels of BNP/NT-proBNP during Admission.

BNP/NT-proBNP Admission Levels (SD) *Please also specify standard deviations of admission levels.*

BNP/NT-proBNP Admission Levels (Median) *Please also specify the median of admission levels.*

BNP/NT-proBNP Admission Levels (IQR) *Please also specify the interquartile range of admission levels.*

BNP/NT-proBNP Discharge Levels (Mean) *Report all Mean levels of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Discharge Levels (SD) *Please also specify standard deviations of Discharge levels.*

BNP/NT-proBNP Discharge Levels (Median) *Report all Median levels of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Discharge Levels (IQR) *Report all interquartile range of BNP/NT-proBNP during Discharge.*

BNP/NT-proBNP Change (Mean) *If provided, please report the Mean change of BNP/NT-proBNP.*

BNP/NT-proBNP Change (SD) *Please also specify standard deviations of change in BNP/NT-proBNP levels.*

BNP/NT-proBNP Change (Median) *Please also specify the median of change in BNP/NT-proBNP levels.*

BNP/NT-proBNP Change (IQR) *Please also specify interquartile range of change in BNP/NT-proBNP levels.*

Specify BNP/NT-proBNP Units *Specify units (pg/ml, pmol/l) for corresponding BNP/NT-proBNP Levels.*

Confidence Level (%) *Where reported, specify level of confidence (e.g. 95%, 90%)*

Model Used *Specify type of statistical model used. e.g. cox proportional, logistic regression*

Adjusted/Unadjusted *Please report whether the model used was adjusted or unadjusted.*

Covariates in the Model, if Adjusted *If model is adjusted, please report the variable that were adjusted for. E.g. Age, Gender, LVEF, BNP cutpoint, etc.*

HR (Hazard Ratio) *Please record as reported.*

HR LCI/UCI (lower/upper confidence interval for hazard ratio) *Please record as reported.*

RR (Risk Ratio/Relative Risk) *Please record as reported.*

RR LCI/UCI (lower/upper confidence interval for risk ratio) *Please record as reported.*

OR (Odds Ratio) *Please record as reported.*

OR LCI/UCI (lower/upper confidence interval for odds ratio) *Please record as reported.*

Positive LR (positive likelihood ratio) *Please record as reported.*

Positive LR.lower/upper (lower/upper confidence interval for positive likelihood ratio) *Please record as reported.*

Negative LR (negative likelihood ratio) *Please record as reported.*

Negative LR.lower/upper (lower/upper confidence interval for negative likelihood ratio) *Please record as reported.*

Sensitivity *Please express sensitivity in proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).*

Sens.lower/upper (sensitivity lower/upper) *Please express sensitivity's confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65).*

Specificity *Please express specificity as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)*
Spec. lower/upper (specificity lower/upper) *Please express specificity confidence level limits as proportions (e.g. if study have expressed sensitivity in percentage (e.g. 65%), report it as 0.65)*

AUC (Area under the curve) *Please record as a proportion.*

Any Comments *Please use this column for any comments.*

Appendix E. Assessment of Risk of Bias

Assessment of Risk of Bias: Prognosis Studies

Risk of bias of prognosis studies was assessed using a modified version of the guidelines proposed by Hayden, et al.

To enhance the appropriateness of Hayden's guidelines to this review, several modifications were made to the guidelines prior to commencing the assessment of risk of bias. We modified the tool by adding a seventh area of bias (i.e., study design) for which we asked whether the included studies were designed to test the prognostic value of BNP or NT-proBNP (the studies were not secondary analyses of data collected for other purposes).

The tool was further modified by the revising or adding several domains to the areas of bias, as described in Table 1, and expanded on below:

- Prognostic factor measurement:
  - For the 'other prognostic factors measured appropriately' domain, we decided this domain would only be applicable if a study in question compares BNP or NT-proBNP to some other prognostic indicator
  - We added a new domain: "For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data were reported"
  - We added a second new domain: "For other prognostic factors, the extent of and reasons for indeterminate test results or missing data were reported (applicable when a study in question compares BNP/NT-proBNP to other prognostic indicators)"
- Outcome measurement:
  - We added a new domain: "The study avoided the use of a composite outcome".

Hayden, et al., provide a guide to using their tool, which we also adapted for use with our modified version. The modifications that have been made to the tool involved the elimination of several signaling questions that we felt were not relevant to the review:

- Study Attrition:
  - We dropped "Attempts to collect information on participants who dropped out of the study are described" because authors of included studies would largely be unable to accomplish this task;
- Prognostic Factor Measurement:
  - We eliminated "Adequate proportion of the study sample has complete data for prognostic factors" and "Appropriate methods are used if imputation is used for missing prognostic factor data" because BNP or NT-proBNP is routinely collected and imputation, even if performed, would not likely be reported by study authors;
- Measuring and Accounting for Confounding:
  - We dropped "The method and setting of confounding measurement are the same for all study participants" because BNP or NT-proBNP is the focus of most studies and detailed reporting of confounders would not be of the highest priority for study authors;
- Analysis:
  - We eliminated "The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model" and "There is no selective reporting of results" because we felt that commenting on model building and

selective reporting would not be suitable for this review, especially given the diversity of strategies that BNP or NT-proBNP researchers may employ in their work.

The final modification involved a change in the response options used to express the degree of bias. Hayden, et. al. originally suggested 'yes', 'no', 'partly', and 'unsure' as possible responses to each domain and potential bias item. However, in accordance with the methodology checklist for prognostic studies adapted from Hayden's work and developed by the National Institute for Health and Clinical Excellence (NICE), we opted for the simplified response categories of 'yes', 'no' and 'unclear'. Within each domain, an answer of 'no' corresponds to a high risk of bias, 'unclear' corresponds to a possible or unclear risk of bias, and 'yes' corresponds to a low risk of bias.

Assessment of Risk of Bias: Diagnosis Studies

The QUADAS-2was used to assess the risk of bias of diagnostic studies. The investigators tailored the QUADAS-2 to this review by discussing whether some of the tool's signaling questions should be removed from consideration. The signaling questions are intended to help researchers judge the risk of bias in each of the four domains on the QUADAS-2. This discussion took place prior to the start of quality assessment. We decided to omit the following signaling questions from "Flow and Timing":

- *"Was there an appropriate interval between index test(s) and reference standard:"* Since the inclusion criteria for the diagnosis questions required that all blood samples had to be collected on admission or discharge, we deemed this question to be irrelevant.
- *"Did all patients receive a reference standard?"*: This question was not relevant to the review because the inclusion criteria specified the use of standard diagnostic criteria for determining HF in included studies (the criteria had to be applied independent of BNP or NT-proBNP test values). This question would only be applicable if there are specific reference standards to determine whether these test values are used or if the screening question was not specific enough to exclude studies where only some patients were diagnosed with HF.

Each signalling question requires a 'yes', 'no', or 'unclear' response. We developed decision rules to consolidate 'yes', 'no', or 'unclear' responses to the signaling questions into a single 'yes', 'no', or 'unclear' response for each risk of bias question (one risk of bias question per domain).

The decision rules are shown in Table E-1 below.

Table E-1. Decision rules to consolidate responses to QUADAS-2 signaling questions into responses to QUADAS-2 risk of bias questions

Domains 1 and 4: Patient Selection and Flow and Timing (3 questions each domain)
All yes's* = low risk of bias;
All no's* = high risk of bias; or
All unclear* = unclear.
Mixed categories default to the lowest category:
2 yes, 1 no* = high risk of bias;
2 yes, 1 unclear* = unclear;
2 no, 1 yes* = high risk of bias;
2 no, 1 unclear* = high risk of bias;
2 unclear, 1 no* = high risk of bias;
2 unclear, 1 yes* = unclear; or
1 yes, 1 no, 1 unclear* = unclear.
Domains 2 and 3 : Index Test and Reference Standard (2 questions each domain)
Both yes's* = low risk of bias;
Both no's* = high risk of bias;
Both unclear* = unclear;
1 yes, 1 no* = high risk of bias;
1 yes, 1 unclear* = unclear; or
1 no, 1 unclear* = high risk of bias.

*Mix of responses to signaling questions.

QUADAS-2 requires an assessment of the extent to which each included study is applicable to the review. Applicability is rated 'high', 'low', or 'unclear' and is assessed separately for three questions. We assessed applicability for each question as described below.

- "*Are there concerns that the included patients and setting do not match the review questions?*": Studies excluding patients with chest trauma, hemodialysis, asthma, COPD, and dyspnea clearly due to causes other than HF (e.g., pneumothorax, coronary ischemia, myocardial infraction) were not seen as a threat to applicability (rated high in applicability). Studies excluding patients with any other diagnosis or comorbidity besides the ones mentioned above raised concerns about applicability. For example, studies excluding patients because of increased body mass index may have unclear or low applicability because BNP and NT-proBNP decrease as body mass increases. Studies that excluded patients on certain medications, excluded difficult-to-diagnose patients or included only easy-to-diagnose patients, restricted the sample to males or females only, or restricted the sample to certain age groups, were regarded as having unclear or low applicability.
- "*Are there concerns that the index test, its conduct, or its interpretation differ from the review question?*": Since we included studies that utilized FDA approved assay methods, we determined a priori that concerns about applicability were unlikely to exist in this domain (most studies would be rated high in applicability).
- "*Is there concern that the target condition as defined by the reference standard does not match the review question?*": We employed a broad list of acceptable reference tests in this review, so we determined a priori that concerns about applicability were unlikely to exist for most studies in this domain. However, since HF is typically diagnosed using a battery of tests and criteria, applicability was classified as unclear or low in the case of included studies that employed an unusually large number of tests or criteria. Similarly, applicability was classified as unclear or low in studies that employed a single reference test or criterion.

Investigators with previous experience conducting systematic reviews assessed the quality of all RCTs and cross-sectional studies. For quality assessments conducted using the NOS, Hayden, et al. criteria, and QUADAS-2, investigators trained a pool of raters. Training included a description of the background and objectives of the systematic review, an examination of the quality assessment instruments to explain the meaning of questions and develop a standardized approach to answering the questions, and pilot rating phases to test the instruments and resolve inconsistencies in interpreting and answering questions.

Grading the Strength of the Body of Evidence

In principle, a body of evidence from randomized trials starts with a presumed high strength of evidence, and is downgraded across the domains when there are important overall risk of bias of contributing studies, inconsistency in direction of intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome rather than a clinical health outcome), and imprecision. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence is graded based on the following four domains: overall risk of bias by outcome, consistency, directness, and precision. A methodologist and a content expert grades the strength of the body of evidence as "High," "Moderate," "Low," or "Insufficient" (Table E-2). A third methodologist with clinical background adjudicated to resolve disagreements.

Given the results we found, optional domains such as, dose-response association and existence of confounders, were not applicable in this comparative effectiveness review. Given the uncertainties involved in interpreting asymmetry tests for publication bias,

mainly in the presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.

The strength of evidence was graded insufficient when the following occur: no evidence for an outcome, direction of estimates were inconsistent between studies without an identifiable cause, or the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). That is, when the effect estimate associated with confidence intervals was not only non-significant, but wide enough such that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the estimate as imprecise. If an effect estimate is rated as imprecise, this reflects our uncertainty about clinically important benefits, harms or clinically unimportant differences in effect estimates between the contrasting interventions. Customarily only a subset of important outcomes are chosen to grade the strength of evidence—outcomes that are most meaningful for decision-making given a specific Key Question.

Table E-2. Strength of evidence grades and definitions

Strength of evidence grades and definitions Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Appendix F. Quality Assessment Forms

Newcastle Ottawa Scale, Case-Control Studies

1. **Is this a Case/Control study?**
Yes (continue)
No (STOP) (specify type of study)

2. Is the case definition adequate?
Yes, with independent validation*
Yes, eg. record linkage or based on self reports
No description

3. Representativeness of the cases
Consecutive or obviously representative series of cases*
Potential for selection biases or not stated

4. Selection of controls
Community controls*
Hospital controls
No description

5. Definition of Controls
No history of disease (endpoint)*
No description of source

6. Comparability of cases and controls on the basis of the design or analysis
Study controls for (select the most important factor)*:
Study controls for any additional factor* (This could be modified to indicate specific control for a second important factor.)

7. Ascertainment of exposure
Secure record (e.g. surgical records)*
Structured interview where blind to case/control status *
Interview not blinded to case/control status
Written self-report or medical record only
No description

8. Same method of ascertainment for cases and controls
Yes*
No

9. Non-response rate
Same rate for both groups*
Non respondents described
Rate different and no designation

10. Were potential confounders measured and adequately addressed in the analysis?
Yes
No

11. Was the statistical analysis described?
Yes
No

12. Did the authors mention missing data in manuscript?
Yes
No

Newcastle Ottawa Scale -Cohort Studies

1. Is this a Cohort study?
Yes (continue)
No (STOP) (specify type of study)

2. Representativeness of the exposed cohort
Truly representative of the average in the community* (please describe the average cohort)
Somewhat representative of the average in the community* (please describe the average cohort)
Selected group of users eg. nurses, volunteers
No description of the derivation of the cohort

3. Selection of the non-exposed cohort
Drawn from the same community as the exposed cohort*
Drawn from a different source
No description of the derivation of the non-exposed cohort

4. Ascertainment of exposure
Secure record (eg. surgical records)*
Structured interview*
Written self-report
No description

5. Demonstration that outcome of interest was not present at start of study
Yes*
No

6. Comparability of cohorts on the basis of the design or analysis
Study controls for (select the most important factor)*:
Study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)
No relevant adjustments for confounding

7. Assessment of outcome
Independent blind assessment*
Record linkage*
Self report
No description

8. Was follow up long enough for outcomes to occur
Yes (select an adequate follow up period for outcome of interest)*
No

9. Adequacy of follow up of cohorts
Complete follow up- all subjects accounted for*
Subjects lost to follow up unlikely to introduce bias (small number lost) (report an adequate %)*
Follow up rate and no description of those lost (report an adequate %)
No statement

10. Were potential confounders measured and adequately addressed in the analysis?
Yes
No
Unclear

11. Was the statistical analysis described?
Yes
No
Unclear

12. Did the authors mention missing data in manuscript?
Yes
No

QA: Modified Jadad Scale
1. Is this a RCT study?
Yes (continue)
No (STOP) (specify type of study)

2. Double blinding is reported
Yes (1 point)
No

3. Double blinding is appropriate
Yes (1 point)
No (-1 point)
Not described

4. Reported as randomized
Yes (1 Point)
No

5. Randomization is appropriate
Yes (1 point)
No (-1 point)
Not Described

6. Withdrawals are reported by number and reason per arm
Yes (1 point)
No

7. Jadad Score (/5)

8. Method(s) used to assess adverse events is described
Yes (1 point)
No

9. Method(s) of statistical analysis is described
Yes (1 point)
No

10. Inclusion and/or exclusion criteria reported
Yes (1 point if at least one of the requirements is reported)
No

11. Modified Jadad score (/8)

12. Was the allocation adequately concealed? E.g pharmacy controlled randomization scheme, sequentially numbered opaque, sealed envelope, sequentially numbered / coded identical containers, central randomization by phone?
Yes
No
Unclear

13. Was the analysis based on intention to treat principle?
Yes
No
Unclear

14. Was the sample size justified?
Yes
No
Unclear

15. Was the outliers reported and appropriately dealt with in the analysis?
Yes
No

16. Is the role of the study sponsor/ funder (i.e. manufacturer of the device) appropriate?

Is the role of the study sponsor/ funder (i.e. manufacturer of the device) appropriate?
(This question evaluates the role of the study sponsor in the potentially influencing the study conduct, interpretation, or reporting. We ask raters to judge whether "the role of the study sponsor (i.e. manufacturer of the device) appropriate?".)

For low risk of bias, raters would indicate YES (role appropriate) with respect to the following: 1) The funder/ sponsor is identified, and 2) Their specific input/role within the study is also specified such that there is NO or MINIMAL potential to influence study conduct, interpretation, or reporting. For example, a sponsor may provide a device to the study researchers but then had no subsequent involvement in the study development, conduct and reporting. We are looking for a statement from the authors declaring no involvement.

For high risk of bias the raters indicate NO (role is NOT appropriate) with respect to the following: 1) The funder is identified AND their role/input within the study is not explicitly specified 2) The funder is not identified AND their role/input within the study is not explicitly stated. The category of UNSURE is used when information about the study sponsor, device manufacturer, and any potential conflict of interest of the study authors is conflicting or not well reported within the study.)

Yes
No
Unsure

<u>QA: Cross-Sectional Design</u>
1. Is this a Cross-Sectional study?
Yes (continue)
No (STOP) (specify type of study)

Study Population
2. Did the authors clearly describe the population from which the participants were drawn?
Yes
No
Unclear

3. Were the inclusion and/or exclusion criteria described (no specific criteria)?
Yes
No
Unclear

4. Were the participants in the study representative of the population from which they were recruited?
Yes
No
Unclear

Outcome Measurements
5. Was the outcome defined clearly (i.e., was the measure described in sufficient detail to be replicated)?
Yes
No
Unclear

6. Were those measuring the main outcome unaware of the exposure status?
Yes
No
Unclear

Exposure Measurements
7. Was the exposure defined clearly (i.e., was the test method described in sufficient detail to permit replication)?
Yes
No
Unclear

8. Were those measuring the exposure unaware of outcome status?
Yes
No
Unclear

Statistical Analysis
9. Were potential confounders measured and adequately addressed in the analysis?
Yes
No
Unclear

10. Was the statistical analysis described?
Yes
No
Unclear

11. Were missing data reported?
Yes
No

QA Prognosis: Hayden Criteria

1 Study Participation The study population represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results

1 a. Source population clearly defined.
Yes
No
Unclear

1 b. Study population described.
Yes
No
Unclear

1 c. Study population represents source population, or population of interest.
Yes
No
Comment (optional)

2 Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample)

2 a. Completeness of follow-up described.
Yes
No
Unclear

2 b. Completeness of follow-up adequate.
Yes
No
Unclear

3 Prognostic Factors *The prognostic factors of interest are adequately measured in study participants to sufficiently limit potential bias.*

3 a. BNP/NT-proBNP factors defined.
Yes
No
Unclear

3 b. BNP/NT-proBNP factors measured appropriately.
Yes
No
Unclear

3 c. Other prognostic factors measured appropriately.
Yes
No
Unclear
Not Applicable

3 d. For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported.
Yes
No
Unclear

3 e. For other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported.
Yes
No
Unclear
Not Applicable

4 Outcome Measurement *The outcome(s) of interest are adequately measured in study participants to sufficiently limit bias.*

4 a. Outcome defined.
Yes
No
Unclear

4 b. Outcome measured appropriately.
Yes
No
Unclear
Comment (optional)

4 c. A composite outcome was avoided.
Yes
No
Unclear
Comment (optional)

5 Confounding Measurement *Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest*

5 a. Confounders measured.
Yes
No
Unclear

5 b. Confounders accounted for.
Yes
No
Unclear

6 Analysis *The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results*

6 a. Analysis described.
Yes
No
Unclear
Comment (optional)

7 Study Design *7 a. The study was designed to test the prognostic value of BNP or NT-proBNP (i.e. it was not a secondary analysis of data collected for other purposes).*
Yes
No
Unclear

QA: Diagnostic -QUADAS II
1. Is this a Diagnostic study?
Yes (continue)
No (STOP) (specify type of study)

2. Setting:
Emergency Dept.
Primary Care
Unclear

3. Cut point:

4. Which peptide was assessed?
BNP
Nt-ProBNP
Both

Domain 1: Patient Selection
Methods of patient selection: *(Describe included patients (prior testing, presentation, intended use of index test and setting)*
1. Was a consecutive or random sample of patients enrolled? *(define the population in the box/copy and paste from the article)*
Yes
No
Unclear

2. Was a case-control design avoided?
Yes
No
Unclear
3. Did the study avoid inappropriate exclusions?
Yes
No
Unclear

Domain 1: Risk of Bias (will be judge later)
Could the selection of patients have introduced bias?
Low
High
Unclear

Domain 1: Applicability (please click here for help guide)
Are there concerns that the included patients and setting do not match the review question?
Low
High

Domain 2: Index Test(s)
Index Test(s) in this study:

4. Were the index test results interpreted without knowledge of the results of the reference standard?
Yes
No
Unclear

5. If a threshold was used, was it pre-specified?
Yes
No
Unclear

Domain 2: Risk of Bias (will be judge later)
Could the conduct or interpretation of the index test have introduced bias?
Low
High
Unclear

Domain 2: Applicability (please click here for help guide)
Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
Low
High
Unclear

Domain 3: Reference Standard
Reference standard in this study:
6. Is the reference standard likely to correctly classify the target condition?
Yes
No
Unclear

7. Were the reference standard results interpreted without knowledge of the results of the index test?
Yes
No
Unclear

Domain 3: Risk of Bias (will be judge later)
Could the reference standard, its conduct, or its interpretation have introduced bias?
Low
High
Unclear

Domain 3: Applicability (please click here for help guide)
Are there concerns that the target condition as defined by the reference standard does not match the question?
Low
High
Unclear

Domain 4: Flow and Timing
Describe any patient who did not receive the index test(s) and/or reference standard.
Describe the time interval and any interventions between index test (s) and reference standard.

8. Did all patients receive a reference standard?
Yes
No
Unclear

9. Were all patients included in the analysis?
Yes
No
Unclear

Domain 4: Risk of Bias (will be judge later)
Could the patient flow have introduced bias?
Low
High
Unclear

Hayden Criteria Reference Sheet				
1 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Study Participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results (Hayden, Cote, and Bombardier 2006).	**a. Source population clearly defined**	The study reported ALL of the following: • How the sample was identified (e.g. whether a referral was involved, patient of ambulatory care, etc.); • Place of recruitment (admitted to hospital, outpatient clinic/ambulatory care, hospital setting, community, family practice or equivalent, primary care); • The period of recruitment or the duration of follow-up.	The study DID NOT report ALL of the following: • How the sample was identified (e.g. whether a referral was involved, patient of ambulatory care, etc.); • Place of recruitment (e.g. outpatient clinic/ambulatory care, hospital setting, community, family practice or equivalent); • The period of recruitment or the duration of follow-up.	not reported clearly.
	b. Study population described	The study described ALL of the following: • The inclusion and exclusion criteria for all population groups; • Description of all participants at baseline or the start of the follow-up period; • Whether the population groups came from the general population, or as having HF with acute, chronic, or chronic exacerbation, with or without any co-morbidity.	The study did not describe ALL of the following: • The inclusion and exclusion criteria of the sample; • Description of all participants at the start of the follow-up period. • Whether the population came from the general population or having HF with acute, chronic, or chronic exacerbation, with or without any co-morbidity.	not reported clearly.

Hayden Criteria Reference Sheet				
	c. Study population represents source population, or population of interest	The study meets ALL of the following criteria: • Did not exclude patients based on certain medications, gender, and BMI (exceptions: gender specific study, or other specific study -e.g. BMI). • Strategies for recruiting patients were similar between groups (Viswanathan M, 2012) . • The population would be representative of those seen in practice where BNP/NT-BNP testing is likely to be applied (e.g. outpatient clinics, primary care, etc.). • Inclusion and/or exclusion criteria are applied uniformly to all groups (Viswanathan M 2012).	The study DOES NOT meet ALL of the following criteria: • Did not exclude patients based on certain medications, gender, and BMI (exceptions: gender specific study, or other specific study -e.g. BMI). • Strategies for recruiting patients were similar between groups (Viswanathan M, 2012). • The population would be representative of those seen in practice where BNP/NT-BNP testing is likely to be applied. • Inclusion and exclusion criteria are applied uniformly to all groups (Viswanathan M, 2012).	not reported clearly.
2 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (Hayden, Cote, and	**a. Completeness of follow-up described**	ALL of the following are mentioned: • The study provided a reason for loss of follow-up for ALL TIME POINTS OF OUTCOME ASSESSMENT. • The study provided characteristics for participants who dropped out of the study.	At least ONE of the following is NOT mentioned: • The study provided a reason for loss of follow-up for ALL TIME POINTS OF OUTCOME ASSESSMENT. • The study provided characteristics for participants who dropped out of the study.	not reported clearly.

Hayden Criteria Reference Sheet				
Bombardier 2006).	**b. Completeness of follow-up adequate**	ALL of the above criteria are met: • In cohort studies the length of follow-up is not different between the groups, or in case-control studies, the time period between the exposure and outcome are the same for cases and controls (Viswanathan M 2012). • There was not a high rate of differential or overall attrition (10% is acceptable) (Viswanathan M2012). • Attrition did not result in a difference in group characteristics between baseline and follow-up. (Viswawnathan M 2012)	At least one of the following criteria is not met: • In cohort studies the length of follow-up is not different between the groups, or in case-control studies, the time period between the exposure and outcome are the same for cases and controls (Viswanathan M2012). • There was not a high rate of differential or overall attrition (Viswanathan M2012). • Attrition did not result in a difference in group characteristics between baseline and follow-up (Viswanathan M 2012).	not reported clearly.
3 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Prognostic Factor Measurement The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (Hayden, Cote, and Bombardier 2006).	**a. BNP/NT-proBNP factors defined**	BNP/NT-proBNP cut-points were either pre-specified or an explanation/reasoning for cutpoint/threshold was provided. (note: continuous variables and change in BNP are appropriate)	BNP/NT-proBNP cut-points were NOT either pre-specified and an explanation/reasoning for cutpoint/threshold was NOT provided or a continuous variables or change in BNP variable WAS NOT used.	not reported clearly.
	b. BNP/NT-proBNP factors measured appropriately	The following criteria must be met: • No self-reporting of BNP/NT-proBNP levels were employed. • Method and setting of BNP/NT-proBNP measurement were the same for all study participants.	Self-reporting of BNP/NT-proBNP levels were employed or method and setting of BNP/NT-proBNP measurement were NOT the same for all study participants.	not reported clearly.

Hayden Criteria Reference Sheet				
	c. Other prognostic factors measured appropriately (if applicable)	The following criteria must be met: • No self-reporting of levels of other prognostic factors employed. • Method and setting of other prognostic factor measurement were the same for all study participants.	Self-reporting of levels of other prognostic factors employed or method and setting of other prognostic factor measurement were NOT the same for all study participants.	not reported clearly.
	d. For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data were reported (Viswanathan M 2012).	Study mentioned reasons for indeterminate test results and/or missing values of BNP/NT-proBNP levels.	Study did not mention reasons for indeterminate test results and missing values of BNP/NT-proBNP levels.	Information was unclear to answer if reasons for interdeteminant test results and missing values were reported.
	e. For other prognostic factors, the extent of and reasons for indeterminate test results or missing data were reported (Viswanathan M 2012). (if applicable)	Study mentioned reasons for indeterminate test results and/or missing values of other prognostic factors.	Study did not mention reasons for indeterminate test results and missing values of other prognostic factors.	Information was unclear to answer if reasons for interdeteminant test results and missing values were reported.

Hayden Criteria Reference Sheet				
4 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Outcome Measurement The outcomes of interest are adequately measured in study participants to sufficiently limit bias (Hayden, Cote, and Bombardier 2006).	a. **Outcome defined**	For the primary outcome, the following criteria should be met: • The study defines the primary outcomes as follows: a. mortality as including all (Viswanathan M 2012) cause or cardiac related or heart failure related; b. morbidity as including definition of all cause (any episode of HF that requires admission to a hospital bed beyond the emergency room for any length of time), change in NYHA class, or any measure of quality of life. • The outcome under study should be well defined such that it should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. • The same methods for defining the outcome(s) were the same for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms).	For the primary outcome, the following criteria are NOT met: • The study defines the primary outcomes as follows: a. mortality as including all (Viswanathan M2012) cause or cardiac related or heart failure related; b. morbidity as including definition of all cause (any episode of HF that requires admission to a hospital bed beyond the emergency room for any length of time), change in NYHA class, or any measure of quality of life. • The outcome under study should be well defined such that it should be clear how the investigators determined whether participants experienced, or did not experience, the outcome. • The same methods for defining the outcome(s) were the same for all participants in the study. Often there may be more than one way of measuring an outcome (for example, physical or laboratory tests, questionnaire, reporting of symptoms).	not reported clearly.

Hayden Criteria Reference Sheet				
	b. **Outcome measured appropriately**	For the primary outcome, the following criteria must be met: •The method of measurement used should be valid and reliable to limit misclassification. •The authors use a sufficient method for capturing morbidity and mortality. •For mortality, linkage to electronic death records and hospital registry are good sources, while hospital/medical records are not so reliable (note: family, friends, primary care physicians, hospital records, are not acceptable measurements). •For morbidity, NYHA, Framingham, hospital registries are good sources, while others are not so reliable to detect worsening of heart failure. (note: family, friends, primary care physicians, hospital records, are not acceptable measurements). NOTE: for many studies NYHA and Framingham are sources for establishing initial Heart failure status in these studies. Heart failure is not our outcome for these studies (sometimes worsening of heart failure can be an outcome). Make sure NYHA and Framingham are used to assess the morbidity outcome in question (e.g. all cause hospital readmission, cardiac hospital readmission •All study participants undergo the same measure of outcomes in the same setting.	For the primary outcome, the following criteria was NOT met: • The method of measurement used should be valid and reliable to limit misclassification. • The authors use a sufficient method for capturing morbidity and mortality. • For mortality, linkage to electronic death records and hospital registry are good sources, while hospital/medical records are not so reliable. • For morbidity, NHYA and Framingham are good sources, while others are not so reliable to detect worsening of heart failure. • All study participants undergo the same measure of outcomes in the same setting.	not reported clearly.

Hayden Criteria Reference Sheet				
	c. **A composite outcome was avoided**	The study avoided the use of composite outcomes that combine morbidity and mortality. However, it is adequate if at least one individual outcome is presented in the analysis. Studies that combine different morbidity outcomes are acceptable.	The study DID NOT avoid the use of composite outcomes that combine morbidity and mortality and at least at least one individual outcome is NOT presented in the analysis.	
5 Potential Bias	**Signalling Comments**	**Yes**	**No**	**Unclear**
Confounding Measurement and Account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (Hayden, Cote, and Bombardier 2006).	**a. Confounders measured**	the following criteria are met: • Important confounders (age, renal function, BMI (or other measure of height and weight) are considered in the study design or in the analysis. (For renal function look for the following tests: BUN, Glomerular filtration rate (GFR), Creatinine-blood, creatinine clearance and creatinine-urine or the following keywords renal failure, acute renal failure, ARF, primary acute renal failure, chronic renal failure, CRF, acute interstitial nephritis, acute tubular necrosis, azotemia, dialysis, glomerulonephritis, hemodialysis, obstructive renal failure, renal insufficiency, kidneys, acute kidney failure) • There are clear definitions of the important confounders (including dose, level and duration of exposures). • The measurement of all important confounders is valid and reliable.	At least one of the following are NOT met: • Important confounders (age, renal function, BMI (or other measure of height and weight) are considered in the study design or in the analysis. • There are clear definitions of the important confounders (including dose, level and duration of exposures). • The measurement of all important confounders is valid and reliable.	not reported clearly.

Hayden Criteria Reference Sheet				
	b. Confounders accounted for	Important potential confounders are correctly accounted for in the study design (e.g. matching for key variables, stratification or initial assembly of comparable groups) or in the analysis (multiple regression, etc.).	Important potential confounders are NOT correctly accounted for in the study design (e.g. matching for key variables, stratification or initial assembly of comparable groups) or in the analysis (multiple regression, etc.).	not reported clearly.
6 Analysis	**Signalling Comments**	**Yes**	**No**	**Unclear**
The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (Hayden, Cote, and Bombardier 2006).	**a. Analysis described**	The analysis is clearly described and appropriate for the design of the study. There is no selective reporting of results The presentation of data is sufficient to assess the adequacy of the analysis.	The analysis is not clearly described	not reported clearly.
7 Study Design	***Signalling comments***	**Yes**	**No**	**Unclear**
	a. The study was designed to test the prognostic value of BNP or NT-proBNP (i.e.it was not a secondary analysis of data collected for other purposes).	*Study was a prospective cohort study designed to test BNP as a predictive factor.*	*RCT designed to evaluate treatment interventions and then a re-analysis is undertaken. Cohort studies done to evaluate another question where post-hoc BNP analysis is used to demonstrate prognostic association.*	*not reported clearly.*

Adapted from:
Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144:427–437.
National Institute for Health and Clinical Excellence (January 2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Appendix J: Methodology checklist: prognostic studies 218- 222. Available from: www.nice.org.uk
Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov

Reference List

1. Hayden, J. A., P. Cote, and C. Bombardier. 2006. "Evaluation of the Quality of Prognosis Studies in Systematic Reviews." *Ann.Intern.Med.* 144(6):427-37. doi:144/6/427 [pii].
2. Viswanathan M, Ansari MT Berkman ND Chang S Hartling L McPheeters LM Santaguida PL Shamliyan T Singh K Tsertsvadze A Treadwell JR., Viswanathan M, Ansari MT Berkman ND Chang S Hartling L McPheeters LM Santaguida PL Shamliyan T Singh K Tsertsvadze A Treadwell JR. 2012. "Agency for Healthcare Research and Quality Methods Guide for Comaparative Effectiveness Reviews." *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions.* AHRQ Publication No.12-EHC047-EF.

QUADAS II Reference Sheet

QUADAS-2 HELP SHEET	
1. Was a consecutive or random sample of patients enrolled?	We are interpreting this to be representative of the spectrum of patients seen within the Emergency Departments, Urgent Care departments, or Primary Care Settings, which should include all levels of severity of symptoms or duration. The population would be representative of those seen in practice where the test is likely to be applied. A study should ideally enrol a consecutive or random sample of eligible patients with suspected disease to prevent the potential for bias. If the study is part of a large study were will need to refer to the referenced article to get a full understanding of the study methods. **Yes:** The study clearly indicates that Consecutive or Random sampling was used. A clear description was given that the study includes ALL OR RANDOMLY CHOSEN eligible subjects seen at the Emergency Departments, Urgent Care departments, or Primary Care Settings, and ensures the sampling method represents the entire population. **No:** The study indicates sampling description other than Consecutive or Random. Samples are not randomly recruited OR are only recruited during certain times in the day or at certain course of the study based on the availabilities of the researcher. Samples are not representative of the population. **Unclear:** No or only partial description of how the patients were enrolled. There is uncertainty whether patients were consecutively or randomly obtained.
2. Was a case control design avoided?	Look for a description of a comparison group. **Yes:** The study clearly states there was no comparison group. E.g. Heart Failure (HF) group vs. a group of individuals without the disease. **No:** The study compares HF individuals with a group of individuals without the disease or other diseases. OR the study only select groups of whom they know in advance during the presentation at the Emergency Departments, Urgent Care departments, or Primary Care Settings. **Unclear:** Vague or partial information is reported about whether there was a comparison group.
3. Did the study avoid inappropriate exclusions?	This question only concerns inappropriate exclusions made during initial enrolment. Any exclusions made after analysis is not considered here; question # 11 accounts for this. Please see Table 1 for a description of appropriate and inappropriate exclusions. **Yes:** Inappropriate exclusions were avoided. **No:** There was clear indication of inappropriate exclusion (see Table 1). **Unclear:** Insufficient information to determine whether inappropriate exclusions were made.

QUADAS-2 HELP SHEET	
4. Were the index test results interpreted without knowledge of the results of the reference standard?	This would almost always be "yes" since we are establishing how well an index test (B-type natriuretic peoptide [BNP] or amino-terminal proBNP [NT-proBNP]) can diagnose or exclude HF compared to the reference standard (various diagnoses of HF failure, other than BNP). We assume this bias to be associated with the process of interpretation of BNP results and is related to "review bias" or blinding. **Yes:** The study clearly indicates that BNP cut-points were decided/specified without the knowledge of the results of the reference standard. **No:** The study clearly states that the decision of BNP cut-points were made with the knowledge of the reference standard results. **Unclear:** There is not enough information given to determined whether BNP cut-points were decided/specified without knowledge of the reference standard. (e.g. no indication of blinding or awareness)
5. If a threshold was used, was it pre-specified?	**Yes:** BNP cut-points were established prior to the diagnosis of HF or analysis. **No:** There is evidence that the cut-points of BNP/NT-proBNP were made such in conjunction to what the judicator said about the diagnosis. Or BNP cut-points were based on the outcome of the ROC, Median, or Mean values; in this case it is not pre-specified and should be a "no". **Unclear:** No indication of whether a pre-specified threshold was made.
6. Is the reference standard likely to correctly classify the target condition?	This will almost always be a "yes". One reference standard (e.g. Cardiologist review of records) is considered reasonable to diagnose HF. Most reference standards are well defined diagnostic instruments for HF (clinical presentation, medical treatments and responses to treatment, electrocardiograms, cardiac catheterization investigations, etc.). **Yes:** At least one reference standard was mentioned to diagnose HF, and if diagnosis was not only based on degree of symptoms' severity or classes. **No:** If the final arbitrator of target condition is based on severity of symptoms, e.g. NYHA classes only OR patient's own self-report of HF. **Unclear:** The authors do not give enough information to determine what reference standard was used.
7. Were the reference standard results interpreted without knowledge of the results of the index test?	The index test in this systematic review is the result of BNP levels. The reference test is the diagnostic instruments for HF (clinical presentation, medical treatments and responses to treatment, electrocardiograms, cardiac catheterization investigations, etc.) other than BNP levels. **Yes**: Diagnosis of HF was made without the knowledge of the BNP or NT-proBNP test levels or determination of HF by reference standard were made blinded to the results of the BNP levels. **No:** The diagnosis of HF was made with the knowledge (unaware) of the BNP or NT-proBNP test results or the study clearly states that BNP levels were known by the rater prior to establishing the reference standard; blinding did not occur. **Unclear:** Some information provided but insufficient to determine this item.

QUADAS-2 HELP SHEET	
8. Was there an appropriate interval between index test(s) and reference standard?	**Yes:** The blood collection for BNP levels was taken within 2-3 days after/before standard reference was collected (e.g. 2-3 days between blood and echocardiograph were taken). **No:** The blood collection was taken longer than 2-3 days after/ before standard reference was collected. **Unclear:** the researchers do not give sufficient information to determine the interval between index and standard.
9. Did all patients receive a reference standard?	**Yes:** All patients was administered at least one reference standard. (The reference standard used for diagnosis is stated in the methods. If it is not entirely clear, the "n" in the results may help decide.) **No:** Not all patients were administered a reference standard. **Unclear:** Insufficient information to determine that all patients received at least one the reference standard.
10. Did patients receive the same reference standard?	This item concerns to partial verification bias which occurs when not all of the study participants receive the reference standard (in our context, confirmation of the true HF status). This is a form of selection bias. Information to address this can be found in methods and results. **Yes:** Paper clearly states that all patients received the same reference standard. **No:** Paper clearly describes that different reference standards were used among patients. **Unclear:** Insufficient information to determine whether partial verification was present.
11. Were all patients included in the analysis?	**Yes:** All patients enrolled in the study were included for analysis. This does not include patients that were excluded during study enrolment. **No:** Not all patient were included in the analysis because of missing data, withdrawal, etc. (e.g. refID 60198: Of the 95 patients screened, 11 (11.5%) patients were excluded due to suboptimal images) **Unclear**: Insufficient information if all patient were included for analysis.

Criteria	Appropriate exclusions	Inappropriate exclusions
Age	Study excludes patients younger than 18 years of age.	(Paper specific) Inappropriate if conflicting with objective of the study.
Race	none	(Paper specific) Inappropriate if conflicting with objective of the study.
Gender	none	(Paper specific) Inappropriate if conflicting with objective of the study.
Prior diagnosis/ co-morbidity	Study excludes patients with chest trauma, hemodialysis, asthma, COPD, and Dyspnea clearly due to another cause (e.g. pneumothorax, coronary ischemia, myocardial infarction).	Study excludes patients with any other diagnosis (e.g. exclude patients because of increased BMI, knowing that NPs decrease as BMI increases).
Difficulty or ease of diagnosis	None	Study excludes patients that were too difficult to diagnose or too easy to diagnose.
Medications	None	Study excludes patients on certain medications.
Settings	Study excludes patients recruited at settings other than: non emergency settings, non-urgent care, primary care settings	none
Reference Standard	none	none

Quality Assessment Study Design Description Reference Sheet

Case Control Study

A study that compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls), and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease. Study participants are enrolled based on disease status (i.e., case or control).

Case control studies are observational because no intervention is attempted and no attempt is made to alter the course of the disease. The goal is to retrospectively determine the exposure to the risk factor of interest from each of the two groups of individuals: cases and controls. These studies are designed to estimate odds.

Case control studies are also known as “retrospective studies” and “case-referent studies.”

Case Report

A case report is a descriptive study of a single individual (case report) in which the possibility of an association between an observed effect and a specific exposure is based on a detailed clinical evaluation and history of the individual.

Case Series

A case series is a descriptive study that follows a group of patients who all have the same diagnosis or who are all undergoing the same procedure/treatment over a certain period of time. Case series do not employ control groups. Results of case series can generate hypotheses that are useful in designing further studies, including randomized controlled trials. However, no causal inferences should be made from case series regarding the efficacy of the investigated treatment.

Cohort Study

A study design that follows prospectively over time one or more populations (called cohorts) to determine which patient characteristics (risk factors) are associated with the development of a disease or outcome. As the study is conducted, the outcome from participants in each cohort is measured and relationships with specific risk factors are determined.

Prospective Cohort Study
In a cohort study, individuals exposed and not exposed (to suspected risk factors) are followed and compared to assess the extent to which each group experiences an outcome of interest -- often illness or death. Participants who are enrolled in the study do not have the outcome of interest at the enrolment date.

Retrospective Cohort Study
Most cohort studies are prospective; however, cohort studies that have reconstructed exposure data from historical records are referred to as retrospective cohort studies. In these studies, exposure and outcome data are followed up without actually following cases, which can result in considerable savings of time and money.

Randomized Controlled Trial
A study design that randomly assigns participants into a treatment/intervention group or a control group. As the study is conducted, the only expected difference between the treatment/intervention and control groups is the outcome variable being studied.

Before-After Design
A study design in which the dependent variable (such as a clinical outcome) is measured before and after an intervention in the same group of individuals. Comparison of outcome measures taken before and after the intervention is made to assess the effect of treatment.

Cross Sectional Study
Studies that conduct measurements on a group of subjects at one point in time. Cross-sectional studies look at both exposure and outcomes at one point in time and may be used to generate hypotheses for further investigation in prospective cohort studies or RCTs.

Crossover Trial
A two-period study design in which each participant serves as their own control. In the first period of the study, participants receive either the treatment or control. Then, after a “washout” period to minimize the effect of the first period, the participant switches to receiving the control or treatment, depending on which they received in the first period. Randomization is used to assign the order in which the treatment and control conditions are administered.

Time series
The defining feature of time series research designs is that each participant or sample is observed multiple times, and its performance is compared to its own prior performance. In other words, each participant or population serves as its own control.

Quasi-Experimental Study
A study design in which researchers manipulate an active independent variable but do not have

full control over the allocation or timing of the intervention. Quasi-Experimental designs are often used when it is not possible to conduct a true experiment with complete random assignment, as is often the case in policy or real-life settings.

Interrupted Time Series Design
Study design in which outcomes are measured repeatedly in a single group of participants both before and after a manipulation or a natural event.

Appendix G. List of Excluded Articles

Aalbers J. Chronic heart failure treatment benefits from pro-BNP-directed therapy. Cardiovasc J Afr 2011;22(1):52.
Exclude: Not a primary study

Abdelwhab S, Elshinnawy S. Pulmonary hypertension in chronic renal failure patients. Am J Nephrol 2008;28(6):990-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abdulla J, Kober L, Torp-Pedersen C. Methods of assessing the functional status of patients with left ventricular systolic dysfunction in interventional studies: Can brain natriuretic peptide measurement be used as surrogate for the traditional methods? Cardiovasc Drugs Ther 2004 May;18(3):219-24.
Exclude: Systematic review

Abdullah SM, Khera A, Das SR, et al. Relation of coronary atherosclerosis determined by electron beam computed tomography and plasma levels of n-terminal pro-brain natriuretic peptide in a multiethnic population-based sample (the Dallas Heart Study). Am J Cardiol 2005 Nov 1;96(9):1284-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abe N, Matsunaga T, Kameda K, et al. Increased level of pericardial insulin-like growth factor-1 in patients with left ventricular dysfunction and advanced heart failure. J Am Coll Cardiol 2006 Oct 3;48(7):1387-95.
Exclude: BNP measure not FDA approved

Abe S, Taguchi I, Inoue T. Does direct inhibition bring direct benefit? Circ J 2012;76(6):1326
Exclude: Not a primary study

Abezov DK, Kamilova UK, Shukurdzhanova SM, et al. Assessment of natriuretic peptide indices and oxidative stress in patients with chronic heart failure. Likars'ka sprava 2010 Jan;Jan-Mar(1-2):53-6.
Exclude: Not in English

Abhayaratna WP, Marwick TH, Smith WT, et al. Characteristics of left ventricular diastolic dysfunction in the community: An echocardiographic survey. Heart 2006;92(9):1259-64.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abhayaratna WP, Marwick TH, Becker NG, et al. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide. Am Heart J 2006 Nov;152(5):941-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abraham MR, Olson LJ, Joyner MJ, et al. Angiotensin-converting enzyme genotype modulates pulmonary function and exercise capacity in treated patients with congestive stable heart failure. Circ 2002 Oct 1;106(14):1794-9.
Exclude: BNP measure not FDA approved

Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail 1998 Mar;4(1):37-44.
Exclude: BNP measure not FDA approved

Abraham WT, Anand IS, Klapholz M, et al. Treatment of anemia with darbepoetin alfa in heart failure. Congest Heart Fail 2010;16(3):87-95.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: Diagnostic performance of cardiac biomarkers. Am J Respir Crit Care Med 2006 Nov 1;174(9):990-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abul Y, Karakurt S, Ozben B, et al. C-reactive protein in acute pulmonary embolism. J Investig Med 2011;59(1):8-14.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Abulhul E, McDonald K, Martos R, et al. Long-term statin therapy in patients with systolic heart failure and normal cholesterol: Effects on elevated serum markers of collagen turnover, inflammation, and B-type natriuretic peptide. Clin Ther 2012 Jan;34(1):91-100.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adamopoulos S, Parissis JT, Iliodromitis EK, et al. Effects of levosimendan versus dobutamine on inflammatory and apoptotic pathways in acutely decompensated chronic heart failure. Am J Cardiol 2006 Jul 1;98(1):102-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adlam D, Silcocks P, Sparrow N. Using BNP to develop a risk score for heart failure in primary care. Eur Heart J 2005 Jun;26(11):1086-93.
Exclude: BNP measure not FDA approved

Adlbrecht C, Huelsmann M, Berger R, et al. Cost analysis and cost-effectiveness of NT-proBNP-guided heart failure specialist care in addition to home-based nurse care. Eur J Clin Invest 2011;41(3):315-22.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Adlbrecht C, Neuhold S, Hulsmann M, et al. NT-proBNP as a means of triage for the risk of hospitalisation in primary care. European Journal of Preventive Cardiology 2012 Feb;19(1):55-61.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aessopos A, Farmakis D, Polonifi A, et al. Plasma B-type natriuretic peptide concentration in beta-thalassaemia patients. Eur J Heart Fail 2007;9(5):537-41.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aggarwal A, Wong J, Campbell DJ. Carvedilol reduces aldosterone release in systolic heart failure. Heart Lung Circ 2006 Oct;15(5):306-9.
Exclude: BNP measure not FDA approved

Aguiar VB, Ochiai ME, Cardoso JN, et al. Relationship between depression, BNP levels and ventricular impairment in heart failure. Arq Bras Cardiol 2010;95(6):732-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ahmed KA, Madhavan M, Prasad A. Brain natriuretic peptide in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): Comparison with acute myocardial infarction. Coron Artery Dis 2012;23(4):259-64.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ahmed W, Zafar S, Alam AY, et al. Plasma levels of B-type natriuretic peptide in patients with unstable angina pectoris or acute myocardial infarction: Prognostic significance and therapeutic implications. Angiol 2007 Jun;58(3):269-74.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aidonidis G, Kanonidis I, Koutsimanis V, et al. Efficiency and safety of prolonged levosimendan infusion in patients with acute heart failure. Cardiol Res Pract 2011;2011:342302.
Exclude: BNP measure not FDA approved

Ait-Oufella H, Tharaux P-L, Baudel J-L, et al. Variation in natriuretic peptides and mitral flow indexes during successful ventilatory weaning: A preliminary study. Intensive Care Med 2007;33(7):1183-6.
Exclude: BNP measure not FDA approved

Ajuluchukwu JNA, Ekure EN, Mbakwem AC, et al. Reliability and accuracy of point-of-care amino-terminal probrain natriuretic peptide in congestive heart failure patients. Internet J Cardiol 2010;9(1):1.
Exclude: BNP measure not FDA approved

Akanji AO, Suresh CG, Al Radwan R, et al. Body mass and atherogenic dyslipidemia as major determinants of blood levels of B-type natriuretic peptides in Arab subjects with acute coronary syndromes. Metab Synd Related Disord 2009 Dec;7(6):563-9.
Exclude: BNP measure not FDA approved

Akashi YJ, Kida K, Suzuki K, et al. The significance of 123I-BMIPP delayed scintigraphic imaging in cardiac patients. Int J Cardiol 2007 Apr 25;117(2):145-51.
Exclude: BNP measure not FDA approved

Akazawa T, Iizuka H, Aizawa M, et al. The degree of newly emerging mitral regurgitation during off-pump coronary artery bypass is predicted by preoperative left ventricular function. J Anesth 2008;22(1):13-20.
Exclude: BNP measure not FDA approved

Akerblom A, Wallentin L, Siegbahn A, et al. Cystatin C and estimated glomerular filtration rate as predictors for adverse outcome in patients with ST-elevation and non-ST-elevation acute coronary syndromes: Results from the Platelet Inhibition and Patient Outcomes study. Clin Chem 2012 Jan;58(1):190-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Akioka K, Takeuchi K, Yanagi S, et al. Prognostic value of Doppler transmittal flow patterns and cardiac natriuretic peptides in patients with chronic congestive heart failure admitted for episodes of acute decompensation. Heart Ves 2000;15(2):53-60.
Exclude: BNP measure not FDA approved

Akpinar O, Acarturk E, Kanadai M, et al. Tissue doppler imaging and NT-proBNP levels show the early impairment of ventricular function in patients with beta-thalassaemia major. Acta Cardiol 2007 Jun;62(3):225-31.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aksoy H, Okutucu S, Kaya EB, et al. Clinical and echocardiographic correlates of improvement in left ventricular diastolic function after cardiac resynchronization therapy. Europace 2010 Sep;12(9):1256-61.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aktas MK, Allen D, Jaber WA, et al. Relation of brain natriuretic peptide level to extent of left ventricular scarring in patients with chronic heart failure secondary to ischemic cardiomyopathy. Am J Cardiol 2009 Jan 15;103(2):243-5.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Akutsu Y, Kaneko K, Kodama Y, et al. Iodine-123 mIBG imaging for predicting the development of atrial fibrillation. JACC Cardiovasc Imaging 2011;4(1):78-86.
Exclude: BNP measure not FDA approved

Al Bannay RA, Husain AA. Role of tissue Doppler imaging in assessing left ventricular diastolic dysfunction severity. Does it hold the same ability? Saudi Med J 2012 Jan;33(1):34-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Al Hweish A, Sultan SS, Mogazi K, et al. Plasma myeloperoxidase, NT-proBNP, and troponin-I in patients on CAPD compared with those on regular hemodialysis. Hemodial Int 2010 Jul;14(3):308-15.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Al Meslmani BM, Fahoum SK, Shamia MG. N-terminal-probrain natriuretic peptide and echocardiography in patients with systolic heart failure. Saudi Med J 2005 Nov;26(11):1695-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Al Meslmani BM, Fahoum SK, Shamia MG. NT-proBNP in monitoring treatment of patients with congestive heart failure. Clin Lab 2007;53(1-2):35-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ala-Kopsala M, Magga J, Peuhkurinen K, et al. Molecular heterogeneity has a major impact on the measurement of circulating N-terminal fragments of A- and B-type natriuretic peptides. Clin Chem 2004 Sep;50(9):1576-88.
Exclude: BNP measure not FDA approved

Albertini J-P, Cohen R, Valensi P, et al. B-type natriuretic peptide, a marker of asymptomatic left ventricular dysfunction in type 2 diabetic patients. Diabetes Metab 2008;34(4):355-62.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Albertsen AE, Nielsen JC, Poulsen SH, et al. DDD(R)-pacing, but not AAI(R)-pacing induces left ventricular desynchronization in patients with sick sinus syndrome: Tissue-Doppler and 3D echocardiographic evaluation in a randomized controlled comparison. Europace 2008 Feb;10(2):127-33.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aldous SJ, Richards AM, Troughton R, et al. ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the emergency department with chest pain. J Card Fail 2012;18(4):304-10.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Eriksson H, Nylander E, et al. Heart failure in the elderly: Characteristics of a Swedish primary health care population. Heartdrug 2002;2(5):211-20.
Exclude: BNP measure not FDA approved

Alehagen U, Lindstedt G, Eriksson H, et al. Utility of the amino-terminal fragment of pro-brain natriuretic peptide in plasma for the evaluation of cardiac dysfunction in elderly patients in primary health care. Clin Chem 2003 Aug;49(8):1337-46.
Exclude: BNP measure not FDA approved

Alehagen U, Dahlstrom U, Lindahl TL. Elevated D-dimer level is an independent risk factor for cardiovascular death in out-patients with symptoms compatible with heart failure. Thromb Haemost 2004 Dec;92(6):1250-8.
Exclude: BNP measure not FDA approved

Alehagen U, Lindstedt G, Levin LA, et al. Risk of cardiovascular death in elderly patients with possible heart failure. B-type natriuretic peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal proBNP) as prognostic indicators in a 6-year follow-up of a primary care population. Int J Cardiol 2005 Apr 8;100(1):125-33.
Exclude: BNP measure not FDA approved

Alehagen U, Svensson E, Dahlstrom U. Natriuretic peptide biomarkers as information indicators in elderly patients with possible heart failure followed over six years: A head-to-head comparison of four cardiac natriuretic peptides. J Card Fail 2007 Aug;13(6):452-61.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Goetze JP, Dahlstrom U. Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (Nt-proBNP) in the elderly. Clin Chim Acta 2007;382(1-2):8-14.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Janzon M. A clinician's experience of using the Cardiac Reader NT-proBNP point-of-care assay in a clinical setting. Eur J Heart Fail 2008 Mar;10(3):260-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Dahlstrom U. Can NT-proBNP predict risk of cardiovascular mortality within 10 years? Results from an epidemiological study of elderly patients with symptoms of heart failure. Int J Cardiol 2009 Apr 3;133(2):233-40.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Dahlstrom U, Lindahl TL. Cystatin C and NT-proBNP, a powerful combination of biomarkers for predicting cardiovascular mortality in elderly patients with heart failure: Results from a 10-year study in primary care. Eur J Heart Fail 2009 Apr;11(4):354-60.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Dahlstrom U, Lindahl TL. Low plasma concentrations of coagulation factors II, VII and XI indicate increased risk among elderly with symptoms of heart failure. Blood Coagul Fibrinolysis 2010 Jan;21(1):62-9.
Exclude: BNP measure not FDA approved

Alehagen U, Dahlstrom U, Rehfeld JF, et al. Prognostic assessment of elderly patients with symptoms of heart failure by combining high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide measurements. Clin Chem 2010 Nov;56(11):1718-24.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alehagen U, Dahlstrom U, Rehfeld JF, et al. Association of copeptin and N-terminal proBNP concentrations with risk of cardiovascular death in older patients with symptoms of heart failure. JAMA 2011 May 25;305(20):2088-95.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Aleman C, Chan SB, Kordick MF. Correlation between chest x-ray and B-type natriuretic peptide in congestive heart failure. Am J Emerg Med 2005 Jul;23(4):501-3.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alibay Y, Beauchet A, El Mahmoud R, et al. Analytical correlation between plasma N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in patients presenting with dyspnea. Clin Biochem 2004 Oct;37(10):933-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Allanore Y, Borderie D, Meune C, et al. N-terminal pro-brain natriuretic peptide as a diagnostic marker of early pulmonary artery hypertension in patients with systemic sclerosis and effects of calcium-channel blockers. Arthritis Rheum 2003 Dec;48(12):3503-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008 Jan;58(1):284-91.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Almenar L, Arnau MA, Martinez-Dolz L, et al. Is there a correlation between brain naturietic peptide levels and echocardiographic and hemodynamic parameters in heart transplant patients? Transplant Proc 2006 Oct;38(8):2534-6.
Exclude: BNP measure not FDA approved

Almog Y, Novack V, Megralishvili R, et al. Plasma level of N terminal pro-brain natriuretic peptide as a prognostic marker in critically ill patients. Anesth Analg 2006 Jun;102(6):1809-15.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alonso-Martinez JL, Urbieta-Echezarreta M, Anniccherico-Sanchez FJ, et al. N-terminal pro-B-type natriuretic peptide predicts the burden of pulmonary embolism. Am J Med Sci 2009 Feb;337(2):88-92.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alqaisi F, Williams LK, Peterson EL, et al. Comparing methods for identifying patients with heart failure using electronic data sources. BMC Health Serv Res 2009;9:237.
Exclude: BNP measure not FDA approved

Alsuwaida A. Influence of erythropoietin dose and albumin level on the plasma brain natriuretic peptide in hemodialysis patients. Nasrat Amrad Wa Ziraat Alkulat 2006 Jun;17(2):171-6.
Exclude: BNP measure not FDA approved

Altay H, Zorlu A, Binici S, et al. Relation of serum parathyroid hormone level to severity of heart failure. Am J Cardiol 2012 Jan 15;109(2):252-6.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Altemose GT, Gritsus V, Jeevanandam V, et al. Altered myocardial phenotype after mechanical support in human beings with advanced cardiomyopathy. J Heart Lung Transplant 1997 Jul;16(7):765-73.
Exclude: BNP measure not FDA approved

Alter P, Rupp H, Rominger MB, et al. Relation of B-type natriuretic peptide to left ventricular wall stress as assessed by cardiac magnetic resonance imaging in patients with dilated cardiomyopathy. Can J Physiol Pharmacol 2007 Aug;85(8):790-9.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alter P, Rupp H, Rominger MB, et al. B-type natriuretic peptide and wall stress in dilated human heart. Mol Cell Biochem 2008 Jul;314(1-2):179-91.
Exclude: BNP measure not FDA approved

Alter P, Rupp H, Rominger MB, et al. Association of hyperhomocysteinemia with left ventricular dilatation and mass in human heart. Clin Chem Lab Med 2010 Apr;48(4):555-60.
Exclude: BNP measure not FDA approved

Altice NF, Madigan EA. Factors associated with delayed care-seeking in hospitalized patients with heart failure. Heart Lung 2012;41(3):244-54.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Alvelos M, Ferreira A, Bettencourt P, et al. The effect of dietary sodium restriction on neurohumoral activity and renal dopaminergic response in patients with heart failure. Eur J Heart Fail 2004 Aug;6(5):593-9.
Exclude: BNP measure not FDA approved

Alvelos M, Ferreira A, Bettencourt P, et al. Effect of saline load and metoclopramide on the renal dopaminergic system in patients with heart failure and healthy controls. J Cardiovasc Pharmacol 2005 Mar;45(3):197-203.
Exclude: BNP measure not FDA approved

Alyan O, Kacmaz F, Ozdemir O, et al. Effects of cigarette smoking on heart rate variability and plasma N-terminal pro-B-type natriuretic peptide in healthy subjects: Is there the relationship between both markers? Ann Noninvasive Electrocardiol 2008 Apr;13(2):137-44.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ambardekar AV, Fonarow GC, Hernandez AF, et al. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: Findings from Get With The Guidelines-Heart Failure (GWTG-HF). Am Heart J 2009;158(4):644-52.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ambrosi P, Singeorzan S, Oddoze C, et al. Correlation of NT-proBNP with diastolic left ventricular function in elderly patients with ischemic stroke. Int J Cardiol 2010 Apr 1;140(1):126-8.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ambrosy AP, Fonarow GC, Albert NM, et al. B-type natriuretic peptide assessment in ambulatory heart failure patients: Insights from IMPROVE HF. J Cardiovasc Med 2012;13(6):360-7.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ameri P, Ronco D, Casu M, et al. High prevalence of vitamin D deficiency and its association with left ventricular dilation: An echocardiography study in elderly patients with chronic heart failure. Nutr Metab Cardiovasc Dis 2010 Nov;20(9):633-40.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Amir O, Reisfeld D, Sberro H, et al. Implications of cheyne-stokes breathing in advanced systolic heart failure. Clin Cardiol 2010;33(3):E8-12.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: Application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circ 2007 Mar 27;115(12):1563-70.
Exclude: Does not meet prognosis, diagnosis, or treatment inclusion criteria

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Appendix H. Key Question 1 Evidence Set

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings

Author Year Country	Study Design (companion study)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Alibay,[1] 2005 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=45), cardiac heart failure (n=60), pulmonary disease (n=55); Reference Standard: 2 cardiologists	Evaluated the influence of creatinine clearance, Age, gender and BMI on plasma BNP and NT-proBNP levels	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=160, Mean age: 80.13y, % Males:38 HF Prevalence: 37.5%	50	99	31	1.43	0.03	NR
					100	98	47	1.85	0.04	NR
					150	94	61	2.41	0.10	0.82
					200	87	64	2.42	0.20	NR
Arenja, [2] 2011 Switzerland	Cohort (BASEL); Ethnicity: NR Comorbidities: hypertension (n=452), CAD (n=212), historical MI (n=111), chronic kidney disease (n=187); Reference Standards: 2 independent cardiologists	To extend this finding to AHF using a sensitive cardiac troponin I (s-cTnI) assay. Secondary aim was to investigate whether quantification of cardiomyocyte damage by s-cTnI would also be useful diagnostically to differentiate between AHF and noncardiac causes of acute dyspnoea.	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	dyspnea (n= 667,age= 76(64-83)y, %males=53); HF prevalence=56.5%	NR	NR	NR	NR	NR	0.96
Arques,[3] 2007 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=19), CAD (n=6), diabetes mellitus (n=10), previous HF (n=16), history of chronic pulmonary disease (n=11); Reference Standard: 2 cardiologists; 1 chest physician	Emergency diagnosis of CHF with a normal left ventricular ejection fraction	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, ≥70y n=41, Mean age: 84y, % Males:41 HF Prevalence: 53.7%	200	96	74	3.63	0.06	NR
					253	86	90	8.23	0.15	0.928
					≥253	96	90	9.10	0.05	NR
					≥253	96	90	9.10	0.05	NR
					≥200	96	84	6.04	0.05	NR
					≥200	96	79	4.55	0.06	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Barcarse,[4] 2004 USA	Cross-sectional (Independent study); Ethnicity: Caucasian (n=78), African-American (n=10), Hispanic (n=6), Asian (n=4); Comorbidities: Hypertension (n=73), CAD (n=44), stroke (n=14), atrial fibrillation (n=13), COPD (n=37), diabetes mellitus (n=41), MI (n=40), CHF (n=58), asthma (n=13), pulmonary embolism (n=3), valvular heart disease (n=14); Reference Standard: 1 cardiologist	Cardiac death, readmission, or visit to the ED within 90 days	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test	Acute SOB n=98, Mean age: 64.6 1.2), % Males:100 HF Prevalence: 58%	110	NR	NR	NR	NR	0.979
				Diagnose CHF, BNP>100 n=33, Mean age: NR % Males: NR HF Prevalence: 58%	590	NR	NR	NR	NR	0.64
Boldanova,[5] 2010 Switzerland	Cross-sectional (BASEL); Ethnicity: NR Comorbidities: Hypertension (n=237), CAD (n=225), stroke (n=91), COPD (n=140), renal disease (n=112), any pulmonary disease (n=226), deep vein thrombosis (n=41), depressive disorder (n=36), previous heart failure (n=64); Reference Standard: 1 physician	Diagnostic accuracy of BNP Prognostic value of BNP (one year mortality)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=452, Mean age: NR % Males: NR HF Prevalence: 49.3%	NR	NR	NR	NR	NR	NR
				Dyspnea, previous history of HF n=64, Mean age: 73 11)y, % Males:61 HF Prevalence: 84%	100	96	45	1.75	0.09	NR
					403	80	77	3.48	0.26	0.84
					500	76	77	3.30	0.31	NR
				Dyspnea, no previous history of HF n=388, Mean age: 73 11)y, % Males:52 HF Prevalence: 43.6%	100	94	59	2.29	0.10	NR
					289	81	83	4.76	0.23	0.883
					500	68	99	68.00	0.32	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[6] 2005 France	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=153), COPD (n=127), MI (n=124), previous CHF (n=128); Reference Standard: Urgentists	Diagnostic-accuracy study	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=381, Mean age: 79±12, % Males: NR HF Prevalence: 30.2%	NR	NR	NR	NR	NR	NR
				Dyspnea, GFR <30 n=41, Mean age: 83 (11)y, % Males: NR HF Prevalence: 48.8%	515	82	89	7.45	0.20	0.89
				Dyspnea, GFR 59-30 n=187, Mean age: 81(10)y, % Males: NR HF Prevalence: 34.2%	480	74	81	3.89	0.32	0.799
				Dyspnea, 89-60 n=141, Mean age: 74(13)y, % Males: NR HF Prevalence: 19.9%	290	76	88	6.33	0.27	0.842
Chenevier-Gobeaux,[7] 2008 France	Cross-sectional (Ray 2005); Ethnicity: NR Chenevier-Gobeaux 2005); Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), previous HF (n=138), malignancy (n=94); Reference Standard: physicians	CHF	BNP [TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=570, Mean age: NR % Males:48 HF Prevalence: 44.4%	NR	NR	NR	NR	NR	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[7] 2008 France (cont'd)	(repeated data) Cross-sectional (Ray 2005); Ethnicity: NR Chenevier-Gobeaux 2005); Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), previous HF (n=138), malignancy (n=94); Reference Standard: physicians	(repeated data) CHF	(repeated data) BNP [TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, ≥85y n=210, Mean age: NR % Males:35 HF Prevalence: 52%	250	85	64	2.36	0.23	NR
					290	80	69	2.58	0.29	0.797
					380	70	73	2.59	0.41	NR
					400	67	75	2.68	0.44	NR
					500	60	79	2.86	0.51	NR
					590	55	85	3.67	0.53	NR
				Acute dyspnea, <85y n=360, Mean age: NR % Males:52 HF Prevalence: 40%	270	73	83	4.29	0.33	0.835
Chenevier-Gobeaux,[8] 2010 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), previous CHF (n=125); Reference Standard: 2 emergency department physicians	Determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, > 60 ys, n=378, Mean age: 78(12)y, % Males:50 HF Prevalence: 30.16%	100 ng/L	99	41	1.68	0.02	0.82
				Tertile 3 eGFR >= 58.6 ml/min/1.73 m2) n=126, Mean age: 73(13)y, % Males:68 HF Prevalence: 17.46%	210 ng/L	86	71	2.97	0.20	0.85

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[8] 2010 France (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), previous CHF (n=125); Reference Standard: 2 emergency department physicians	(repeated data) Determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Tertile 2 eGFR between 44.3 and 58.5 ml/min/1.73m2) n=126, Mean age: 79(11)y, % Males:44 HF Prevalence: 34.13%	280 ng/L	88	72	3.14	0.17	0.86
				Tertile 1 eGFR<44.3 ml/ min/1.73 m2), n=126, Mean age: 83(10)y, % Males:39 HF Prevalence: 38.89%	550 ng/L	85	65	2.43	0.23	0.76
Choi,[9] 2007 Korea	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=183), COPD (n=56), diabetes mellitus (n=80), renal disease (n=15), angina (n=70), Hypertension plus diabetes (n=97), Hypertension plus COPD (n=51), Hypertension plus renal failure (n=44); Reference Standard: the final diagnosis of CHF was defined by transthoracic echocardiography.	Determining the cut off value for diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=1,040, Mean age: NR % Males:56 HF Prevalence: 36.3%	12.5	100	28	1.39	0.00	0.961
					100	99	67	3.00	0.02	NR
					191	96	84	5.82	0.05	NR
					296.5	91	91	10.52	0.10	0.961
					400	85	96	22.29	0.16	NR
					496	70	97	25.96	0.31	NR
					601	61	98	26.35	0.40	NR
					983.5	40	99	33.25	0.61	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chung,[10] 2006 Australia	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Historical MI (n=25), History of HF (n=80), History of respiratory disease (n=93), History of HF and respiratory disease (n=48); Reference Standard: 1 cardiologist	Accurate diagnosis of patients with history of HF using BNP	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Patients with dyspnea , all n=143, Mean age: 79(10), % Males:44 HF Prevalence: 50.3%	100	100	41	1.65	0.00	0.85
					400	87	76	3.63	0.17	NR
				History of HF n=80, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.74
				No history of HF n=63, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.94
				LVEF <50% n=67, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.64
				LVEF ≥50% n=39, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.87
				High serum creatinine n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.81
				Low serum creatinine n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.9

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chung,[10] 2006 Australia (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Historical MI (n=25), History of HF (n=80), History of respiratory disease (n=93), History of HF and respiratory disease (n=48); Reference Standard: 1 cardiologist	(repeated data) Accurate diagnosis of patients with history of HF using BNP	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Initial inter-emergency department likelihood of HF n=44, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.79
				Low or high likelihood of HF n=9, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.86
				Patients > 79 years n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.85
				Patients < 79 years n=NR Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	0.88
Collins,[11] 2006 USA	Cross-sectional (Independent study); Ethnicity: Caucasian (n=166), other (n=177); Comorbidities: Hypertension (n=214), CAD (n=116), congestive HF (n=164), valvular heart disease (n=100), cardiomyopathy (n=65); Reference Standard: 2 senior cardiology fellows	Diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=NR Mean age: NR % Males: NR HF Prevalence: 38.8%	''indeterminate zone'' (100 to <= 500 pg/ml)	NR	NR	NR	NR	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Coste,[12] 2006 France	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: history of HF (n=174); Reference Standard: 2 cardiologists	Diagnosis of acute or decompensated HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=699, Mean age: 72.8y(14.3) % Males:68 HF Prevalence: 60%	NR	NR	NR	NR	NR	NR
				Acute dyspnea , no history CHF n=525, Mean age: NR % Males: NR HF Prevalence: NR%	The cutoff points delimiting the gray zones glow=167 ng/L (95% bootstrap CI: 108 to 219) and gup= 472 ng/L (95% bootstrap CI: 390 to 501)	NR	NR	18.25	0.05	NR
				Acute dyspnea , history of CHF n=174, Mean age: NR % Males: NR HF Prevalence: NR%	gup=334 ng/L (95% bootstrap CI 178 to 465); glow=0	NR	NR	3.35	0.01	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Daniels,[13] 2006 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=618); Comorbidities: COPD (n=542), Diabetes mellitus (n=347), Myocardial infarction (n=384), CHF (n=456); Reference Standard: 2 cardiologists	How obesity affects cutpoints for BNP in diagnosis of heart failure	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=1,368, Mean age: 65y, % Males:56 HF Prevalence: 46.1%	NR	NR	NR	NR	NR	NR
				Dyspnea , BMI <25 n=526, Mean age: 67.3y % Males:55.7 HF Prevalence: 47%	100	94	65	2.63	0.10	0.9
				Dyspnea, 25 ≤BMI <35 n=595, Mean age: 63.2y % Males:58 HF Prevalence: 46.2%	100	92	76	3.88	0.10	0.91
				Dyspnea , BMI z35 n=247, Mean age: 56.7y, % Males:46.3 HF Prevalence: 44.1%	100	77	84	4.85	0.27	0.88
				Dyspnea , BMI <25 n=526, Mean age: 67.3, % Males:55.7 HF Prevalence: 47%	100	90	NR	NR	NR	NR
				Dyspnea , 25 ≤BMI <35 n=595, Mean age: 63.2y, % Males:58 HF Prevalence: 46.2%	110	90	NR	NR	NR	NR
				Dyspnea , BMI z35 n=247, Mean age: 56.7y, % Males:46.3 HF Prevalence: 44.1%	54	90	NR	NR	NR	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Dao,[14] 2001 USA	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: CAD (n=100), COPD (n=90), CHF (n=75); Reference Standard: 2 cardiologists	Final diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	dyspnea, all n=250, Mean age: 63y, % Males:94 HF Prevalence: 38.8%	80	98	92	12.25	0.02	0.98
					100	94	94	15.67	0.06	NR
					115	90	96	22.50	0.10	NR
					120	90	96	22.50	0.10	NR
					150	87	97	29.00	0.13	NR
Defilippi,[15] 2007 USA	Cohort (Independent study); Ethnicity: African-American (n=318); Inclusion criteria = patients with the complaint of dyspnea who presented to the Carolinas Medical Center emergency department who underwent BNP measurement; Comorbidities: Hypertension (n=555), CAD (n=263), atrial fibrillation (n=175), diabetes mellitus (n=305), prior HF (n=287); Reference Standard: 1 cardiologist	All-cause mortality compared the diagnostic accuracies of NT-proBNP and BNP for diagnosing decompensated HF and predicting 1-year all-cause mortality)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=831, Mean age: NR % Males:45.7 HF Prevalence: 52.6%	NR	NR	NR	NR	NR	NR
				No kidney disease eGFR>= 60 n=438, Mean age: 63.5 16.0)y, % Males:43.8 HF Prevalence: 45%	100 ng/L	90	37	1.42	0.27	0.95
				Kidney disease eGFR <60 n=393, Mean age: 69.3y(13.1) % Males:47.8 HF Prevalence: 61%	200 ng/L	82	53	1.74	0.34	0.68

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Dieplinger,[16] 2009 Austria	Cross-sectional (Mueller et al 2005, Gegenhuber et al 2006); Ethnicity: NR Comorbidities: Hypertension (n=141), CAD (n=117), atrial fibrillation (n=83), diabetes mellitus (n=58), history of HF (n=75), NYHA II (n=59), NYHA III (n=53), NYHA IV (n=25); Reference Standard: Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction	Evaluate the utility of established and novel biomarkers for the diagnosis of acute destabilised HF in patients with SOB presenting to an emergency department	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea n=251, Mean age: NR % Males: NR HF Prevalence: 54.6%	160ng/L	90	73	3.33	0.14	0.92
				Dyspnea attributable to acute emergency department HF n=137, Mean age: 69-82y, % Males:93 HF Prevalence: 46.2%	NR	NR	NR	NR	NR	NR
				Dyspnea not attributable to HF n=114, Mean age: 68-82y, % Males:95 HF Prevalence: 8.3%	NR	NR	NR	NR	NR	NR
Gorissen,[17] 2007 The Netherlands	Cross-sectional (Independent study); Acute dyspnea , all n=80, Mean age: 43–90yrs, % males=55; HF Prevalence=50% Ethnicity: NR Comorbidities: NR Reference Standard: consensus on clinical dx (cardiac + pulmonary)	Diagnostic-accuracy study	BNP Centaur (ADVIA - Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=160, Mean age: 80.13y, % Males:38 HF Prevalence: 37.5%	138 ng/L (Centaur)	65	88	5.42	0.40	0.775
					225 ng/L (Triage)	73	78	3.32	0.35	0.783
				Acute dyspnea , <65 n=17, Mean age: NR % Males: NR HF Prevalence: NR%	78 ng/L (Triage)	100	55	2.22	0.00	0.75
					91 ng/L (Centaur)	100	55	2.22	0.00	0.705
				Acute dyspnea , 65-75 n=23, Mean age: NR % Males: NR HF Prevalence: NR%	260 ng/L (Triage)	82	83	4.82	0.22	0.795
					188 ng/L (Centaur)	73	83	4.29	0.33	0.773

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gorissen,[17] 2007 The Netherlands (cont'd)	(repeated data) Cross-sectional (Independent study); Acute dyspnea , all n=80, Mean age: 43–90yrs, % males=55; HF Prevalence=50% Ethnicity: NR Comorbidities: NR Reference Standard: consensus on clinical dx (cardiac + pulmonary)	(repeated data) Diagnostic-accuracy study	(repeated data) BNP Centaur (ADVIA - Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea , >75 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	309 ng/L (Triage)	68	71	2.34	0.45	0.765
					247 ng/L (Centaur)	68	77	2.96	0.42	0.767
				Acute dyspnea , GFR >60 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	202 ng/L (Triage)	81	63	2.19	0.30	0.797
					127 ng/L (Triage)	73	85	4.87	0.32	0.799
				Acute dyspnea , GFR <60 n=40, Mean age: NR % Males: NR HF Prevalence: NR%	229 ng/L(Centaur)	64	70	2.13	0.51	0.669
					309 ng/L (Centaur)	64	74	2.46	0.49	0.69
Gruson,[18] 2008 Belgium	Cohort (Independent study); Ethnicity: NR Comorbidities: NR Reference Standard: 1 cardiologist	Diagnostic accuracy of NT-proBNP in patients in the emergency department (ED) with dyspnea and/or chest pain.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Patients with dyspnea and/or chest pain with cardiovascular and/or pulmonary disorders), all n=137, Mean age: 69y, % Males:56.2 HF Prevalence: 22.6%	NR	NR	NR	NR	NR	0.93
Gruson,[19] 2009 Belgium	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=10), renal disease (n=17), pulmonary disorders (n=21), pulmonary embolism (n=19), ; Reference Standard: clinicians	To evaluate the SOB panel and to assess its reliability in patients presenting in ED with dyspnea and/or atypical thoracic pain	SOB BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Dyspnea, all n=97, Mean age: 30–95y, % Males:43 HF Prevalence: 19.6%	NR	100	59	2.44	0.00	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gruson,[20] 2012 Belgium	Cohort (Independent Study); Ethnicity= NR Comorbidities= hypertension (n=69), atrial fibrillation (n=11), diabetes mellitus (n=30), historical MI (n=20); Reference Standard= clinicians	To evaluate the diagnostic accuracy of circulating levels of proBNP in patients admitted to ED with dyspnea and/or thoracic pain. Moreover, we compared the performances of proBNP assay to two commercial assays for BNP and Nt-proBNP.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	dyspnea and/or chest pain, all (n=156, mean= 67y, %males=54.5); HF Prevalence= 29.5%	100 ng/L	NR	NR	NR	NR	0.91
Havelka,[21] 2011 USA	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference Standard: discharge diagnosis	Diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=54, Mean age:, % Males: 80y* HF Prevalence: NR%	NR	NR	NR	NR	NR	0.77
Knudsen,[22] 2004a Norway	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=52), Angina (n=47), Atrial Fibrillation (n=39), COPD (n=73), Diabetes mellitus (n=24), Historical MI (n=56), CABG (n=14); Reference Standard: 2 cardiologists		BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=155, Mean age: NR % Males:44.5 HF Prevalence: 48.3%	100	NR	NR	NR	NR	NR
				Acute dyspnea, women n=86, Mean age: 78y, % Males: NR HF Prevalence: 40.7%	50	100	37	1.59	0.00	NR
					100	94	55	2.09	0.10	NR
					150	91	59	2.22	0.15	NR
					200	89	63	2.38	0.18	0.86

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[22] 2004a Norway (cont'd)	(repeated data) Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=52), Angina (n=47), Atrial Fibrillation (n=39), COPD (n=73), Diabetes mellitus (n=24), Historical MI (n=56), CABG (n=14); Reference Standard: 2 cardiologists		(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=69, Mean age: 74y, % Males: NR HF Prevalence: 58%	50	95	38	1.53	0.13	NR
					100	90	55	2.01	0.18	NR
					150	93	62	2.44	0.12	NR
					200	90	72	3.26	0.14	0.9
				Acute dyspnea, >76y n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.88
				Acute dyspnea, <76y n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.82
Knudsen,[23] 2004b Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=340), African-American (n=495); Comorbidities: Hypertension (n=547), Acute MI (n=250); Reference Standard: 2 cardiologists, Framingham, NHANES		BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, All n=880, Mean age: 64y, % Males:55 HF Prevalence: 51%	100	90	75	3.60	0.13	NR
					200	80	87	6.15	0.23	NR
					300	71	90	7.10	0.32	NR
					400	64	92	8.00	0.39	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[24] 2005 Multi-national study	Cohort (Breathing Not Properly Study) Ethnicity: NR Comorbidities: diabetes mellitus (n=325), MI (n=353), congestive HF (n=480), arterial Hypertension (n=799); Reference Standard: 2 cardiologists	Diagnosis of acute HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=1,431, Mean age: NR % Males: NR HF Prevalence: 46.1%	NR	NR	NR	NR	NR	NR
				Atrial fibrillation n=292, Mean age: 67–827y, % Males:61.3 HF Prevalence: 46.6%	≥50	99	21	1.24	0.07	NR
					≥100	95	40	1.57	0.14	NR
					≥200	85	73	3.12	0.20	0.084
					≥300	74	80	3.63	0.32	NR
					≥400	64	86	4.70	0.41	NR
					≥500	55	88	4.50	0.51	NR
					≥600	47	89	4.27	0.60	NR
					≥700	43	89	3.86	0.65	NR
					≥800	36	93	5.24	0.69	NR
				No atrial fibrillation n=1,139, Mean age: 49–74y, % Males:59.1 HF Prevalence: 30.2%	≥50	96	65	2.75	0.06	NR
					≥100	89	79	4.15	0.15	NR
					≥200	79	88	6.69	0.24	0.91
					≥300	71	91	7.96	0.32	NR
					≥400	62	93	8.56	0.41	NR
					≥500	55	94	9.03	0.48	NR
					≥600	50	95	9.42	0.53	NR
					≥700	47	96	11.80	0.55	NR
					≥800	47	96	13.06	0.55	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Knudsen,[24] 2005 Multi-national study (cont'd)	(repeated data) Cohort (Breathing Not Properly Study) Ethnicity: NR Comorbidities: diabetes mellitus (n=325), MI (n=353), congestive HF (n=480), arterial Hypertension (n=799); Reference Standard: 2 cardiologists	(repeated data) Diagnosis of acute HF	(repeated data) BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Atrial fibrillation by ECG upon admission n=158, Mean age: NR % Males: NR HF Prevalence: NR%		NR	NR	NR	NR	0.8
				History of atrial fibrillation but no current af n=134, Mean age: NR % Males: HF Prevalence: NR%		NR	NR	NR	NR	0.86
Lainchbury,[25] 2003 New Zealand	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: CAD (n=88), COPD (n=86), previous HF (n=52); Reference Standard: 2 cardiologists	Final clinical diagnosis	BNP- Biosite point-of-care assay [TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, all n=205, Mean age: 70 14), % Males:49 HF Prevalence: 34.1%	20 pmol/L	97	44	1.73	0.07	NR
					30 pmol/L	97	49	1.90	0.06	NR
					60 pmol/L	94	70	3.13	0.09	0.89
					80 pmol/L	83	78	3.77	0.22	NR
					100 pmol/L	77	84	4.81	0.27	NR
			BNP- local research assay (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		33 pmol/L	87	82	4.83	0.16	NR
			BNP- local research assay (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		44 pmol/L	88	82	4.89	0.15	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Logeart,[26] 2002 France	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=65), Prior AMI/angina (n=53), Diabetes mellitus (n=23), Previous CHF (n=80); Reference Standard: 2 cardiologists and 1 pneumologist	No specified end point other than diagnosis	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea, all n=163, Mean age: 67y, % Males:66.8 HF Prevalence: 70.1%	80	97	27	1.33	0.11	NR
					100	96	31	1.39	0.13	NR
					150	93	45	1.69	0.16	NR
					200	93	56	2.11	0.13	NR
					250	91	68	2.84	0.13	NR
					300	88	87	6.77	0.14	0.93
					400	79	93	11.29	0.23	NR
Lokuge,[27] 2010 Australia	RCT (SOB); Inclusion criteria: Patients presenting to the Alfred and the Northern Hospital EDs with a chief complaint of dyspnea; Ethnicity: NR Comorbidities: Hypertension (n=308), atrial fibrillation (n=172), COPD (n=388), diabetes mellitus (n=121), ischemic heart disease (n=253), prior HF (n=220), renal failure (n=69); Reference Standard: 1 cardiologist, emerg.or resp.	Accuracy of HF diagnosis	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea n=306, Mean age: 74 11)y, % Males:54 HF Prevalence: 48.4%	101	92	51	1.88	0.16	0.87
					265*	83	81	4.37	0.21	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[28] 2002 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: COPD (n=650), diabetes mellitus (n=397), MI (n=523), CHF (n=523); Reference Standard: 2 cardiologists	Final diagnosis of CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,586 Mean age: 64y % Males:56 HF Prevalence: 47%	50	97	62	2.55	0.05	NR
					80	93	74	3.58	0.09	NR
					100	90	76	3.75	0.13	0.91
					125	87	79	4.14	0.16	NR
					150	85	83	5.00	0.18	NR
Maisel,[29] 2003 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=879), Prior AMI/angina (n=308), Atrial fibrillation (n=256), COPD (n=600), Diabetes mellitus (n=367), Myocardial infarction (n=385), CHF (n=527), CABG (n=176); Reference Standard: 2 cardiologists	This study examines B-type natriuretic peptide (BNP) levels in patients with systolic versus non-systolic dysfunction presenting with SOB for the purpose of diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,586, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	90	73	3.33	0.14	0.9
					200	81	85	5.40	0.22	NR
					300	73	89	6.64	0.30	NR
					400	63	91	7.00	0.41	NR
				CHF n=452, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	95	14	1.10	0.36	NR
					200	89	NR	NR	NR	NR
					300	83	39	1.36	0.44	0.66
					400	74	50	1.48	0.52	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[30] 2004 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: NR Reference Standard: 2 cardiologists	Final diagnosis of CHF or non-CHF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=1,586 Mean age: 64yrs % Males=56 HF Prevalence: 47%	100	90	73	3.34	0.13	NR
					200	81	85	5.46	0.22	NR
					300	73	89	6.36	0.31	NR
					400	63	91	7.04	0.41	NR
				18 to 69 yrs n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	86	82	4.69	0.17	0.915
					200	77	91	8.45	0.25	NR
					300	69	94	11.10	0.33	NR
					400	60	95	11.23	0.43	NR
				70 to 105 yrs n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	94	53	2.00	0.12	0.844
					200	85	72	3.03	0.21	NR
					300	75	77	3.27	0.32	NR
					400	65	83	3.85	0.42	NR
				Male n=883, Mean age: NR % Males: 100 HF Prevalence: 47.7%	100	92	76	3.84	0.10	0.918
					200	84	88	6.93	0.18	NR
					300	73	90	7.49	0.30	NR
					400	64	93	9.00	0.39	NR
				n=703 Mean age: NR % Males: NR HF Prevalence: 45.7%	100	88	59	2.16	0.20	0.87
					200	78	82	4.27	0.27	NR
					300	72	87	5.40	0.32	NR
					400	61	89	5.55	0.44	NR
				Caucasian n=773 Mean age: NR % Males: NR HF Prevalence: 49.9%	100	93	69	2.96	0.10	0.888
					200	82	82	4.63	0.21	NR
					300	72	86	5.11	0.33	NR
					400	60	90	5.86	0.44	NR
				African-American n=715 Mean age: NR % Males: NR HF Prevalence: 43.9%	100	87	76	3.61	0.17	0.903
					200	81	88	6.45	0.22	NR
					300	74	91	8.24	0.28	NR
					400	66	93	8.79	0.37	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Maisel,[31] 2010 Multi-national study	Cross-sectional (BACH); Ethnicity: Caucasian (n=1090), African-American (n=476), other (n=60); Comorbidities: arrhythmia (n=405), dyslipidemia (n=570), Hypertension (n=1080), CAD (n=504), obstructive lung disease (n=201). prior AMI/angina (n=61), stroke (n=165), ACS (n=38), COPD (n=471), diabetes mellitus (n=462), historical MI (n=300), asthma (n=318), pneumonia (n=112), pulmonary embolism (n=85), chronic renal insufficiency (n=246); Reference Standard: 2 cardiologists	Diagnosis of AHF, where the non-inferiority of MR-proANP compared with BNP was evaluated and 90-day survival, where the superiority of the utility of MR-proADM versus BNP for predicting survival over a period of 90 days	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea, all n=1,641, Mean age: NR % Males: NR HF Prevalence: 34.6%	100	96	62	2.51	0.07	0.91
					300	NR	NR	NR	NR	0.9
McCullough,[32] 2002a Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=230), African-American (n=161), other (n=26); Comorbidities: Hypertension (n=196), prior AMI/angina (n=58), AF (n=54), diabetes mellitus (n=66), historical MI (n=60), MI (n=60), prior CABG (n=26), prior CHD (n=125); Reference Standard: 2 cardiologists, Framingham, NHANES	Diagnosis of HF	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea all n=417, Mean age: 62.2y, % Males:55.2 HF Prevalence: 20.9%	100	93	77	4.10	0.09	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
McCullough,[33] 2002b Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=854), prior AMI/angina (n=371), atrial fibrillation (n=245), COPD (n=580), diabetes mellitus (n=356), stable angina (n=205), prior CHF (n=511), prior CABG (n=168); Reference Standard: 2 cardiologists	Diagnostic accuracy	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=1,538, Mean age: 64y, % Males:56 HF Prevalence: 47%	100	90	73	3.33	0.14	0.9
Morrison,[34] 2002 USA	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=209), CAD (n=173), COPD (n=128), coronary artery bypass graft (n=71), CHF (n=135); Reference Standard: 2 cardiologists, Framingham criteria, echocardiography, nuclear medicine, ejection fractions, or left ventriculography done at cardiac catheterization.	The purpose of this study was to determine if BNP levels could accurately differentiate CHF from dyspnea of pulmonary etiology.	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=321, Mean age: NR % Males: NR HF Prevalence: 42%	94	86	98	43.00	0.14	0.99
					105	86	94	14.33	0.15	NR
					135	90	90	9.00	0.11	NR
					195	94	85	6.27	0.07	NR
					240	96	79	4.57	0.05	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Mueller,[35] 2005 & Gegenhuber,[36] 2006 Austria	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=117), atrial fibrillation (n=83), diabetes mellitus (n=58), renal disease (n=74), arterial Hypertension (n=141); Reference Standard: Framingham	Diagnostic accuracy of BNP/NT-proBNP	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA))	Dyspnea all n=251, Mean age: 58-82y, % Males:93 HF Prevalence: 55%	100 ng/L	96	61	2.46	0.07	NR
					118 ng/L	95	64	2.64	0.08	NR
					160 ng/L	90	73	3.33	0.14	NR
					295 ng/L	80	86	5.71	0.23	NR
Noveanu,[37] 2009 Switzerland	RCT (BASEL); Ethnicity: NR Comorbidities: Hypertension (n=237), CAD (n=225), COPD (n=140), diabetes mellitus (n=103), renal disease (n=112), asthma (n=29), pulmonary embolism (n=31); Reference Standard: internal med specialist	360 days mortality, 360-D in-hospital, 360 day treatment cost, in-hospital mortality, Time to treatment; Hospital admission; Time to discharge, Initial treatment cost	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, all n=452, Mean age: NR % Males: NR HF Prevalence: NR%	NR	NR	NR	NR	NR	NR
				SOB, BMI >30 n=86, Mean age: 72 15)y, % Males:59 HF Prevalence: 44%	100	91	68	2.84	0.13	NR
					182	85	83	5.00	0.18	0.884
					500	56	96	14.00	0.46	NR
				SOB, BMI <30 n=366, Mean age: 65 14), % Males: HF Prevalence: 50%	100	96	56	2.18	0.07	NR
					298	84	81	4.42	0.20	0.885
					500	73	89	6.64	0.30	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Pahle,[38] 2009 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: Hypertension (n=879), atrial fibrillation (n=145), diabetes mellitus (n=353), historical MI (n=362), previous HF (n=503); Reference Standard: 2 cardiologists, Framingham, NHANES	Utility of BNP measurement for diagnosing HF in the emergency department	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=1,583, Mean age: 64 17)y, % Males:56 HF Prevalence: 47%	NR	NR	NR	NR	NR	NR
				Dyspnea, history of hypertension n=879, Mean age: 56-77y, % Males:54 HF Prevalence: 54.3%	50	97	56	2.20	0.05	NR
					100	90	72	3.21	0.14	NR
					120	88	76	3.67	0.16	NR
					140	86	78	3.91	0.18	NR
					160	85	80	4.25	0.19	NR
					194	NR	NR	NR	NR	0.88
					180	83	83	4.88	0.20	NR
					200	82	85	5.47	0.21	NR
					300	74	88	6.17	0.30	NR
				Dyspnea, no history of hypertension n=608, Mean age: 45-75y, % Males:60 HF Prevalence: 34.5%	50	98	70	3.27	0.03	NR
					100	90	83	5.29	0.12	NR
					115	NR	NR	NR	NR	0.93
					120	87	85	5.80	0.15	NR
					140	83	88	6.92	0.19	NR
					160	82	89	7.45	0.20	NR
					180	80	92	10.00	0.22	NR
					200	79	93	11.29	0.23	NR
					300	68	95	13.60	0.34	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Pahle,[38] 2009 Multi-national study (cont'd)	(repeated data) Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: Hypertension (n=879), atrial fibrillation (n=145), diabetes mellitus (n=353), historical MI (n=362), previous HF (n=503); Reference Standard: 2 cardiologists, Framingham, NHANES	(repeated data) Utility of BNP measurement for diagnosing HF in the emergency department	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, elevate emergency department BP n=843, Mean age: 54=78y, % Males:51.8 HF Prevalence: 51.7%	50	97	61	2.49	0.05	NR
					100	91	78	4.14	0.12	NR
					120	88	80	4.40	0.15	NR
					140	87	82	4.83	0.16	NR
					150	NR	NR	NR	NR	0.9
					160	85	84	5.31	0.18	NR
					180	82	87	6.31	0.21	NR
					200	81	87	6.23	0.22	NR
					300	72	91	8.00	0.31	NR
				Dyspnea, no elevate emergency department BP n=740, Mean age: 49-76y, % Males:60 HF Prevalence: 42.4%	50	97	63	2.62	0.05	NR
					100	89	76	3.71	0.14	NR
					120	87	78	3.95	0.17	NR
					140	84	81	4.42	0.20	NR
					160	84	84	5.25	0.19	NR
					180	82	87	6.31	0.21	NR
					200	81	89	7.36	0.21	NR
					205	NR	NR	NR	NR	0.9
					300	73	91	8.11	0.30	NR
Parrinelo,[39] 2008 Italy	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=196), diabetes mellitus (n=56), ischemic heart disease (n=72), previous CHF (n=80), chronic obstructive pulmonary disease or asthma (n=112); Reference Standard: cardiologist, Framingham	Diagnosis of acute decompensated heart failure	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	SOB n=292, Mean age:67.5y, % Males:53.5 HF Prevalence: 58.9%	≥100	95	88	7.58	0.06	NR
					≥127	95	93	14.15	0.06	0.97

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Potocki,[40] 2010 Germany	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=195), CAD (n=80), COPD (n=98), diabetes mellitus (n=52), chronic kidney disease (n=80), previous HF (n=69); Reference Standard: 2 cardiologists	Compare the accuracy of MR-proANP with that of NT-proBNP to diagnose HF	BNP (Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Micro-particle Enzyme Immunoassay (MEIA))	Dyspnea n=287, Mean age: 77 68–83)y, % Males:52 HF Prevalence: 53.7%	BNP	NR	NR	NR	NR	NR
Ray,[41] 2005 France	Cross-sectional (EPIDASA STUDY); Ethnicity: NR Comorbidities: chronic respiratory failure (n=35), cardiac disease (n=64); Reference Standard: 2 independent experts (pulmonologist, cardiologist, emergency physician, or geriatric or internal physician)	Final diagnosis (CPE or no CPE)	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Dyspnea, 65 and older n=202, Mean age: 65–100y, % Males:49 HF Prevalence: 43.6%	250	73	91	8.11	0.30	0.85
Ray,[42] 2006 France	Cross-sectional (EPIDASA study) Ethnicity: NR Comorbidities: cardiac insufficiency (n=63), chronic respiratory insufficiency (n=76), venous thromboembolic disease (n=36); Reference Standard: 2 of cardiologists,	Diagnosis of cardiac pulmonary edema or no CPE	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea >65 yrs n=308, Mean age: 80y, % Males:49 HF Prevalence: 45.7%	100	90	59	2.20	0.17	NR
					150	85	71	2.93	0.21	NR
					200	82	84	5.13	0.21	NR
					250	78	90	7.80	0.24	0.874
					300	72	92	9.00	0.30	NR
					350	67	92	8.38	0.36	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
	pulmonologist, general medicine intern., geriatrician, emergency department physician				400	60	95	12.00	0.42	NR

Ro,[43] 2011
 	
USA
	Cross-Sectional Design (Independent Study);
	Ethnicity:
	caucasian (n=231), African American (n=8), hispanic (n=9), asian (n=1), other unspecified (n=1);
	Comorbidities:
	hypertension (n=196), CAD (n=143), acute MI (n=101), COPD (n=63), diabetes melitus (n=98), pulmonary embolism (n=13), chronic kidney disease (n=48), stable angina (n=44), unstable angina (n=21);
	Reference Standard:
	cardiologist, discharge diagnosis, echo
		To compare the ease of use, performance, and diagnostic accuracy of Triage BNP (Biosite, San Diego, CA) and i-STAT BNP (Abbott, East Windsor, NJ) POC devices in patients with symp-toms suggestive of heart failure in an ED setting.	I-STAT BNP		100	94.4	43.3	1.66	0.13	0.84

			BNP (TRIAGE - BNP Test) I-STAT BNP (i-STAT BNP test)		100	87.7	52.5	1.85	0.23	0.81
Rogers,[44] 2009a Multi-national study	Cohort (HEARD-IT); Ethnicity: Caucasian (n=344), African-American (n=370); Comorbidities: history of HF (n=384), Reference Standard: 2 cardiologists	To create a model that adjusts B-type natriuretic peptide (BNP) for specific covariates to better distinguish cardiac from non-cardiac dyspnea	BNP (Abbott AxSYM® BNP MEIA, ADVIA - Centaur®, BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Dyspnea n=740, Mean age: NR % Males: NR HF Prevalence: 49.7%	100	96	69	3.10	0.06	0.937
					400	NR	93	NR	NR	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
					Adjust BNP cut-off with 96% sen	96	73	3.56	0.05	0.948
Rogers,[45] 2009b USA	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: atrial fibrillation (n=107), COPD (n=43), history of HF (n=164); Reference Standard: 4 physicians	Diagnostic performance for BNP, distinguishing cardiac from non-cardiac dyspnea	BNP (i-STAT BNP test)	Dyspnea, all n=335, Mean age: 72 11)y, % Males: NR HF Prevalence: 42.1%	100	91	54	1.98	0.17	0.858
					400	NR	92	NR	NR	NR
				Dyspnea, age >= 75 years n=171, Mean age: NR % Males: NR HF Prevalence: NR%	100	94	41	1.59	0.15	NR
					184	91	66	2.68	0.14	NR
				Dyspnea, atrial fibrillation n=109, Mean age: NR % Males: NR HF Prevalence: NR%	100	92	26	1.24	0.31	NR
					150	91	39	1.49	0.23	NR
					449	91	78	4.14	0.12	NR
				Dyspnea, creatinine>= 2 mg/dl n=47, Mean age: NR % Males: NR HF Prevalence: NR%	100	100	30	1.43	0.00	NR
				Dyspnea, BMI >= 35 kg/m2 n=85, Mean age: NR % Males: NR HF Prevalence: NR%	25	91	25	1.21	0.36	NR
					100	64	61	1.64	0.59	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Sanz,[46] 2006 Spain	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: systolic dysfunction (n=5), atrial fibrillation (n=8), COPD (n=11), ischemic heart disease (n=5), cardiomyopathy hypertensive (n=9), valvular (n=7); Reference Standard: Symptoms and signs and the following clinical and laboratory emergency department: physical examination, blood test, ECG, chest x-radiography, and in some cases, echocardiography criteria (10)	The aim of this study was to evaluate the value of NT-proBNP and BNP in patients with acute dyspnea in the ED. diagnostic accuracy of different assays.	BNP - ADVIA (ADVIA - Centaur® BNP Assay, TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	Acute dyspnea n=100, Mean age: 75 14.77)y, % Males:67 HF Prevalence: NR%	79	95	96	22.16	0.05	NR
					100	86	98	39.09	0.14	NR
					116	93	96	21.11	0.07	NR
					100	95	89	8.58	0.05	NR
					NR	NR	NR	NR	NR	0.965
					NR	NR	NR	NR	NR	0.975
Shah,[47] 2009a NR	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), atrial fibrillation (n=81), diabetes mellitus (n=121), CHF or cardiomyopathy (n=147); Reference Standard: panel of experts and antihypertensive and lipid lowering treatment to prevent heart attack trial criteria	Mortality after one-year	BNP (TRIAGE - BNP Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea n=412, Mean age: NR % Males: NR HF Prevalence: 37%	100	NR	NR	NR	NR	NR
				Acute dyspnea, LVEF ≤40% n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.88

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shah,[47] 2009a NR (cont'd)	(repeated data) Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), atrial fibrillation (n=81), diabetes mellitus (n=121), CHF or cardiomyopathy (n=147); Reference Standard: panel of experts and antihypertensive and lipid lowering treatment to prevent heart attack trial criteria	(repeated data) Mortality after one year	(repeated data) BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea, LVEF≥50% n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.57
				Acute dyspnea, dx of diastolic function n=NR Mean age: NR % Males: NR HF Prevalence: NR%	100	NR	NR	NR	NR	0.67
Shah,[48] 2009b USA	Cohort (Independent study); Ethnicity: Caucasian (n=136), African-American (n=264), other (n=12); Comorbidities: Hypertension (n=268), CAD (n=177), diabetes mellitus (n=124), historical MI (n=99), renal disease (n=140), heart failure (n=148); Reference Standard: 2 physicians	1 year all-cause mortality	BNP (TRIAGE - B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems)	Acute dyspnea n=412 Mean age: NR % Males: NR HF Prevalence: 35.7%	100	NR	NR	NR	NR	0.9
Steg,[49] 2005 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: NR Comorbidities: NR	Confirmation of the diagnosis CHF or non-CHF patients	BNP (TRIAGE – BNP Test)	Dyspnea n=709 Mean age: 66.4 14.7)y % Males:43.3	50	95	50	1.90	0.10	NR
					80	92	72	3.29	0.11	NR
					100	89	73	3.30	0.15	NR
					125	83	83	4.88	0.20	NR
					150	84	80	4.20	0.20	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
	Reference Standard: 2 cardiologists, Framingham, NHANES			HF Prevalence: 69%	162	86	79	4.10	0.18	NR
Villacorta,[50] 2002 Brazil	Cross-sectional (Independent study) Ethnicity: NR Comorbidities: Hypertension (n=36), CAD (n=30), prior AMI/angina (n=18), atrial fibrillation (n=8), COPD (n=31), renal disease (n=6), coronary (n=14), previous CHD (n=26); Reference Standard: 1 cardiologist	Ability of BNP in diagnosing CHF	BNP (TRIAGE - BNP Test)	Acute dyspnea n=70, Mean age: 72.4y % Males: NR HF Prevalence: 51.4%	200	100	97	33.33	0.00	0.99
Wang,[51] 2010 Taiwan	Cross-sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=38), CAD (n=18), COPD (n=13), diabetes mellitus (n=25), prior HF (n=15); Reference Standard: 2 cardiologists	Diagnosing AHF in patients with acute dyspnea with available plasma BNP	BNP (Abbott AxSYM® BNP MEIA)	Acute dyspnea n=84 Mean age: 73y % Males: 48 HF Prevalence: 58.3%	100	94	34	1.43	0.18	NR
					500	65	74	2.54	0.47	NR

Table H-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at emergency department settings (continued)

Author Year Country	Study Design (companion study)	Objectives/ end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Wu,[52] 2004 Multi-national study	Cross-sectional (Breathing Not Properly Study) Ethnicity: Caucasian (n=773), African-American (n=715), Other (n=98); Comorbidities: Hypertension (n=679), prior AMI/angina (n=308), atrial fibrillation (n=256), COPD (n=600), historical (n=385), prior CABG (n=176), prior (n=527); Reference Standard: 2 cardiologists	Effect of diabetes on BNP concentrations in patients presenting to the ED with dyspnea	BNP (TRIAGE - BNP) Test	Dyspnea all n=1,586 Mean age: NR % Males: NR HF Prevalence: 46.6%	100ng/L	NR	NR	NR	NR	NR
				Dyspnea, without diabetes n=1,219 Mean age: 65.6(13.02)y % Males:59.4 HF Prevalence: 40%	100ng/L	NR	NR	NR	NR	0.88
				Dyspnea, with diabetes n=367 Mean age: 63.5(17.6)y % Males:5.4 HF Prevalence: 59%	100ng/L	NR	NR	NR	NR	0.878

Abbreviations: AHF = acute heart failure; AMI = acute myocardial infarction; AUC = area under the Curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-type natriuretic peptide for Acute Shortness of Breath Evaluation; BMI = body mass index; BP = blood pressure; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CAGB = coronary artery bypass graft; CHD = chronic heart disease; CHF = chronic heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPE = cardiogenic pulmonary edema; ECG = electrocardiogram; ED = emergency department; eGFR = estimated glomerular filtration rate; EPIDASA = Epidemiological study of acute dyspnea in elderly patients; GFR = glomerular filtration rate; glow = lower gray zone; gup = upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = heart failure; KD = kidney disease; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVEF = left ventricular ejection fraction; MEIA = microparticle enzyme immunoassay; mg/dL = milligram per deciliter; MI = myocardial infarction; mL/min/1.73m2 = milliliter per minute per 1.73 meters squared; MR-proANP = midregional pro-A-type natriuretic peptide; ng/L = Nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = Not reported; NT-proBNP = N-Terminal proBNP; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; RCT = Randomized controlled trial; SOB = Shortness of breath; USA = United States of America; yrs = years

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Alibay,[1] 2005	Cross-sectional	Dyspnea, all	160 80.13y 38	38	2 cardiologists	BNP	50	99	31	1.43	0.03	NR
						BNP	100	98	47	1.85	0.04	NR
						BNP	150	94	61	2.41	0.10	0.82
						BNP	200	87	64	2.42	0.20	NR
Arenja,[2] 2011 BASEL	Cohort	Dypsnea	667 76(64-83)y 53	56.5	2 independent cardiologists	BNP	NR	NR	NR	NR	NR	0.96
Arques,[3] 2007	Cross-sectional	Dyspnea, ≥70y	41 84y 41	54	2 cardiologists; 1 chest physician	BNP	200	96	74	3.63	0.06	NR
						BNP	253	86	90	8.23	0.15	0.92
						BNP	≥253	96	90	9.10	0.05	NR
						BNP	≥253	96	90	9.10	0.05	NR
						BNP	≥200	96	84	6.04	0.05	NR
						BNP	≥200	96	79	4.55	0.06	NR
Barcarse,[4] 2004	Cross-sectional	Acute shortness of breath	98 64.6(1.2) 100	58	1 cardiologist	BNP	110	NR	NR	NR	NR	0.97
		Diagnose CHF, BNP>100	33 NR NR	58	1 cardiologist	BNP	590	NR	NR	NR	NR	0.64
Boldanova,[5] 2010 BASEL	Cross-sectional	Dyspnea, all	452 NR NR	49	1 physician	BNP	NR	NR	NR	NR	NR	NR
		Dyspnea, previous history of HF	64 73(11)y 61	84	1 physician	BNP	100	96	45	1.75	0.09	NR
						BNP	403	80	77	3.48	0.26	0.84
						BNP	500	76	77	3.30	0.31	NR
		Dyspnea, no previous history of HF	388 73(11)y 52	44	1 physician	BNP	100	94	59	2.29	0.10	NR
						BNP	289	81	83	4.76	0.23	0.88
						BNP	500	68	99	68.00	0.32	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Chenevier-Gobeaux,[6] 2005	Cross-sectional	Dyspnea, all	381 79(12)y NR	30	Urgentists	BNP	NR	NR	NR	NR	NR	NR
		Dyspnea, GFR <30y	41 83(11)y NR	49	Urgentists	BNP	515	82	89	7.45	0.20	0.89
		Dyspnea, GFR 59 to 30y	187 81(10)y NR	34	Urgentists	BNP	480	74	81	3.89	0.32	0.79
		Dyspnea, 89 to 60y	141 74(13)y NR	20	Urgentists	BNP	290	76	88	6.33	0.27	0.84
Chenevier-Gobeaux,[7] 2008 Ray and Chenevier-Gobeaux 2005	Cross-sectional	Dyspnea, all	570 NR 48	44	physicians	BNP	NR	NR	NR	NR	NR	NR
		Acute dyspnea, ≥85y	210 NR 35	52	physicians	BNP	250	85	64	2.36	0.23	NR
						BNP	290	80	69	2.58	0.29	0.79
						BNP	380	70	73	2.59	0.41	NR
						BNP	400	67	75	2.68	0.44	NR
						BNP	500	60	79	2.86	0.51	NR
						BNP	590	55	85	3.67	0.53	NR
		Acute dyspnea, <85y	360 NR 52	40	physicians	BNP	270	73	83	4.29	0.33	0.83

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Chenevier-Gobeaux,[8] 2010	Cross-sectional	Dyspnea, >60y,	378 78 (12)y 50	30	2 emergency department physicians	BNP	100 ng/L	99	41	1.68	0.02	0.82
		Tertile 3 (eGFR ≥58.6 ml/min/1.73 m2)	126 73 (13)y 68	17	2 emergency department physicians	BNP	210 ng/L	86	71	2.97	0.20	0.85
		Tertile 2 (eGFR between 44.3 and 58.5 ml/min/1.73m 2)	126 79 (11)y 44	34	2 emergency department physicians	BNP	280 ng/L	88	72	3.14	0.17	0.86
		Tertile 1 (eGFR<44.3 ml/ min/1.73 m2),	126 83 (10)y 39	39	2 emergency department physicians	BNP	550 ng/L	85	65	2.43	0.23	0.76
Choi,[9] 2007	Cross-sectional	Dyspnea, all	1040 NR 56	36	The final diagnosis of CHF was defined by transthoracic echocardiography.	BNP	12.5	100	28	1.39	0.00	0.96
						BNP	100	99	67	3.00	0.02	NR
						BNP	191	96	84	5.82	0.05	NR
						BNP	296.5	91	91	10.52	0.10	0.96
						BNP	400	85	96	22.29	0.16	NR
						BNP	496	70	97	25.96	0.31	NR
						BNP	601	61	98	26.35	0.40	NR
						BNP	983.5	40	99	33.25	0.61	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Chung,[10] 2006	Cross-sectional	Patients with dyspnea, all	143 79(10) 44	50	1 cardiologist	BNP	100	100	41	1.65	0.00	0.85
						BNP	400	87	76	3.63	0.17	NR
		History of HF	80 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.74
		No history of HF	63 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.94
		LVEF <50%	67 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.64
		LVEF ≥50%	39 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.87
		High serum creatinine	NR NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.81
		Low serum creatinine	NR NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.9
		Initial intermediate likelihood of HF	44 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.79
		Low or high likelihood of HF	9 NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.86
		Patients ≥79 years	NR NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.85
		Patients <79 years	NR NR NR	NR	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.88

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Collins,[11] 2006	Cross-sectional	Dyspnea	NR NR NR	39	2 senior cardiology fellows	BNP	''Indeterminate zone'' (100 to ≤500 pg/mL)	NR	NR	NR	NR	NR
Coste,[12] 2006	Cross-sectional	Acute dyspnea	699 72.8 (14.3)y 68	60	2 cardiologists	BNP	NR	NR	NR	NR	NR	NR
		Acute dyspnea, no history CHF	525 NR NR	NR	2 cardiologists	BNP	The cutoff points delimiting the gray zones glow=167 ng/L (95% bootstrap CI 108 to 219) and gup= 472 ng/L (95% bootstrap CI 390 to 501)	NR	NR	18.25	0.05	NR
		Acute dyspnea, history of CHF	174 NR NR	NR	2 cardiologists	BNP	gup=334 ng/L (95% bootstrap CI 178 to 465); glow=0	NR	NR	3.35	0.01	NR
Daniels,[13] 2006 Breathing Not Properly Study	Cross-sectional	Dyspnea, all	1,368 65y 56	46	2 cardiologists	BNP	NR	NR	NR	NR	NR	NR
		Dyspnea, BMI <25	526 67.3y 55.7	47	2 cardiologists	BNP	100	94	65	2.63	0.10	0.9

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Daniels,[13] 2006 Breathing Not Properly Study (cont'd)	Cross-sectional	Dyspnea, 25 ≤BMI <35	595 63.2y 58	46	2 cardiologists	BNP	100	92	76	3.88	0.10	0.91
		Dyspnea, BMI ≥35	247 56.7y 46.3	44	2 cardiologists	BNP	100	77	84	4.85	0.27	0.88
		Dyspnea, BMI <25	526 67.3y 55.7	47	2 cardiologists	BNP	1	90	NR	NR	NR	NR
		Dyspnea, 25 ≤BMI <35	595 63.2y 58	46	2 cardiologists	BNP	110	90	NR	NR	NR	NR
		Dyspnea, BMI ≥35	247 56.7y 46.3	44	2 cardiologists	BNP	54	90	NR	NR	NR	NR
Dao,[14] 2001	Cross-sectional	Dyspnea, all	250 63y 94	39	2 cardiologists	BNP	80	98	92	12.25	0.02	0.98
						BNP	100	94	94	15.67	0.06	NR
						BNP	115	90	96	22.50	0.10	NR
						BNP	120	90	96	22.50	0.10	NR
						BNP	150	87	97	29.00	0.13	NR
Defilippi,[15] 2007	Cohort	Dyspnea all	831 NR 45.7	53	1 cardiologist	BNP	NR	NR	NR	NR	NR	NR
		No kidney disease (kd), eGFR ≥60	438 63.5(16.0)y 43.8	45	1 cardiologist	BNP	100 ng/L	90	37	1.42	0.27	0.95
		Kidney disease eGFR <60	393 69.3(13.1)y 47.8	61	1 cardiologist	BNP	200 ng/L	82	53	1.74	0.34	0.68
Dieplinger,[16] 2009 Mueller, et al. 2005, Gegenhuber, et al. 2006	Cross-sectional	Dyspnea	251 NR NR	55	Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction	BNP	160 ng/L	90	73	3.33	0.14	0.92

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Dieplinger,[16] 2009 Mueller, et al. 2005, Gegenhuber, et al. 2006 (cont'd)	Cross-sectional	Dyspnea attributable to acute destabilized emergency department HF	137 69 to 82y 93	46	Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction	BNP	NR	NR	NR	NR	NR	NR
		Dyspnea not attributable to HF	114 68 to 82y 95	8	Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction	BNP	NR	NR	NR	NR	NR	NR
Gorissen,[17] 2007	Cross-sectional	Acute dyspnea, all	80 43 to 90y 55	50	Consensus on clinical diag (cardiologist + pulmonologist)	BNP Centaur	138 ng/L	65	88	5.42	0.40	0.77
						BNP Triage	225 ng/L	73	78	3.32	0.35	0.78
		Acute dyspnea, <65	17 NR NR	NR	Consensus on clinical diag (cardiologist + pulmonologist)	BNP Triage	78 ng/L	100	55	2.22	0.00	0.75
						BNP Centaur	91 ng/L	100	55	2.22	0.00	0.70
		Acute dyspnea, 65-75y	23 NR NR	NR	Consensus on clinical diag (cardiologist + pulmonologist)	BNP Triage	260 ng/L	82	83	4.82	0.22	0.79
						BNP Centaur	188 ng/L	73	83	4.29	0.33	0.77
		Acute dyspnea, >75y	40 NR NR	NR	Consensus on clinical diag (cardiologist + pulmonologist)	BNP Triage	309 ng/L	68	71	2.34	0.45	0.76
						BNP Centaur	247 ng/L	68	77	2.96	0.42	0.76
		Acute dyspnea, GFR >60	40 NR NR	NR	Consensus on clinical diag (cardiologist + pulmonologist)	BNP Triage	202 ng/L	81	63	2.19	0.30	0.79
						BNP Triage	127 ng/L	73	85	4.87	0.32	0.79
		Acute dyspnea,	40 NR	NR	Consensus on clinical diag	BNP Centaur	229 ng/L	64	70	2.13	0.51	0.66

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
		GFR <60	NR		(cardiologist + pulmonologist)	BNP Centaur	309 ng/L	64	74	2.46	0.49	0.69
Gruson,[18] 2008	Cohort	Patients with dyspnea and/or chest pain (with cardiovascular and/or pulmonary disorders), all	137 69y 56.2	23	1 cardiologist	BNP	NR	NR	NR	NR	NR	0.93
Gruson,[19] 2009	Cross-sectional	Dyspnea, all	97 30–95y 43	20	Clinicians	SOB BNP	NR	100	59	2.44	0.00	NR
Gruson,[20] 2012	Cohort	Dyspnea and/or chest pain, all	156 67y 54.5	29.5	Clinicians	BNP	100 ng/L	NR	NR	NR	NR	0.91
Havelka,[21] 2011	Cross-sectional	Dyspnea, all	54 80y* 46	NR	Discharge diagnosis	BNP	NR	NR	NR	NR	NR	0.77
Knudsen,[23] 2004a Breathing Not Properly Study	Cross-sectional	Acute dyspnea, all	880 64y 55	51	2 cardiologists, Framingham, NHANES	BNP	100	90	75	3.60	0.13	NR
						BNP	200	80	87	6.15	0.23	NR
						BNP	300	71	90	7.10	0.32	NR
						BNP	400	64	92	8.00	0.39	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Knudsen,[22] 2004b	Cross-sectional	Dyspnea all	155 NR 44.5	48	2 cardiologists	BNP	100	NR	NR	NR	NR	NR
		Acute dyspnea, women	86 78y* NR	41	2 cardiologists	BNP	50	100	37	1.59	0.00	NR
						BNP	100	94	55	2.09	0.10	NR
						BNP	150	91	59	2.22	0.15	NR
						BNP	200	89	63	2.38	0.18	0.86
		Acute dyspnea, men	69 74y* NR	58	2 cardiologists	BNP	50	95	38	1.53	0.13	NR
						BNP	100	90	55	2.01	0.18	NR
						BNP	150	93	62	2.44	0.12	NR
						BNP	200	90	72	3.26	0.14	0.9
		Acute dyspnea, ≥76y	NR NR NR	NR	2 cardiologists	BNP	100	NR	NR	NR	NR	0.88
		Acute dyspnea, <76y	NR NR NR	NR	2 cardiologists	BNP	100	NR	NR	NR	NR	0.82

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Knudsen,[24] 2005 Breathing Not Properly Study	Cohort	Dyspnea all	1,431 NR NR	46	2 cardiologists	BNP	NR	NR	NR	NR	NR	NR
		Atrial fibrillation	292 67 to 827y 61.3	47	2 cardiologists	BNP	≥50	99	21	1.24	0.07	NR
						BNP	≥100	95	40	1.57	0.14	NR
						BNP	≥200	85	73	3.12	0.20	0.084
						BNP	≥300	74	80	3.63	0.32	NR
						BNP	≥400	64	86	4.70	0.41	NR
						BNP	≥500	55	88	4.50	0.51	NR
						BNP	≥600	47	89	4.27	0.60	NR
						BNP	≥700	43	89	3.86	0.65	NR
						BNP	≥800	36	93	5.24	0.69	NR
		No atrial fibrillation	1,139 49 to 74y 59.1	30	2 cardiologists	BNP	≥50	96	65	2.75	0.06	NR
						BNP	≥100	89	79	4.15	0.15	NR
						BNP	≥200	79	88	6.69	0.24	0.91
						BNP	≥300	71	91	7.96	0.32	NR
						BNP	≥400	62	93	8.56	0.41	NR
						BNP	≥500	55	94	9.03	0.48	NR
						BNP	≥600	50	95	9.42	0.53	NR
						BNP	≥700	47	96	11.80	0.55	NR
						BNP	≥800	47	96	13.06	0.55	NR
		Atrial fibrillation by ECG upon admission	158 NR NR	NR	2 cardiologists	BNP	NA	NR	NR	NR	NR	0.80
		History of atrial fibrillation but no current AF	134 NR	NR	2 cardiologists	BNP	NA	NR	NR	NR	NR	0.86

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Lainchbury,[25] 2003	Cross-sectional	Acute Dyspnea, all	205 70(14)y 49	34	2 cardiologists	BNP-Biosite point-of-care assay	20pmol/L 69 pg/mL	97	44	1.73	0.07	NR
						BNP-Biosite point-of-care assay	30pmol/L 103 pg/mL	97	49	1.90	0.06	NR
						BNP-Biosite point-of-care assay	60pmol/L 206 pg/mL	94	70	3.13	0.09	0.89
						BNP-Biosite point-of-care assay	80pmol/L 275 pg/mL	83	78	3.77	0.22	NR
		Acute dyspnea, all	205 70(14)y 49	34	2 cardiologists	BNP-Biosite point-of-care assay	100pmol/L 345 pg/mL	77	84	4.81	0.27	NR
						BNP-local clinical assay	44pmol/L	88	82	4.89	0.15	NR
Logeart,[26] 2002	Cross-sectional	Acute dyspnea, all	163 67y 66.8	70	2 cardiologists and 1 pneumologist	BNP	80	97	27	1.33	0.11	NR
						BNP	100	96	31	1.39	0.13	NR
						BNP	150	93	45	1.69	0.16	NR
						BNP	200	93	56	2.11	0.13	NR
						BNP	250	91	68	2.84	0.13	NR
						BNP	300	88	87	6.77	0.14	0.93
						BNP	400	79	93	11.29	0.23	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Lokuge,[27] 2010 SOB	RCT	Dyspnea	306 74(11)y 54	48	1 cardiologist, emerg or respirologist.	BNP	101	92	51	1.88	0.16	0.87
						BNP	265*	83	81	4.37	0.21	NR
Maisel,[28] 2002 BNP	Cross-sectional	Acute dyspnea	1,586 64y 56	47	2 cardiologists	BNP	50	97	62	2.55	0.05	NR
						BNP	80	93	74	3.58	0.09	NR
						BNP	100	90	76	3.75	0.13	0.91
						BNP	125	87	79	4.14	0.16	NR
						BNP	150	85	83	5.00	0.18	NR
Maisel,[29] 2003 Breathing Not Properly Study	Cross-sectional	Acute dyspnea	1,586 64y 56	47	2 cardiologists	BNP	100	90	73	3.33	0.14	0.9
						BNP	200	81	85	5.40	0.22	NR
						BNP	300	73	89	6.64	0.30	NR
						BNP	400	63	91	7.00	0.41	NR
		CHF	452 64y 56	47	2 cardiologists	BNP	100	95	14	1.10	0.36	NR
						BNP	200	89	NR	NR	NR	NR
						BNP	300	83	39	1.36	0.44	0.66
						BNP	400	74	50	1.48	0.52	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Maisel,[30] 2004 Breathing Not Properly Study	Cross-sectional	Dyspnea	1,586 64y 56	47	2 cardiologists	BNP	100	90	73	3.34	0.13	NR
						BNP	200	81	85	5.46	0.22	NR
						BNP	300	73	89	6.36	0.31	NR
						BNP	400	63	91	7.04	0.41	NR
		18 to 69y	NR NR NR	NR	2 cardiologists	BNP	100	86	82	4.69	0.17	0.91
						BNP	200	77	91	8.45	0.25	NR
						BNP	300	69	94	11.10	0.33	NR
						BNP	400	60	95	11.23	0.43	NR
		70 to 105y	NR NR NR	NR	2 cardiologists	BNP	100	94	53	2.00	0.12	0.84
						BNP	200	85	72	3.03	0.21	NR
						BNP	300	75	77	3.27	0.32	NR
						BNP	400	65	83	3.85	0.42	NR
		Male	883 NR NR	48	2 cardiologists	BNP	100	92	76	3.84	0.10	0.91
						BNP	200	84	88	6.93	0.18	NR
						BNP	300	73	90	7.49	0.30	NR
						BNP	400	64	93	9.00	0.39	NR
		Female	703 NR NR	46	2 cardiologists	BNP	100	88	59	2.16	0.20	0.87
						BNP	200	78	82	4.27	0.27	NR
						BNP	300	72	87	5.40	0.32	NR
						BNP	400	61	89	5.55	0.44	NR
		Caucasian	773 NR NR	50	2 cardiologists	BNP	100	93	69	2.96	0.10	0.88
						BNP	200	82	82	4.63	0.21	NR
						BNP	300	72	86	5.11	0.33	NR
						BNP	400	60	90	5.86	0.44	NR
		African American	715 NR NR	44	2 cardiologists	BNP	100	87	76	3.61	0.17	0.90
						BNP	200	81	88	6.45	0.22	NR
						BNP	300	74	91	8.24	0.28	NR
						BNP	400	66	93	8.79	0.37	NR
Maisel,[31] 2010 BACH	Cross-sectional	Acute dyspnea, all	1,641 NR NR	35	2 cardiologists	BNP	100	96	62	2.51	0.07	0.91
						BNP	300	NR	NR	NR	NR	0.9

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
McCullough,[32] 2002a Breathing Not Properly Study	Cross-sectional	Dyspnea all	417 62.2y 55.2	21	2 cardiologists, Framingham, NHANES	BNP	100	93	77	4.10	0.09	NR
McCullough,[33] 2002b Breathing Not Properly Study	Cross-sectional	Acute dyspnea	1538 64y 56	47	2 cardiologists	BNP	100	90	73	3.33	0.14	0.9
Morrison,[34] 2002	Cross-sectional	Acute dyspnea	321 NR NR	42	2 cardiologists, Framingham criteria, echocardiography, nuclear medicine, ejection fractions, or left ventriculography done at cardiac catheterization.	BNP	94	86	98	43.00	0.14	0.99
						BNP	105	86	94	14.33	0.15	NR
						BNP	135	90	90	9.00	0.11	NR
						BNP	195	94	85	6.27	0.07	NR
						BNP	240	96	79	4.57	0.05	NR
Mueller,[35] 2005 & Gegenhuber,[36] 2006	Cross-sectional	Dyspnea all	251 58-82y 93	55	Framingham	BNP	100 ng/L	96	61	2.46	0.07	NR
						BNP	118 ng/L	95	64	2.64	0.08	NR
						BNP	160 ng/L	90	73	3.33	0.14	NR
						BNP	295 ng/L	80	86	5.71	0.23	NR
Noveanu,[37] 2009 BASEL	RCT	Dyspnea, all	452 NR NR	NR	Internal medicine specialist	BNP	NR	NR	NR	NR	NR	NR
		Shortness of breath, BMI ≥30	86 72(15)y 59	44	Internal medicine specialist	BNP	100	91	68	2.84	0.13	NR
						BNP	182	85	83	5.00	0.18	0.88
						BNP	500	56	96	14.00	0.46	NR
		Shortness of breath, BMI <30	366 65(14)y 58	50	Internal medicine specialist	BNP	100	96	56	2.18	0.07	NR
						BNP	298	84	81	4.42	0.20	0.88
						BNP	500	73	89	6.64	0.30	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Pahle,[38] 2009 Breathing Not Properly Study	Cross-sectional	Dyspnea	1,583 64(17)y 56	47	2 cardiologists, Framingham, NHANES	BNP	NR	NR	NR	NR	NR	NR
		Dyspnea, history of hypertension	879 56-77y 54	54	2 cardiologists, Framingham, NHANES	BNP	50	97	56	2.20	0.05	NR
						BNP	100	90	72	3.21	0.14	NR
						BNP	120	88	76	3.67	0.16	NR
						BNP	140	86	78	3.91	0.18	NR
						BNP	160	85	80	4.25	0.19	NR
						BNP	194	NR	NR	NR	NR	0.88
						BNP	180	83	83	4.88	0.20	NR
						BNP	200	82	85	5.47	0.21	NR
						BNP	300	74	88	6.17	0.30	NR
		Dyspnea, no history of hypertension	608 45-75y 60	35	2 cardiologists, Framingham, NHANES	BNP	50	98	70	3.27	0.03	NR
						BNP	100	90	83	5.29	0.12	NR
						BNP	115	NR	NR	NR	NR	0.93
						BNP	120	87	85	5.80	0.15	NR
						BNP	140	83	88	6.92	0.19	NR
						BNP	160	82	89	7.45	0.20	NR
						BNP	180	80	92	10.00	0.22	NR
						BNP	200	79	93	11.29	0.23	NR
						BNP	300	68	95	13.60	0.34	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Pahle,[38] 2009 Breathing Not Properly Study (cont'd)	Cross-sectional	Dyspnea, elevated emergency department BP	843 54-78y 51.8	52	2 cardiologists, Framingham, NHANES	BNP	50	97	61	2.49	0.05	NR
						BNP	100	91	78	4.14	0.12	NR
						BNP	120	88	80	4.40	0.15	NR
						BNP	140	87	82	4.83	0.16	NR
						BNP	150	NR	NR	NR	NR	0.90
						BNP	160	85	84	5.31	0.18	NR
						BNP	180	82	87	6.31	0.21	NR
						BNP	200	81	87	6.23	0.22	NR
						BNP	300	72	91	8.00	0.31	NR
		Dyspnea, no elevated emergency department BP	740 49-76y 60	42	2 cardiologists, Framingham, NHANES	BNP	50	97	63	2.62	0.05	NR
						BNP	100	89	76	3.71	0.14	NR
						BNP	120	87	78	3.95	0.17	NR
						BNP	140	84	81	4.42	0.20	NR
						BNP	160	84	84	5.25	0.19	NR
						BNP	180	82	87	6.31	0.21	NR
						BNP	200	81	89	7.36	0.21	NR
						BNP	205	NR	NR	NR	NR	0.90
						BNP	300	73	91	8.11	0.30	NR
Parrinelo,[39] 2008	Cross-sectional	Shortness of breath	292 67.5y 53.5	59	Cardiologist, Framingham	BNP	≥100	95	88	7.58	0.06	NR
						BNP	≥127	95	93	14.15	0.06	0.97
Potocki,[40] 2010	Cross-sectional	Dyspnea	287 77 (68–83)y 52	54	2 cardiologists	BNP	BNP	NR	NR	NR	NR	NR
Ray,[41] 2005 EPIDASA study	Cross-sectional	Dyspnea, ≥65y	202 65–100y 49	44	2 independent experts (pulmonologist, cardiologist, emergency physician, or geriatric or internal physician)	BNP	250	73	91	8.11	0.30	0.85

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Ray,[42] 2006 EPIDASA study	Cross-sectional	Acute dyspnea >65y	308 80y 49	46	2 of cardiologists, pulmonologist, general medicine internist, geriatric, ED physician	BNP	100	90	59	2.20	0.17	NR
						BNP	150	85	71	2.93	0.21	NR
						BNP	200	82	84	5.13	0.21	NR
						BNP	250	78	90	7.80	0.24	0.87
						BNP	300	72	92	9.00	0.30	NR
						BNP	350	67	92	8.38	0.36	NR
						BNP	400	60	95	12.00	0.42	NR
Ro,[43] 2011	Cross-sectional design	Symptoms of HF	250 70.7±13.8y 58.8	42	1 cardiologist, discharge diagnosis, echocardiography	I-STAT BNP	100	94.4	43.3	1.66	0.13	0.84
						Triage BNP	100	87.7	52.5	1.85	0.23	0.81
Rogers,[44] 2009a HEARD-IT	Cohort	Dyspnea	740 NR NR	50	2 cardiologists	BNP	100	96	69	3.10	0.06	0.93
						BNP	400	NR	93	NR	NR	NR
						BNP	Adjust BNP cut-off with 96% sen	96	73	3.56	0.05	0.948
Rogers,[45] 2009b	Cross-sectional	Dyspnea, all	335 72(11)y NR	42	4 physicians	BNP	100	91	54	1.98	0.17	0.85
						BNP	400	NR	92	NR	NR	NR
		Dyspnea, age ≥75y	171 NR NR	NR	4 physicians	BNP	100	94	41	1.59	0.15	NR
						BNP	184	91	66	2.68	0.14	NR
		Dyspnea, atrial fibrillation	109 NR NR	NR	4 physicians	BNP	100	92	26	1.24	0.31	NR
						BNP	150	91	39	1.49	0.23	NR
						BNP	449	91	78	4.14	0.12	NR
		Dyspnea, creatinine ≥2 mg/dl	47 NR NR	NR	4 physicians	BNP	100	100	30	1.43	0.00	NR
		Dyspnea, BMI ≥35 kg/m2	85 NR NR	NR	4 physicians	BNP	25	91	25	1.21	0.36	NR
						BNP	100	64	61	1.64	0.59	NR

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Sanz,[46] 2006	Cross-sectional	Acute dyspnea	100 75(14.77)y 67	NR	Clinical, laboratory, imaging, and ECG data	BNP - ADVIA	79	95	96	22.16	0.05	NR
						BNP - ADVIA	100	86	98	39.09	0.14	NR
						BNP - Access	116	93	96	21.11	0.07	NR
						BNP - Access	100	95	89	8.58	0.05	NR
						BNP - ADVIA	NR	NR	NR	NR	NR	0.96
						BPN - Access	NR	NR	NR	NR	NR	0.97
Shah,[47] 2009	Cross-sectional	Acute dyspnea	412 NR NR	37	Panel of experts and "antihypertensive- and lipid lowering treatment to prevent heart attack" trial criteria	BNP	100	NR	NR	NR	NR	NR
		Acute dyspnea, LVEF ≤40%	NR NR NR	NR	Panel of experts and "antihypertensive- and lipid lowering treatment to prevent heart attack" trial criteria	BNP	100	NR	NR	NR	NR	0.88
		Acute dyspnea, LVEF≥50%	NR NR NR	NR	Panel of experts and "antihypertensive- and lipid lowering treatment to prevent heart attack" trial criteria	BNP	100	NR	NR	NR	NR	0.57
		Acute dyspnea, diagnosis of diastolic function	NR NR NR	NR	Panel of experts and "antihypertensive- and lipid lowering treatment to prevent heart attack" trial criteria	BNP	100	NR	NR	NR	NR	0.67

Table H-2. Detailed diagnostic properties of papers evaluating BNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author, Year, Companion	Study Design	Population Type	n Mean Age % Males	HF Prevalence (%)	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Shah,[48] 2009	Cohort	Acute dyspnea	412 NR NR	36	2 physicians	BNP	100	NR	NR	NR	NR	0.90
Steg,[49] 2005 Breathing Not Properly Study	Cross-sectional	Dyspnea	709 66.4(14.7)y 43.3	69	2 cardiologists, Framingham, NHANES	BNP	50	95	50	1.90	0.10	NR
						BNP	80	92	72	3.29	0.11	NR
						BNP	100	89	73	3.30	0.15	NR
						BNP	125	83	83	4.88	0.20	NR
						BNP	150	84	80	4.20	0.20	NR
						BNP	162	86	79	4.10	0.18	NR
Villacorta,[50] 2002	Cross-sectional	Acute dyspnea	70 72.4y 60.4	51	1 cardiologist	BNP	200	100	97	33.33	0.00	0.99
Wang,[51] 2010	Cross-sectional	Acute dyspnea	84 73y 48	58	2 cardiologists	BNP	100	94	34	1.43	0.18	NR
						BNP	500	65	74	2.54	0.47	NR
Wu,[52] 2004 Breathing Not Properly Study	Cross-sectional	Dyspnea all	1586 NR NR	47	2 cardiologists	BNP	100 ng/L	NR	NR	NR	NR	NR
		Dyspnea, without diabetes	1219 65.6 (13.02)y 59.4	40	2 cardiologists	BNP	100 ng/L	NR	NR	NR	NR	0.88
		Dyspnea, with diabetes	367 63.5(17.6)y 5.4	59	2 cardiologists	BNP	100 ng/L	NR	NR	NR	NR	0.87

Abbreviations: AUC = area under the curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation; BMI = body mass index; BNP=B-Type Natriuretic Peptide; BP=blood pressure; CHF = congestive heart failure; CI = confidence interval; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EPIDASA = Epidemiological Study of Acute Dyspnea in Elderly Patients; GFR = glomerular filtration rate; glow = lower gray zone; gup=upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = heart failure; KD = kidney disease; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVEF = left ventricular ejection fraction; mg/dL = milligram per deciliter; mL/min/m2 = milliliter per minute per meters squared; NA = not applicable; ng/L = nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = not reported ; pg/mL = picograms per milliliter; RCT = randomized controlled trial; SOB = shortness of breath; y = year(s)

Figure H-1. Summary forest plot of sensitivity and specificity (ED BNP, manufacturer cut-point), bivariate mixed effect model

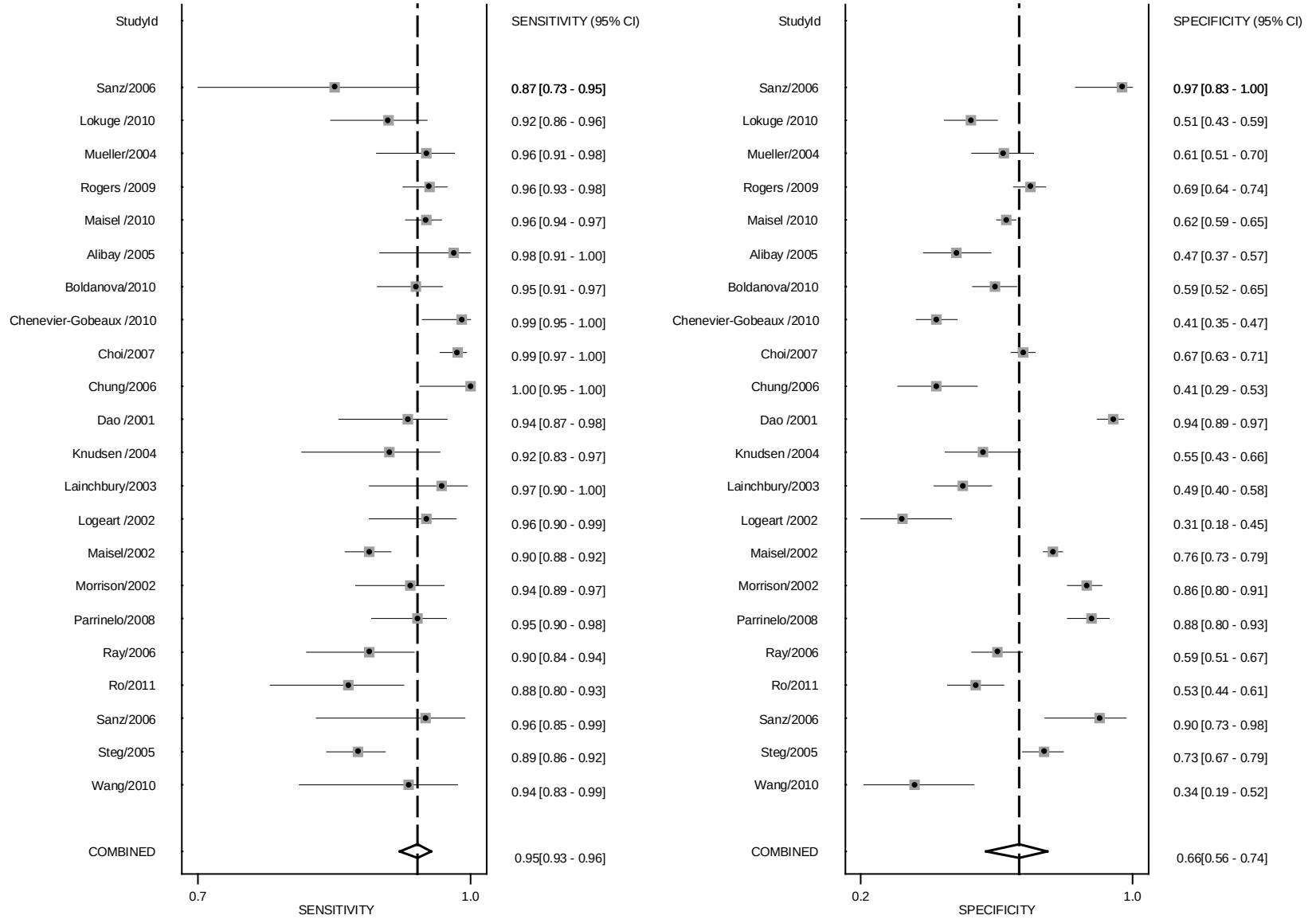


Figure H-2. Summary forest plot of sensitivity and specificity (ED BNP, optimum cut-point), bivariate mixed effect model

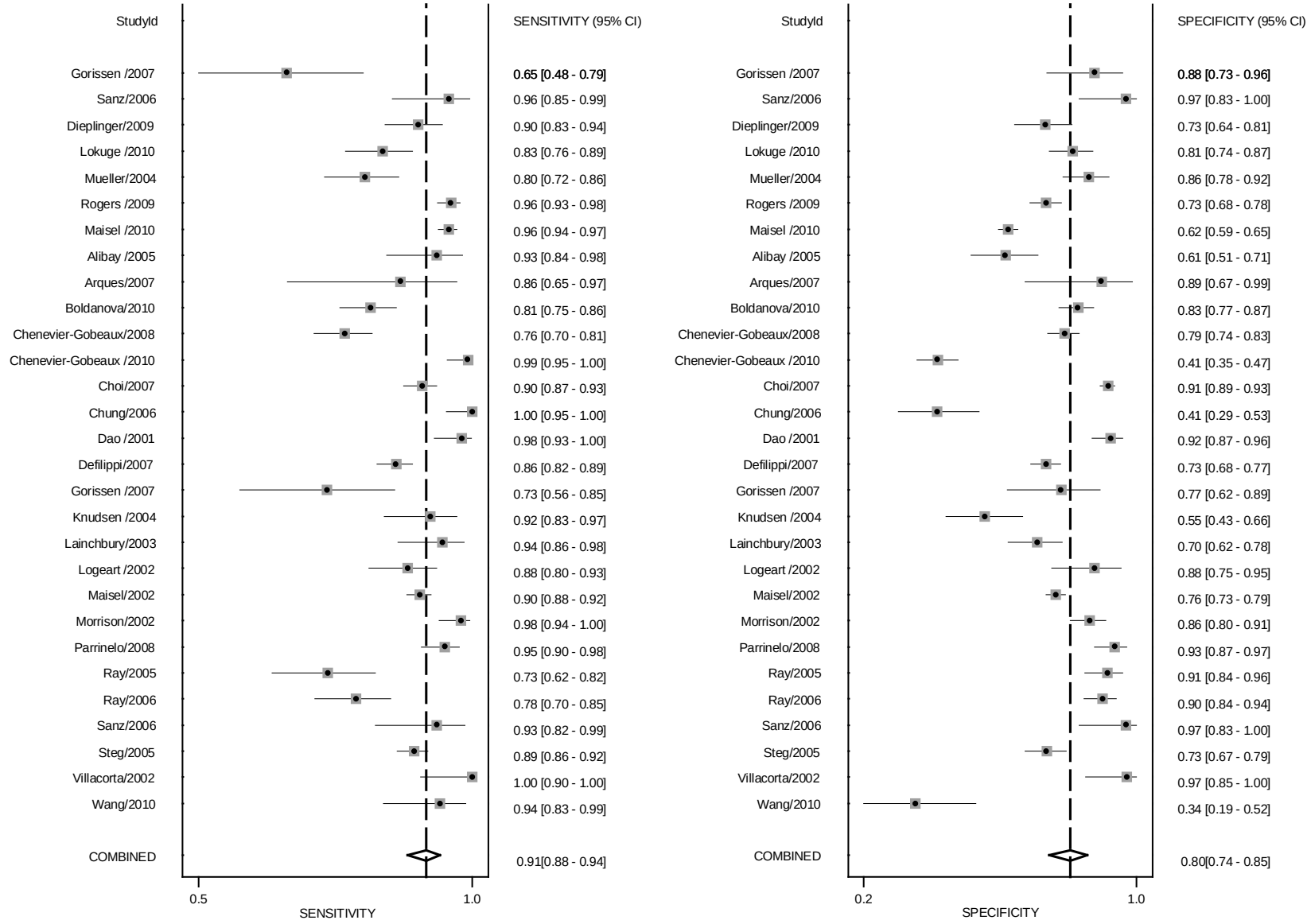


Figure H-3. Summary forest plot of sensitivity and specificity (ED BNP, lowest cut-point), bivariate mixed effect model

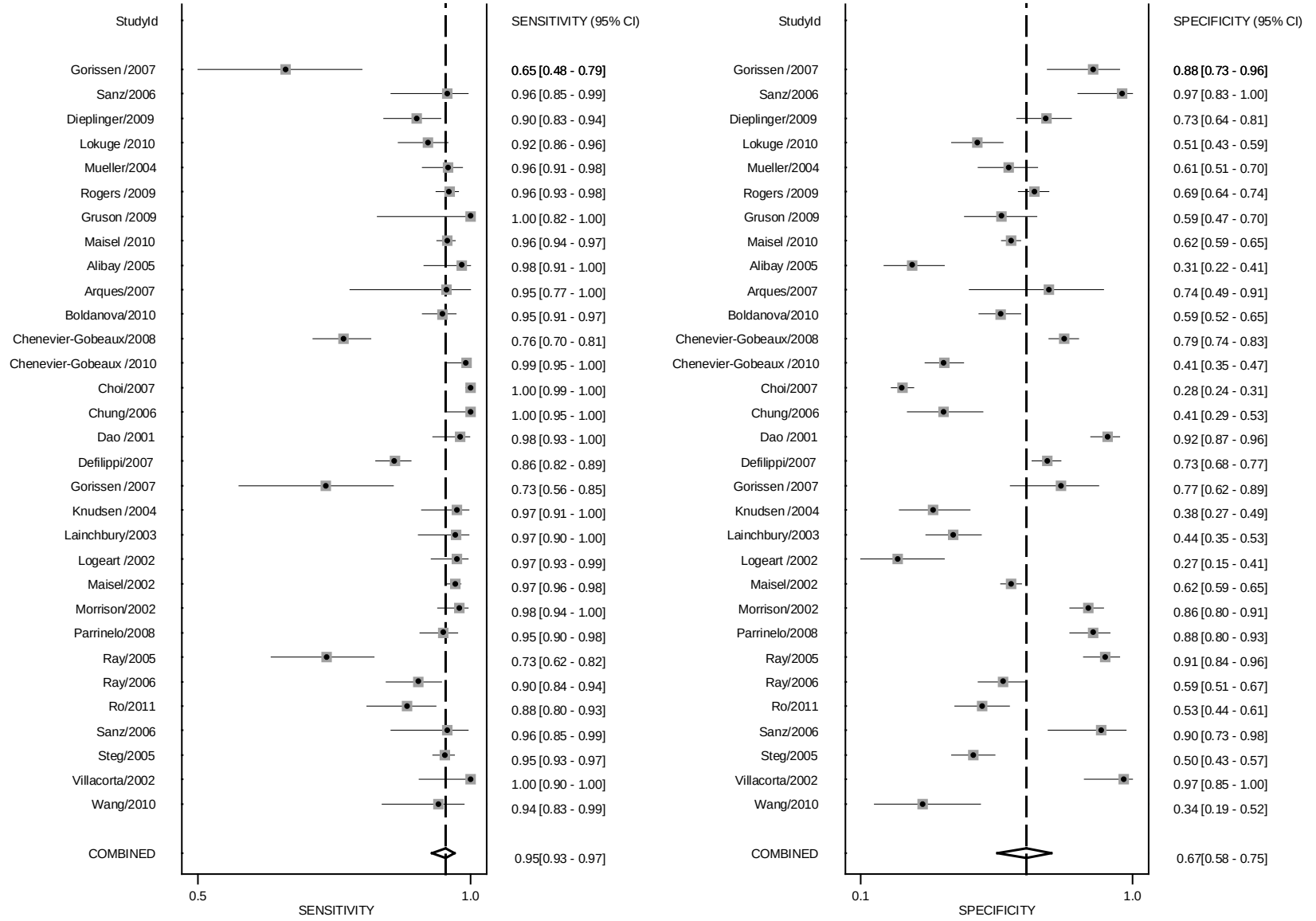


Figure H-4. Summary forest plot of LR+ and LR- (ED BNP, manufacturer cut-point), bivariate mixed effect model

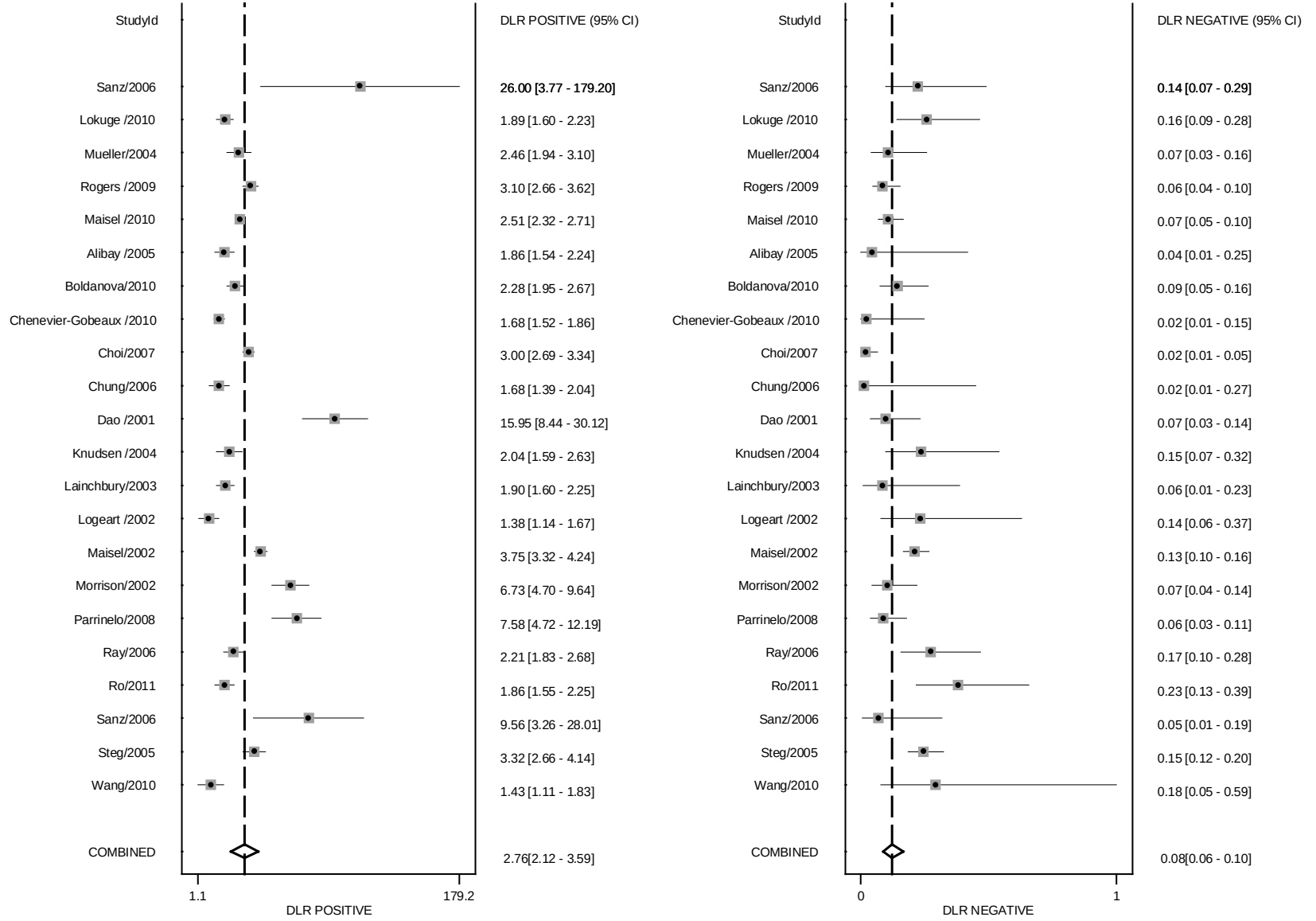


Figure H-5. Summary forest plot of LR+ and LR- (ED BNP, optimum cut-point), bivariate mixed effect model

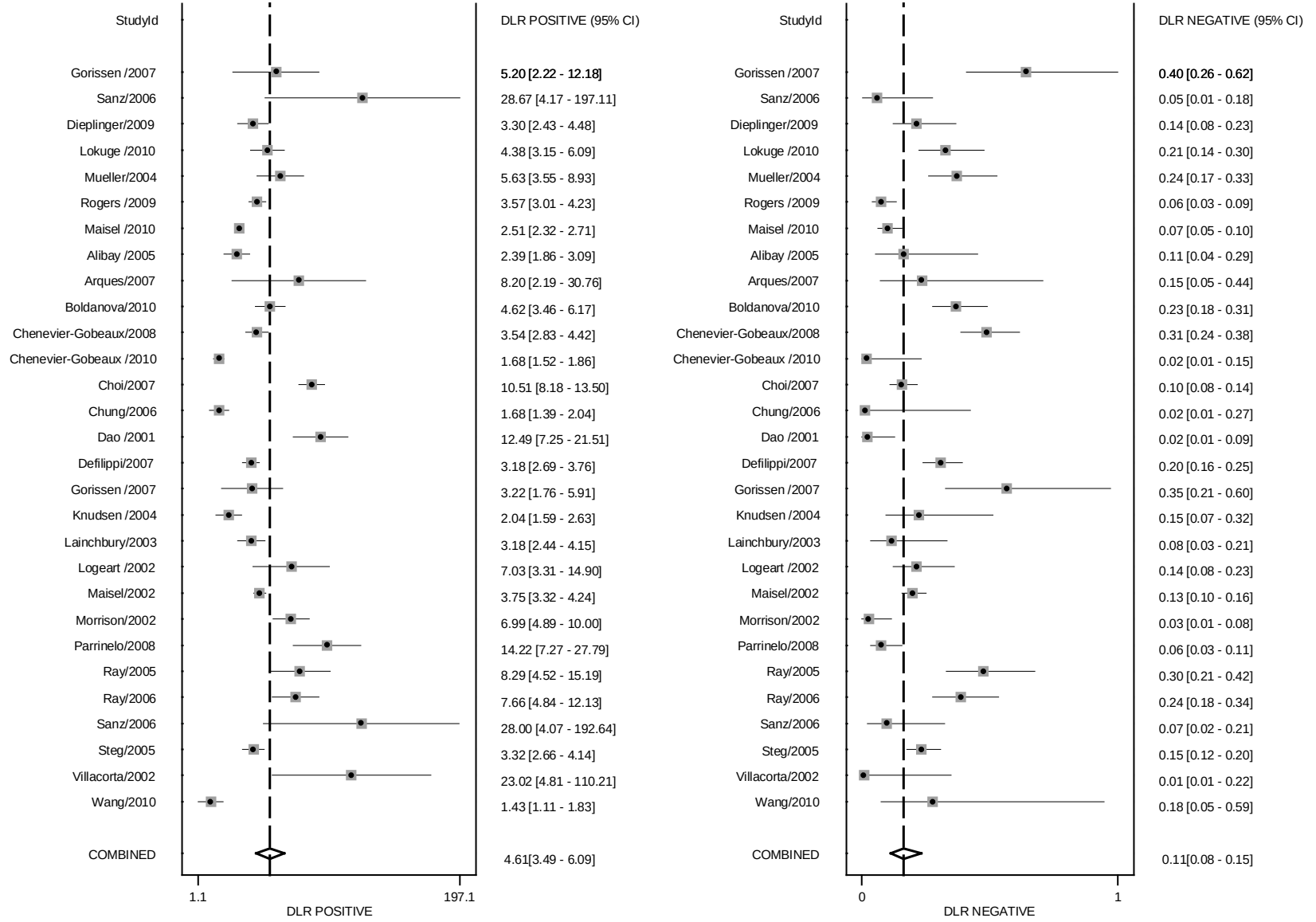


Figure H-6. Summary forest plot of LR+ and LR- (ED BNP, lowest cut-point), bivariate mixed effect model

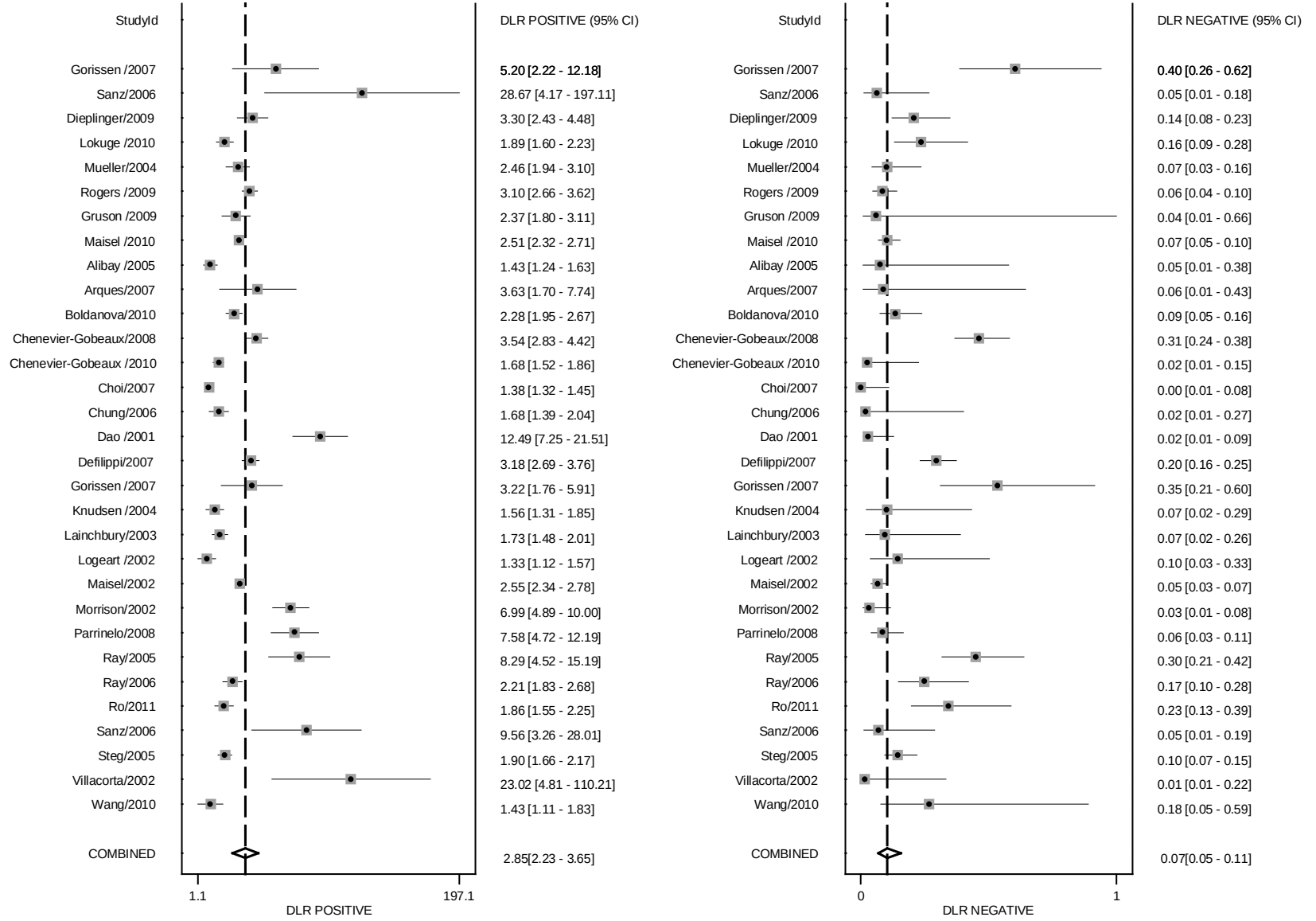


Figure H-7. Summary forest plot of LogDOR and DOR (ED BNP, manufacturer cut-point), bivariate mixed effect model

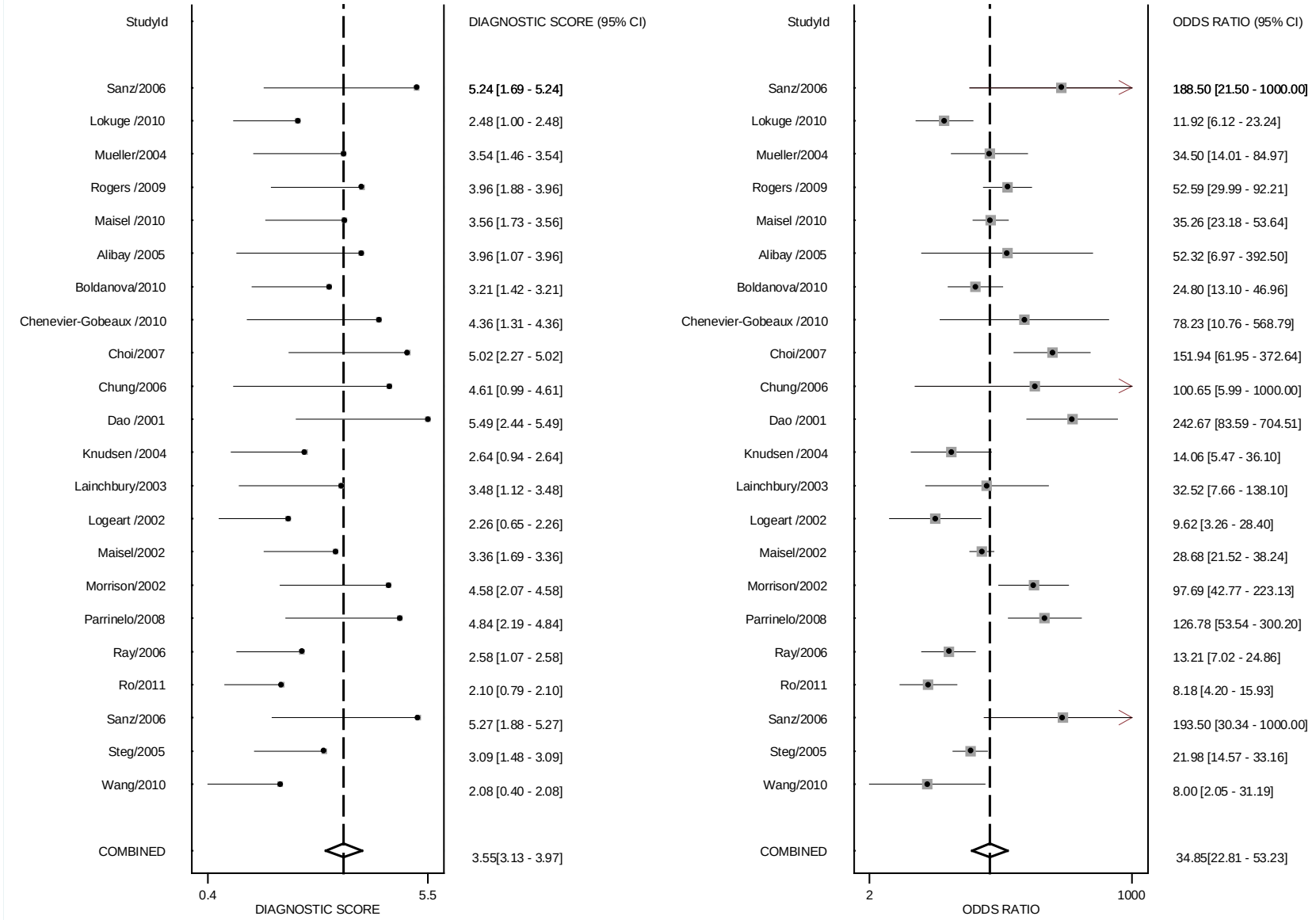


Figure H-8. Summary forest plot of LogDOR and DOR (ED BNP, optimum cut-point), bivariate mixed effect model

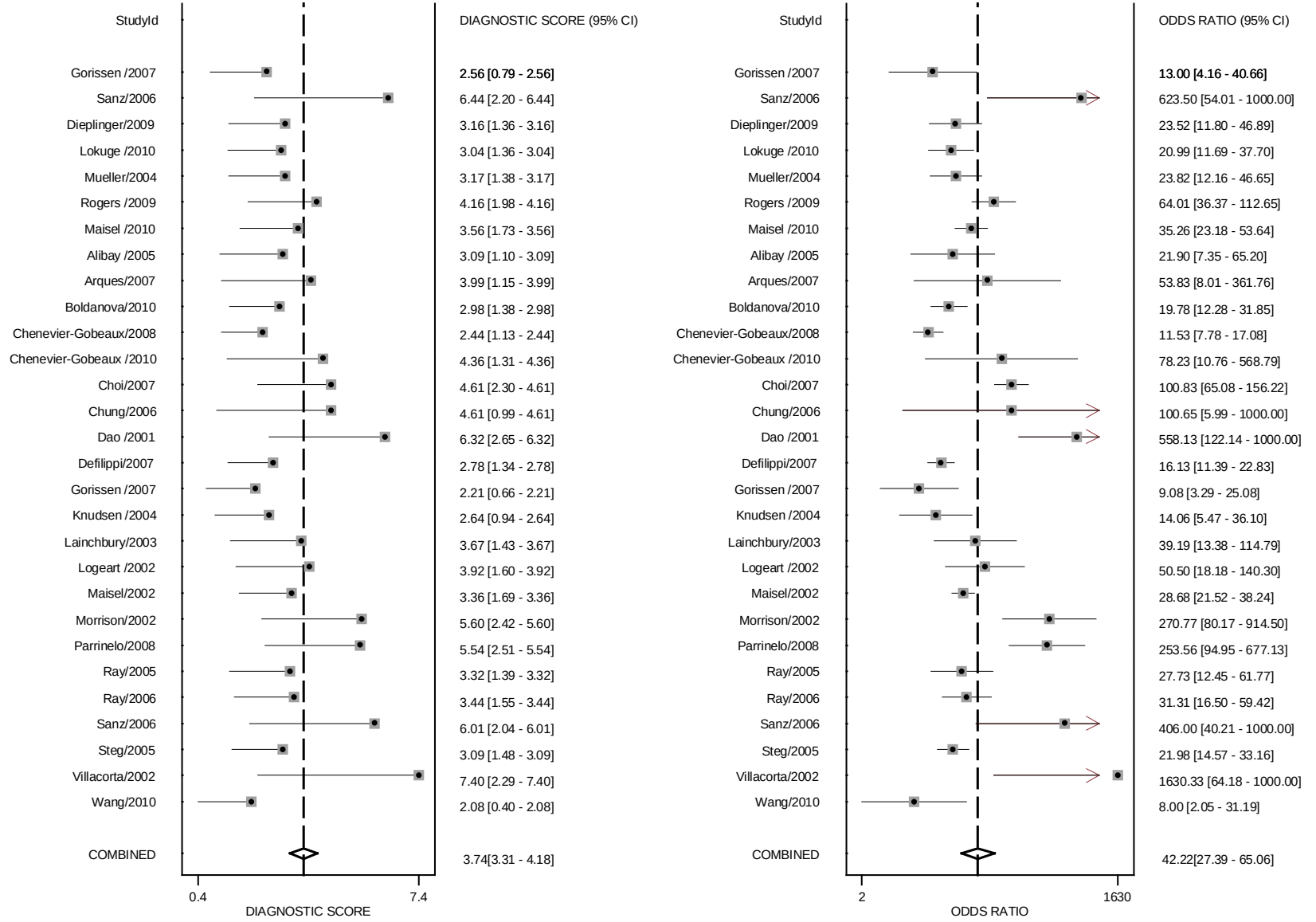


Figure H-9. Summary forest plot of LogDOR and DOR (ED BNP, lowest cut-point), bivariate mixed effect model

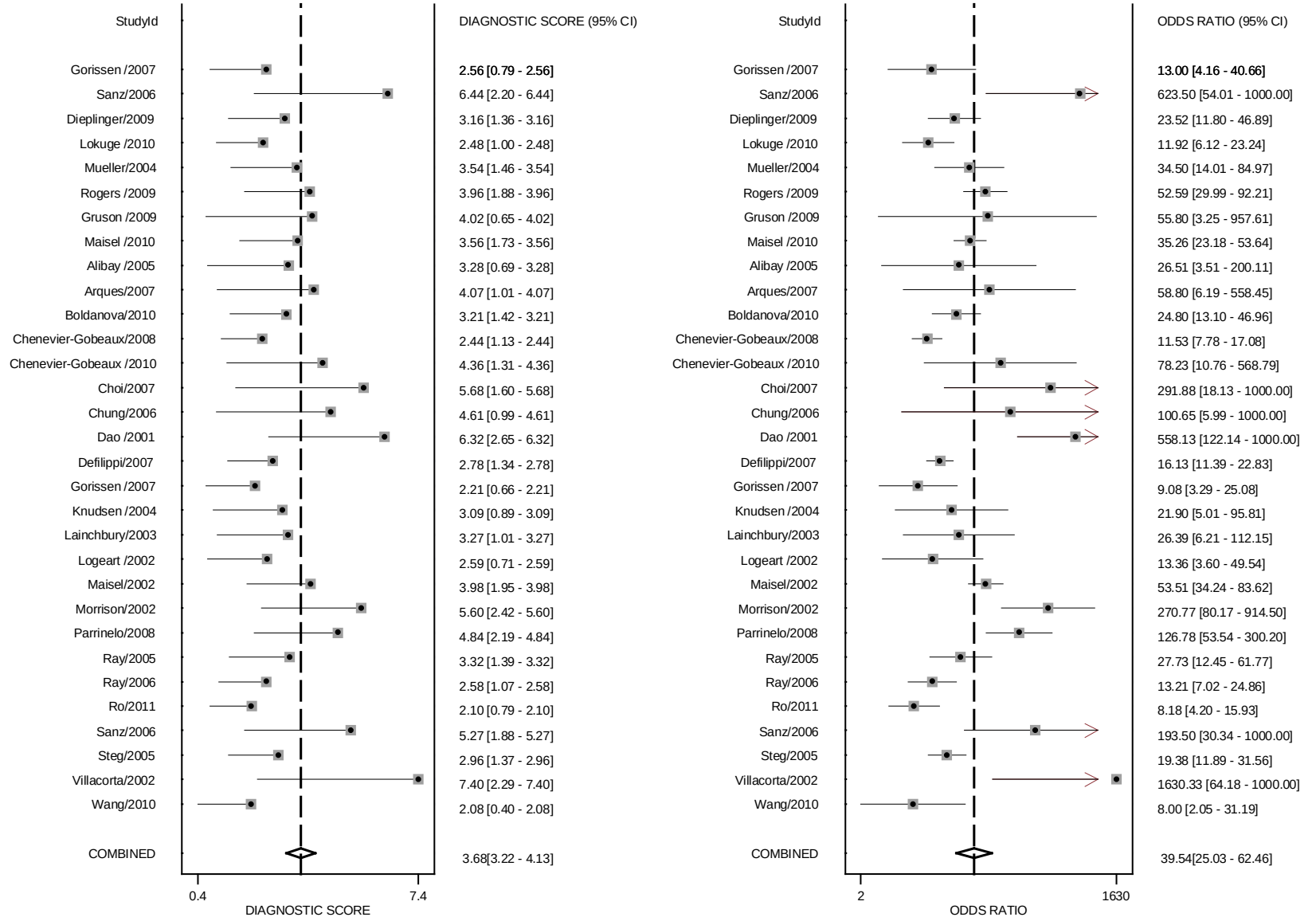


Figure H-10. Summary ROC-curve (ED BNP, manufacturer cut-point), bivariate mixed effect model

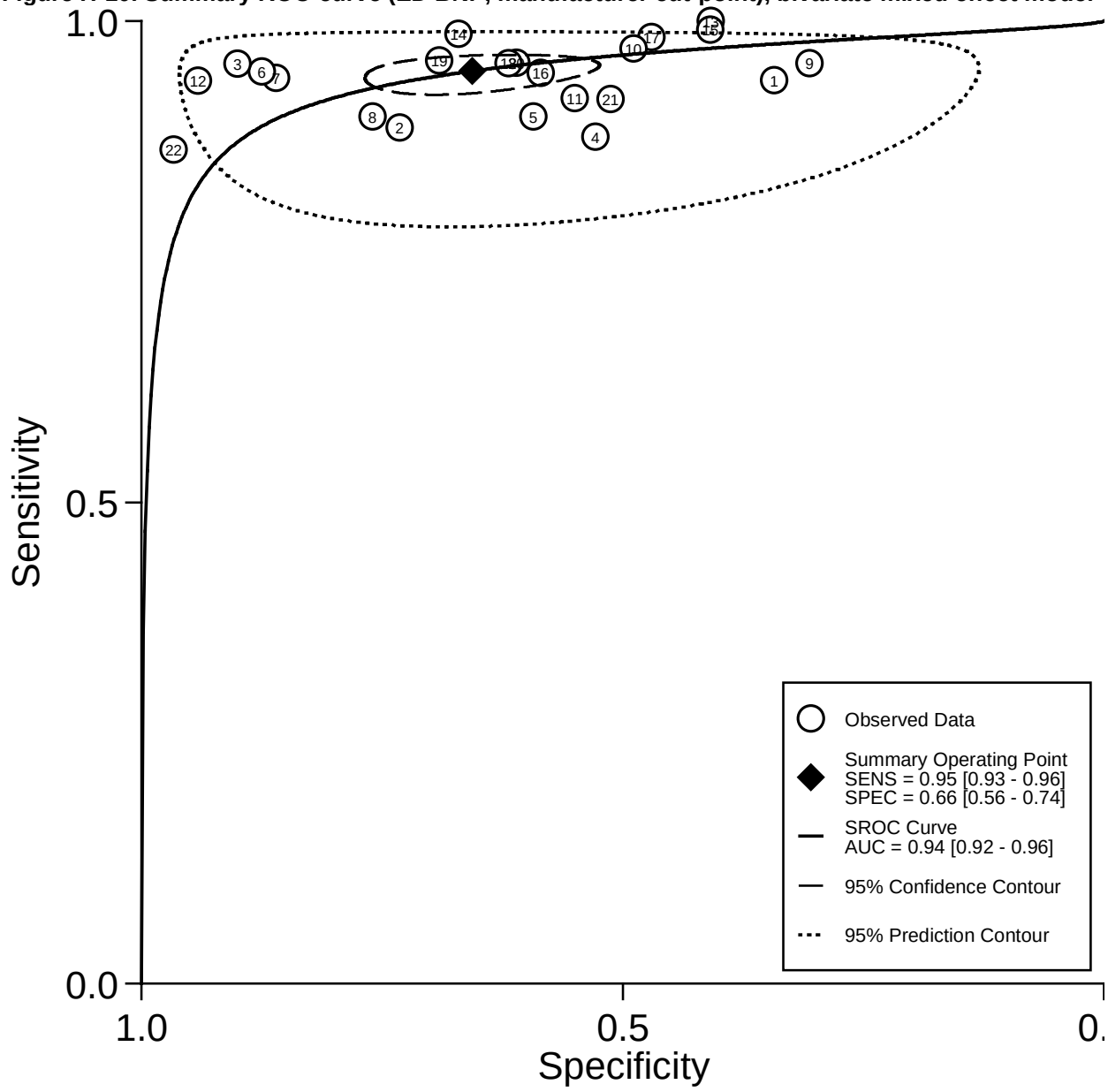


Figure H-11. Summary ROC-curve (ED BNP, optimum cut-point), bivariate mixed effect model

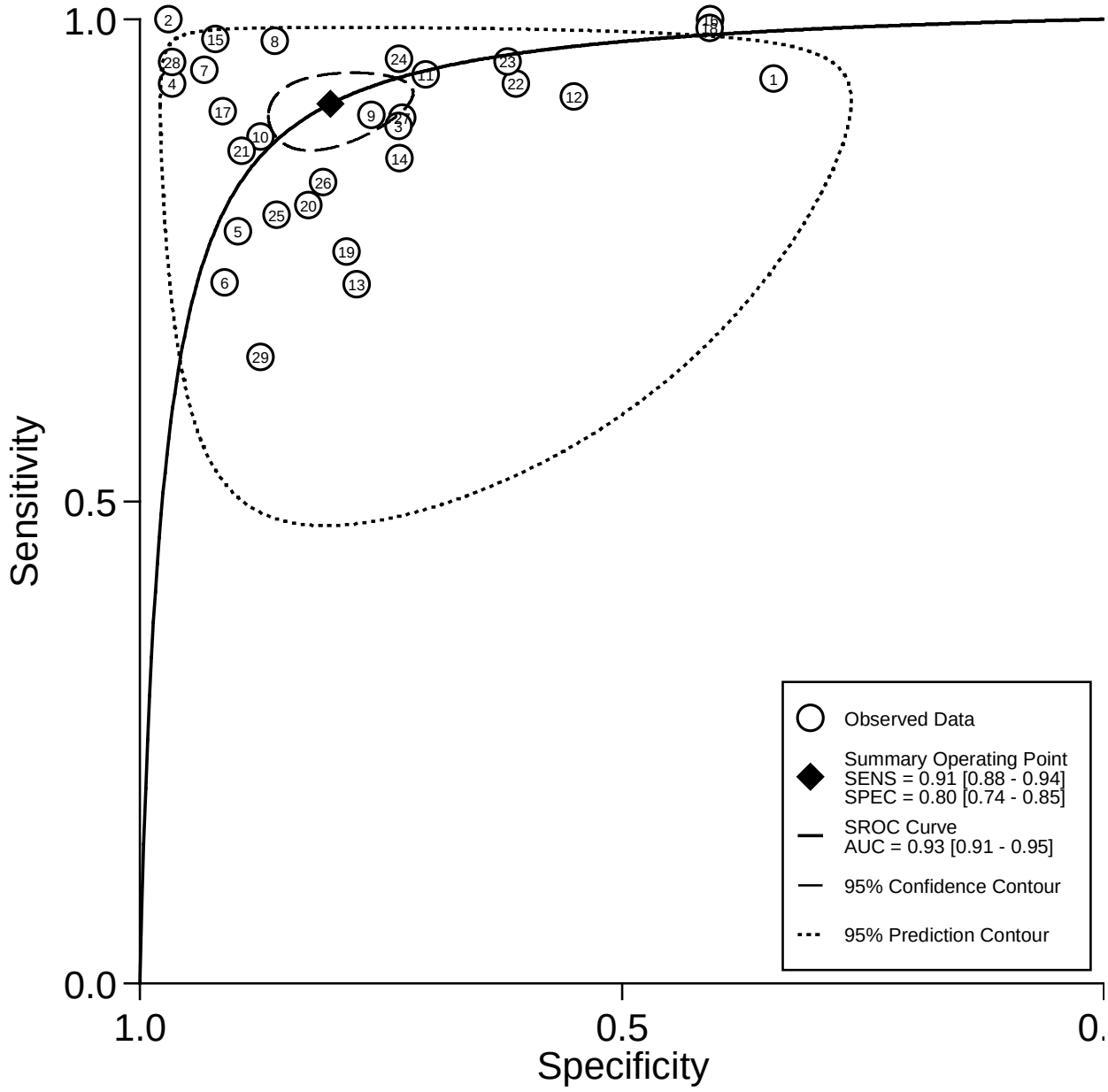


Figure H-12. Summary ROC-curve (ED BNP, lowest cut-point), bivariate mixed effect model

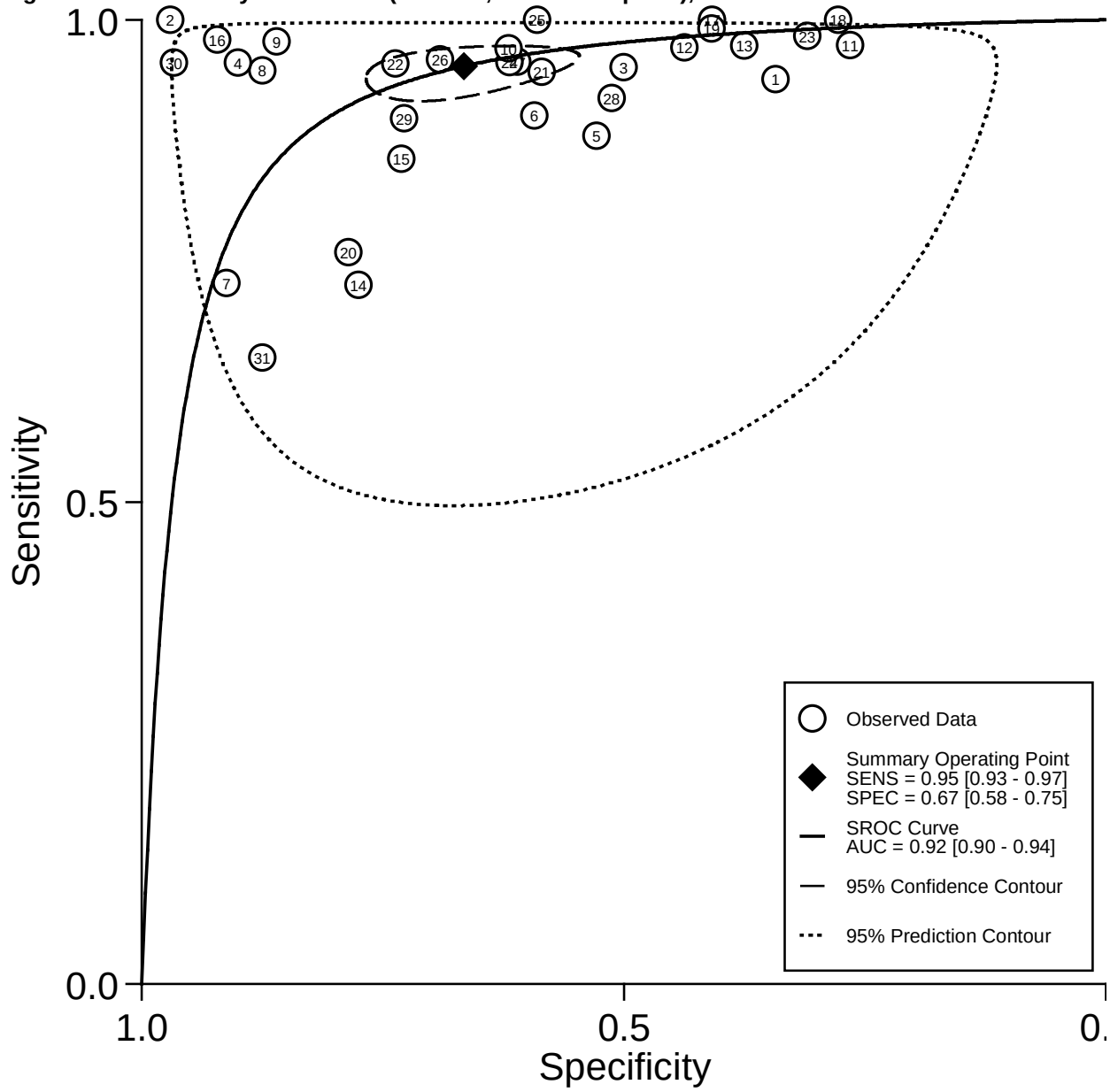


Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Alibay,[1] 2005 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=45), Cardiac Heart Failure (n=60), Pulmonary Disease (n=55); Reference standard: 2 Cardiologists	To examine the analytical correlation between non-radio-immunometric plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), and to evaluate whether NT-proBNP or BNP was superior in the emergency diagnosis of heart failure and whether this was influenced by age, gender, body mass index (BMI) and renal function. Data were collected prospectively from patients admitted to the emergency department for acute dyspnea.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=160 age= 80.1(13.5)y, %males=47.5 HF Prev=38%	280	100	5	1.05	0.00	NR
					600	100	51	2.04	0.00	NR
					1,000	97	63	2.62	0.05	NR
					1,250	87	66	2.56	0.20	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Anwaruddin,[53] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: (n=293), AA=trial fibrillation (n=80), Diabetes (n=37), Historical MI (n=79), Previous CHF (n=151); Reference standard: 2 Cardiologists	60 day mortality and diagnosis of CHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(GFR<30) 78.0(7.6)y; (GFR 30-59) 73.1(12.4)y; (GFR60-89) 60.7(15.7)y; (GFR≥90) 51.3(15.7)y, %males=59.3 HF Prev=35%; 140 patients underwent echo.	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	NR	NR	NR	NR	NR
				GFR ≥60 ml/min/1.73 m2 n=NR age=NR %males=NR HF Prev=21%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	85	88	7.08	0.17	0.95
					450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	97	68	3.03	0.04	0.88
					1,200	89	72	3.18	0.15	NR
				GFR < 44 ml/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	1,200	92	70	3.07	0.11	0.89

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Bayes-Genıs,[54] 2004 Spain	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=19), Hypertension (n=58), Prior AMI/angina (n=31), COPD (n=51), Diabetes (n=37), CHF (n=40); Reference standard: 2 Cardiologists	Utility of NT-proBNP for the diagnosis of ventricular dysfunction and to evaluate the changes in NT-proBNP concentrations after intensive treatment initiated during admission.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=89 age= (Decompensated HF) 71(10)y; (Masked HF) 76(7)y; (normal) 62(13)y, %males=60.67 HF Prev=83%; 30 cut for ruling out cardiac origin dyspnea;115 to rule in.	30 pmol/L	98.6	46.7	1.85	0.03	NR
					50 pmol/L	95.7	60	2.39	0.07	NR
					70 pmol/L	94.3	73.3	3.53	0.08	NR
					90 pmol/L	91.4	73.3	3.42	0.12	NR
					115 pmol/L	91.4	93.3	13.64	0.09	0.96
					130 pmol/L	90	93.3	13.43	0.11	NR
Bayes-Genis,[55] 2007 Multinational Study	Cross-Sectional (ICON); Ethnicity: NR Comorbidities: Hypertension (n=586), CAD (n=430), Obstructive lung disease (n=412), Prior AMI/angina (n=267), AF (n=232), Diabetes (n=275), Prior HF (n=373); Reference standard: Cardiologists/physicians	Mortality at 1 year diagnostic accuracy	NT-proBNP (ELECSYS -proBNP Immunoassay)	Lean, BMI lower than 25.0 n=412 age=70.5(15.7)y, %males=48.8 HF Prev=NR%	NR	NR	NR	5.34	0.02	NR
				Overweight, BMI of 25.0 to 29.9 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	13.32	0.03	NR
				obese, BMI>=30.0 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	7.54	0.08	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Behnes,[56] 2009 Germany	Cross-Sectional (MANPRO); Ethnicity: NR Comorbidities: Arrhythmia (n=107), HBP (n=268), CAD (n=157), Stroke (n=11), Vascular disease (n=62), COPD (n=96), Diabetes (n=120), IHD (n=111), MI (n=89), Renal disease (n=72), CHD (n=194), VHD (n=177), hypercholesterolemia (n=122), DVT (n=10); Reference standard: 1 Physician	Hospitalization and admission to intensive care	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Acute dyspnea/ peripheral edema n=401 age=67.4y, %males=5 HF Prev=30%	100	98	27	1.34	0.07	NR
					200	98	40	1.63	0.05	NR
					300	96	48	1.85	0.08	0.85
					400	94	54	2.04	0.11	NR
Behnes,[57] 2011 Germany	Cross-Sectional (MANPRO); Ethnicity: NR Comorbidities: Hypertension (n=268), CAD (n=157), Acute MI (n=89), AF (n=107), COPD (n=96), Diabetes (n=120), Renal disease (n=72) hypercholesterolemia (n=122), CHF systolic (n=91), CHF diastolic (n=76), Pneumonia (n=42); Reference standard: Diagnoses of AF and CHF were based on clinically assessed final diagnoses of the individual hospital stay of each individual patient according to European Guidelines	Association of serum levels of TGF-beta 1 and AF and CHF	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Dyspnea n=401 age=67.4y, %males=5 HF Prev=30%	NR	NR	NR	NR	NR	NR
				Dyspnea n=NR age=NR %males=NR HF Prev=27%	270	0.95	NR	NR	NR	0.73
				Dyspnea n=NR age=NR %males=NR HF Prev=30%	300	NR	NR	NR	NR	0.85

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Berdague,[58] 2006 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Respiratory insufficiency (n=42), Asymptomatic left ventricular (n=44), Pulmonary Embolism (n=11); Reference standard: 2 Cardiologists	Value of NT-proBNP assay for etiologic diagnosis of acute dyspnea in elderly patients in the emergency setting.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea,>70. n=254 age=81(7)y, %males=48 HF Prev=56%	1,000	97	49	1.90	0.06	NR
					1,200	97	65	2.77	0.05	NR
					1,630	92	55	2.04	0.15	NR
					2,000	87	72	3.11	0.18	NR
					2,300	81	75	3.24	0.25	NR
					3,000	75	80	3.75	0.31	NR
					4,500	64	86	4.57	0.42	NR
					5,500	58	87	4.46	0.48	NR
Chenevier-Gobeaux,[6] 2005 France	Cross-Sectional (Independent study); Ethnicity: NR Hypertension (n=153), COPD (n=127), Myocardial infarction (n=124), Previous CHF (n=128); Reference standard: 2 urgentists	(i) To determine correlations between eGFR and brain natriuretic peptide (NT-proBNP and BNP) levels in patients with cardiac-related dyspnea or non-cardiac- related dyspnea , and (ii) to determine the influence of eGFR on NT-proBNP and BNP values in the diagnosis of cardiac-related dyspnea in patients presented by night to the Emergency Department (ED).	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=381 age=79(1y, %males=NR HF Prev=30%	NR	NR	NR	NR	NR	NR
				eGFR≥90,CKD Level1 n=NR age=NR %males=NR HF Prev=8%	NR	NR	NR	NR	NR	NR
				eGFR 60-89 ml/min/1.73 m2, CKD Level 2 n=NR age=NR %males=NR HF Prev=20%	1,360	77	86	5.50	0.27	0.8476

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[6] 2005 France (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Hypertension (n=153), COPD (n=127), Myocardial infarction (n=124), Previous CHF (n=128); Reference standard: 2 urgentists	(repeated data) (i) To determine correlations between eGFR and brain natriuretic peptide (NT-proBNP and BNP) levels in patients with cardiac-related dyspnea or non-cardiac- related dyspnea , and (ii) to determine the influence of eGFR on NT-proBNP and BNP values in the diagnosis of cardiac-related dyspnea in patients presented by night to the Emergency Department (ED).	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	eGFR 30-59 ml/min/1.73 m2, CKD Level 3 n=NR age=NR %males=NR HF Prev=34%	1,980	62	80	3.10	0.48	0.7314
				eGFR 15–29 ml/min/1.73 m2; CKD Level 4 n=NR age=NR %males=NR HF Prev=45%	6,550	82	79	3.90	0.23	0.8025
Chenevier-Gobeaux,[7] 2008 France	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=272), CAD (n=180), COPD (n=167), Previous HF (n=138), Malignancy (n=94); Reference Standard: 2 Emergency physicians or a pulmonologist and cardiologist	CHF (To evaluate the accuracy of BNP and NT-proBNP for the diagnosis of CHF (CHF) in dyspnea patients aged <85 years admitted to the Emergency Department (ED), and to define threshold values in this oldest-old population.)	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (all) n=570 age=(<85 non CHF) 75(6)y; (<85 CHF) 77(6)y; (≥85 non CHF) 91(4)y; (≥85 CHF) 90(4)y, %males=47.89 HF Prev=44%	NR	NR	NR	NR	NR	NR
					1,700	74	77	3.22	0.34	0.786
					1,750	85	59	2.07	0.25	NR
					2,100	82	63	2.22	0.29	NR
					2,800	74	70	2.47	0.37	NR
					3,300	69	75	2.76	0.41	NR
					4,900	57	80	2.85	0.54	NR
					6,000	53	85	3.53	0.55	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Chenevier-Gobeaux,[8] 2010 France	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: hypertension (n=152), prior AMI/angina (n=124), COPD (n=125), Previous CHF (n=125); Reference standard: 2 emergency physicians	To determine the relationship between the estimated glomerular filtration rate (eGFR) and MR-proANP concentrations in dyspnea emergency patients and to compare the diagnostic performance of MR-proANP with that of NT-proBNP and BNP with respect to renal function	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (age 60+) n=378 age=78(1y) %males=50.26 HF Prev=30%	300 ng/L	100	27	1.37	0.00	NR
				Tertile 3 (eGFR >=58.6 mL/min/1.73 m2) n=NR age=NR %males=NR HF Prev=17%	>1,500 ng/L	82	82	4.56	0.22	NR
				Tertile 2 (eGFR between 44.3 and 58.5 mL/min/1.73m2) n=NR age=NR %males=NR HF Prev=34%	>1,700 ng/L	88	71	3.03	0.17	NR
				Tertile 1 (eGFR<44.3 mL/ min/1.73 m2), n=NR age=NR %males=NR HF Prev=39%	>4,000 ng/L	79	60	1.98	0.35	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
deFilippi,[15] 2007 USA	Cohort (Independent study); Ethnicity: African-American (n=318); Comorbidities: Hypertension (n=555), CAD (n=263), Atrial Fibrillation (n=175), Diabetes (n=305), Prior HF (n=287); Reference standard: 2 Cardiologists	Compared the diagnostic accuracies of NT-proBNP and BNP for diagnosing decompensated HF and predicting 1-year all-cause mortality, and to determine whether the natriuretic peptide cutoffs derived from previously published studies of prospectively recruited all-comers cohorts remained optimal in this clinician-selected cohort	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=831 age=(eGFR<60) 69.3 (13.y) (eGFR≥60) 63.5(16)y, %males=45.7 HF Prev=53%	NR	NR	NR	NR	NR	NR
				eGFR<60 n=NR age=NR %males=NR HF Prev=61%	1,200 ng/L	81	49	1.59	0.39	NR
				eGFR≥60 n=NR age=NR %males=NR HF Prev=45%	900 ng/L for age≥50 , 450 ng/L for age<50	81	52	1.70	0.36	NR
Gorrisen,[17] 2007 Netherlands	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 Cardiologist, 1 Pulmonologist	To evaluate the analytical and diagnostic performance of two different BNP tests and one NT-pro-BNP test in the diagnosis of CHF in the ED.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=80 age=74(10)y, %males=55 HF Prev=50%	1,550 ng/L	80	65	2.29	0.31	0.774
				< 65 years n=NR age=NR %males=NR HF Prev=NR%	591 ng/L	55	100	NA	0.45	0.614
				65–75 years n=NR age=NR %males=NR HF Prev=NR%	1,922 ng/L	75	73	2.78	0.34	0.75

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gorrisen,[17] 2007 Netherlands (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 Cardiologist, 1 Pulmonologist	(repeated data) To evaluate the analytical and diagnostic performance of two different BNP tests and one NT-pro-BNP test in the diagnosis of CHF in the ED.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	> 75 years n=NR age=NR %males=NR HF Prev=NR%	1,737 ng/L	71	84	4.44	0.35	0.831
				GFR >60 mL/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	1,118 ng/L	85	73	3.15	0.21	0.781
				GFR <=60 mL/min/1.73 m2 n=NR age=NR %males=NR HF Prev=NR%	2,592 ng/L	70	64	1.94	0.47	0.702
Green,[59] 2008 USA	Cohort (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=293), CAD (n=166), Obstructive lung disease (n=217), Diabetes (n=156), Historical MI (n=77), Prior heart failure (n=151); Reference standard: 2 Cardiologists	Adverse outcomes, including death and rehospitalization	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=592 age=(Clinical uncertainty present) 69(14)y; (Clinical uncertainty absent) 59(18)y, %males=50.5 HF Prev=34%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75;1,800 pg/mL in >75 years	NR	NR	NR	NR	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Green,[59] 2008 USA (cont'd)	(repeated data) Cohort (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=293), CAD (n=166), Obstructive lung disease (n=217), Diabetes (n=156), Historical MI (n=77), Prior heart failure (n=151); Reference standard: 2 Cardiologists	(repeated data) Adverse outcomes, including death and rehospitalization	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Clinical certainty group n=NR age=NR %males=NR HF Prev=24%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75; 1,800 pg/mL in >75 years	92	86	6.57	0.09	0.88
				Clinical uncertainty group n=NR age=NR %males=NR) HF Prev=56%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75; 1,800pg/mL in >75 years	90	84	5.63	0.12	NR
Gruson,[18] 2008 Belgium	Cohort (Independent study); Ethnicity: NR Comorbidities: NR Reference standard: 1 cardiologist	To evaluate the diagnostic accuracy of circulating N-terminal- pro-atrial natriuretic peptide (Nt-proANP), the extremity of the proANP amino-terminal fragment, assessed by radio-immunoassay, in patients admitted to the ED with dyspnea and/or chest pain. Moreover, we compared the performances of Nt-proANP assay to two commercial assays for BNP and Nt-proBNP.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (CHF) n=137 age=69y, %males=56 HF Prev=23%	NR	NR	NR	NR	NR	O.91

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gruson,[20] 2012 Belgium	Cohort (Independent Study); Ethnicity=NR Comorbidities=hypertension (n=69), AF (n=11), diabetes mellitus (n=30), historical MI (n=20); Reference Standard=clinicians	To evaluate the diag- nostic accuracy of circulating levels of proBNP in patients admitted to ED with dyspnea and/or thoracic pain. Moreover, we compared the performances of proBNP assay to two commercial assays for BNP and Nt-proBNP.	NT-proBNP (ELECSY-proBNP Immunoassay)	dyspnea and/or chest pain, all (n=156, mean=67y, %males=54.5); HF Prevalance=29.5 %	100 ng/L	NR	NR	NR	NR	0.92
Januzzi,[60] 2005 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Caucasian (n=188), Hypertension (n=294), CAD (n=166), Prior AMI/angina (n=79), COPD (n=216); Reference standard: 2 Cardiologists	Comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	All patients n=599 age=(Acute CHF) 72.8(13.6)y; no acute CHF) 56.9(16.3)y, %males=5 HF Prev=35%	300	99	68	3.09	0.01	NR
					450	98	76	4.08	0.03	NR
					600	96	81	5.05	0.05	NR
				Dyspnea n=NR age=NR %males=NR HF Prev=34.89%	900	90	85	6.00	0.12	0.94

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Januzzi,[60] 2005 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Caucasian (n=188), Hypertension (n=294), CAD (n=166), Prior AMI/angina (n=79), COPD (n=216); Reference standard: 2 Cardiologists	(repeated data) Comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	All patients n=599 age=(Acute CHF) 72.8(13.6)y; no acute CHF) 56.9(16.3)y, %males=5 HF Prev=35%	1,000	87	86	6.21	0.15	NR
				<50 years old n=NR age=NR %males=NR HF Prev=NR%	450	93	95	18.60	0.07	0.98
				≥50 yrs old n=NR age=NR %males=NR HF Prev=NR%	900	91	80	4.55	0.11	0.93
				<50 years old n=NR age=NR %males=NR HF Prev=NR%	900	73	96	18.25	0.28	NR
Januzzi,[61] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: African-American (n=46); Comorbidities: Hypertension (n=666), CAD (n=502), COPD (n=465), Historical MI (n=314), Prior HF (n=427); Reference standard: 2 Cardiologists	To establish broader standards for NT-proBNP testing in a study involving four sites in three continents.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=1,256 age=68.3(15.9)y, %males=5 HF Prev=57%	300	99	60	2.48	0.02	NR
					Age specific cutpoint	90	84	5.63	0.12	NR
				<50 years old n=NR age=NR %males=NR HF Prev=%	450	97	93	13.86	0.03	0.99

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Januzzi,[61] 2006 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: African-American (n=46); Comorbidities: Hypertension (n=666), CAD (n=502), COPD (n=465), Historical MI (n=314), Prior HF (n=427); Reference standard: 2 Cardiologists	(repeated data) To establish broader standards for NT-proBNP testing in a study involving four sites in three continents.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	50-75 years old n=NR age=NR %males=NR HF Prev=%	900	90	82	5.00	0.12	0.93
				>75 years old n=NR age=NR %males=NR HF Prev=%	1,800	85	73	3.15	0.21	0.86
Krauser,[62] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: African-American (n=44); Comorbidities: Hypertension (n=292), CAD (n=167), Acute MI (n=78), AF (n=75), Diabetes (n=157), Heart failure (n=150); Reference standard: 2 Cardiologists	The utility of NT- proBNP for the diagnosis and exclusion of HF in African-American and female patients with acute dyspnea.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(men) 61.7(16)y, %males=(women) 63.2(17)y) HF Prev=35%	NR	NR	NR	NR	NR	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Krauser,[62] 2006 USA (cont'd)	(repeated data) Cross-Sectional (PRIDE); Ethnicity: African-American (n=44); Comorbidities: Hypertension (n=292), CAD (n=167), Acute MI (n=78), AF (n=75), Diabetes (n=157), Heart failure (n=150); Reference standard: 2 Cardiologists	(repeated data) The utility of NT- proBNP for the diagnosis and exclusion of HF in African-American and female patients with acute dyspnea.	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	African American n=NR age=NR %males=NR HF Prev=30%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 years) and 1,800 pg/mL (age >75 years)	100	90	10.00	0.00	0.96
				Non-African-American n=NR age=NR %males=NR HF Prev=35%	NR	NR	NR	NA	NA	0.94
				Female n=NR age=NR %males=NR HF Prev=35%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 yrs) and 1,800 pg/mL (age >75 yrs)	89	90	8.90	0.12	0.95
				Male n=NR age=NR %males=NR HF Prev=35%	NR	NR	NR	NR	NR	0.94

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Lainchbury,[25] 2003 New Zealand	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=88), COPD (n=86), Previous heart failure (n=52); Reference standard: 2 Cardiologists	Final clinical diagnosis	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=205 age=70(14)y, %males=49 HF Prev=34%; Echo performed in 171 patients.	140	87	71	3.00	0.18	0.76
					240	83	82	4.61	0.21	0.83
					340	80	87	6.15	0.23	0.85
					440	74	90	7.40	0.29	0.85
					540	68	92	8.50	0.35	0.84
Liteplo,[63] 2009 USA	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=37), AF (n=23), COPD (n=29), Diabetes (n=21), Renal disease (n=17), Asthma (n=6), Prior CHF (n=46); Reference standard: 2 emergency physicians.	Optimal protocol and test threshold for the US test to diagnose CHF, to compare the diagnostic efficiency of US with NT-ProBNP levels in diagnosing CHF, and to determine if US adds incremental diagnostic information when combined with NT-ProBNP	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=94 age=74(14)y, %males=59 HF Prev=43%	450/900/1800	85	62.96	2.29	0.24	

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Martinez-Rumayor,[64] 2010 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Hypertension (n=292), CAD (n=168), COPD (n=70), Diabetes (n=157), Historical MI (n=77), Asthma (n=94), Cardiomyopathy (n=63), History of prior HF (n=150); Reference standard: 2 Cardiologists	To define more clearly the relationship between the information provided by the chest radiograph (CXR)and the natriuretic peptide (NT-proBNP) test as part of the evaluation of dyspneic patients presenting to the emergency department with suspected acute HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected AHF n=599 age= normal CXR) 59y*, %males=(Abnormal CXR) 71y* HF Prev=35%	'Rule in cut-off points', (450/900/1800 pg/ ml for ages <50/50–75/>75 years)	90	86	6.43	0.12	NR
				Normal CXR n=NR age=NR %males=NR HF Prev=21%	NR	NR	NR	NR	NR	0.94
				Abnormal CXR n=NR age=NR %males=NR HF Prev=56%	NR	NR	NR	NR	NR	0.92
Mueller,[35] 2005 & Gegenhuber,[36] 2006 Austria	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: CAD (n=117), AF (n=83), Diabetes (n=58), Renal disease (n=74), Arterial hypertension (n=141); Reference standard: 1 Internist, Framingham criteria	To compare head to head the diagnostic accuracy of BNP and NT-proBNP with respect to CHF in patients consulting ED with SOB as a chief complaint and to assess appropriate cut off concentrations for this clinical setting by means of two currently developed commercially available assays for BNP and NT-proBNP.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=251 age=(HF) 76y, (no CHF) 69y %males=NR HF Prev=55%	292 ng/L	95	53	2.02	0.09	NR
					125/450 ng/L	94	46	1.74	0.13	NR
					476 ng/L	90	65	2.57	0.15	NR
					825 ng/L	87	81	4.58	0.16	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Moe,[65] 2007 Canada	Cross-Sectional (BACH); Ethnicity: Caucasian (n=464); Comorbidities: Hypertension (n=266), COPD (n=145), Diabetes (n=127), Historical MI (n=151), HF/left ventricular dysfunction (n=171); Reference standard: 2 Cardiologists	The duration of the initial ED visit and the total direct medical costs of treatment as primary end points and initial hospital length of stay, in-hospital and 60-day mortality, and rehospitalization	NT-proBNP (ELECSYS -proBNP Immunoassay))	Dyspnea n=500 age=70yrs %males=51.6 HF Prev=46%	NR	NR	NR	NR	NR	0.86
				NT-proBNP group n=NR age=NR %males=NR HF Prev=NR	NR	NR	NR	NR	NR	NR
				Usual care n=NR age=NR %males=NR HF Prev=NR	NR	NR	NR	NR	NR	NR
Nazerian,[66] 2010 Italy	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=84), AF (n=50), COPD (n=49), Ischemic heart disease (n=47), Previous CHF (n=30), Rest dyspnea (n=83), Heart enlargement (n=64), Orthopnea (n=40); Reference standard: 2 Cardiologists, 1 respiratory physician, Boston criteria for CHF.	Outcome measure was Acute Left Ventricular Heart Failure (aimed for Diagnostic Accuracy of Emergency Doppler Echocardiography for Identification of Acute Left Ventricular Heart Failure in Patients with Acute Dyspnea: Comparison with Boston Criteria and N-terminal Pro-hormone Brain Natriuretic Peptide	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=145 age= (HF) 81(8)y, (non HF) 75(1y) %males=NR HF Prev=44%	≤300	98	22	1.26	0.09	NR
					≥2,200	83	70	2.77	0.24	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
O'Donoghue,[67] 2007 USA	Cross-Sectional (PRIDE); Ethnicity: NR African-American (n=8), Comorbidities: Diabetes (n=157) Prior hypertension (n=294), Prior MI (n=80), Previous cardiomyopathy (n=63), Previous chronic obstructive Pulmonary disease (n=214); Reference standard: 2 Cardiologists	Diagnosis of acute HF 1 year mortality	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=NR %males=50.58 HF Prev=35%	NR	NR	NR	NR	NR	NR
				With DM n=NR age=NR %males=NR HF Prev=56%	optimal diagnostic cutpoints of 450 pg/mL (age <50 years), 900 pg/mL (age 50 to 75 years) and 1,800 pg/mL (age >75 years)	92	90	9.20	0.09	0.94
				No DM n=NR age=NR %males=NR HF Prev=27%	NR	NR	NR	NR	NR	NR
Oh,[68] 2009 Korea	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=5), hypertension (n=50), AF (n=28), Diabetes (n=33), Ischemic heart disease (n=44); Reference standard: ECHO - blinded analysis	Correlation between higher levels of RDW and elevated E/E' in patients with AHF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Clinical diagnosis of AHF n=100 age=64.3(13.y, %males=60 HF Prev=44%	NR	NR	NR	NR	NR	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Oh,[68] 2009 Korea (cont'd)	(repeated data) Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Dyslipidemia (n=5), hypertension (n=50), AF (n=28), Diabetes (n=33), Ischemic heart disease (n=44); Reference standard: ECHO - blinded analysis	(repeated data) Correlation between higher levels of RDW and elevated E/E' in patients with AHF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	RDW tertile 1 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
				RDW tertile 2 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
				RDW tertile 3 n=NR age=NR %males=NR HF Prev=NR%	NR	NR	NR	NR	NR	NR
Potocki,[40] 2010 Germany	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=195), CAD (n=80), COPD (n=98), diabetes (n=52), Previous HF (n=69), Chronic kidney disease (n=80); Reference standard: 2 Cardiologists	Accuracy of MR-proANP with that of NT-proBNP to diagnose HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=287 age=77y*, %males=5 HF Prev=54%	1,560	85	85	5.67	0.18	0.92

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Prosen,[69] 2011 Slovenia	Cohort (Independent study); Ethnicity: NR Comorbidities: Arrhythmia (n=59), COPD (n=78), Historical MI (n=22), Troponin T>0.03 ng/ml (n=57), Previous CHF (n=40), Previous asthma/COPD (n=25); Reference standard: Cardiologists, ICU physicians, Boston, Framingham	To determine the diagnostic accuracy of bedside lung ultrasound, NT-proBNP and clinical assessment in differentiating heart failure related acute dyspnea from pulmonary (COPD/asthma)-related acute dyspnea in the pre-hospital setting	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=218 age=(HF) 70.9(11.7)y; (Pulmonary edema) 52.3(15.3)y, %males=70 HF Prev=NR%	1,000	92	89	8.36	0.09	0.9
Ray,[41] 2005 France	Cross-Sectional (EPIDASA TRIAL); Ethnicity: NR Comorbidities: Chronic respiratory failure (n=35), Cardiac disease (n=64); Reference standard: Pulmonologist, cardiologist, emergency physician, or geriatric or internal medicine	Compare the usefulness of two rapid analytical methods for BNP and proBNP in the diagnosis of CPE in patients aged 65 and older with acute dyspnea	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=202 age=80(9)y, %males=49.5 HF Prev=44%; Echo done in only 45%, population selected for age 65 and over	≥1,500	75	76	3.13	0.33	0.8
Robaei,[70] 2011 Australia	RCT (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=47), Diabetes (n=12), Historical MI (n=25), Respiratory disease (n=32), Prior congestive cardiac failure (n=26), History of HF (n=24); Reference standard: 1 cardiologist	Diagnostic uncertainty and accuracy of NT-proBNP in patients presenting with dyspnea .	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=68 age=73(16)y, %males=44.1; HF Prev=40%	450 pg/mL for patients ages <50 years and 900 pg/mL for patients 50-75; 1,800pg/mL in >75 years	81	66	2.38	0.29	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Sakhuja,[71] 2005 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Prior AMI/angina (n=13), AF (n=16), Left bundle branch block (n=10), QRS duration >=120 ms (n=23), LV hypertrophy (n=6), Median LVEF (n=15); Reference standard: 2 Cardiologists	Evaluating usefulness of combining NT-proBNP and prolonged QRS complex for noninvasive prediction of impaired LV function	NT-proBNP (ELECSYS -proBNP Immunoassay)	Shortness of breath n=135 age=(LVEF<50) 70y*; (LVEF>50)73y*, %males=48.89 HF Prev=36%	Optimal cutpoint	96	44	1.71	0.09	NR
Sanz,[46] 2006 Spain	Cross-Sectional (Independent study); Ethnicity: NR Comorbidities: (n=5), AF (n=8), COPD (n=11), Ischemic heart disease (n=5), Cardiomyopathy hypertensive (n=9), valvar (n=7); Reference standard: Clinicians	To evaluate the value of NT-proBNP and BNP in patients with acute dyspnea in the emergency room, Diagnostic accuracy of different assays.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Acute dyspnea n=75 age=75(14.8)y, %males=67 HF Prev=60%	817	97.7	93.5	15.03	0.02	0.979
					300	100	50	2.00	0.00	NR
Shah,[48] 2009a USA	Cohort (Shah, 2009b); Ethnicity: Caucasian (n=136), African-American (n=264), Other (n=12); Comorbidities: Hypertension=(n=268), CAD (n=177), Diabetes (n=124), Historical MI (n=99), Renal disease (n=140), Heart failure (n=148); Reference standard: Panel of physicians	1 year all-cause mortality	NT-proBNP (DIMENSION -NT-proBNP (PBNP) Flex® reagent cartridge method)	Acute dyspnea n=412 age=58(14)y, %males=6 HF Prev=36%	NR	NR	NR	NR	NR	0.86

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shah,[47] 2009b	Cohort (Independent study); Ethnicity: NR Comorbidities: Hypertension (n=267), CAD (n=178), Atrial Fibrillation (n=81), Diabetes (n=121), CHF or Cardiomyopathy (n=147); Reference standard: Panel of physicians	Mortality after one year	NT-proBNP (DIMENSION - EXLTm N-terminal Pro-Brain Natriuretic Peptide (NTP) Flex® Reagent Cartridge (RF623))	diagnosis of LVEF ≤40% n=NR age=NR %males=NR HF Prev=37%	300	NR	NR	NR	NR	0.86
				diagnosis of diastolic dysfunction n=NR age=NR %males=NR HF Prev=NR%	300	NR	NR	NR	NR	0.67
				diagnosis of diastolic dysfunction in patients with preserved systolic function (LVEF≥50%) n=NR age=NR %males=NR HF Prev=NR%	300	NR	NR	NR	NR	0.6
Shaikh, [72] 2011 Karachi	Cohort; Ethnicity (Independent Study)=NR Comorbidities=hypertension (n=82), AF (n=12); COPD (n=21), DM (n=51), paroxysmal nocturnal dyspnea (n=58), edema (n=61); Reference Standard=NR	To determine the diagnostic significance of NT-proBNP estimation in patients presented with acute dyspnea in emergency department.	NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	dyspnea (all patients) (n=100, age=61±14y, %males=48); HF prevalance=79%	300	100	42.85	1.75	0.00	NR
			NT-proBNP (ELECSY-proBNP Immunoassay)		900	96.2	80.95	5.05	0.05	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shaikh, [72] 2011 Karachi (cont'd)	(repeated data) Cohort (Independent Study); Ethnicity=NR Comorbidities=hypertension (n=82), AF (n=12); COPD (n=21), DM (n=51), paroxysmal nocturnal dyspnea (n=58), edema (n=61); Reference Standard=NR	(repeated data) To determine the diagnostic significance of NT-proBNP estimation in patients presented with acute dyspnea in emergency department.	NT-proBNP (ELECSY-proBNP Immunoassay)	age <50 (n=22, age=NR %males=NR HF prevalence=NR	450	100	33.33	1.50	0.00	NR
			NT-proBNP (rule in) (ELECSY-proBNP Immunoassay)	age>50 (n=78,age=NRy, %males= NR); HF prevalence=NR	900	96.82	86.66	7.26	0.04	NR
			NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	age <75 (n=NR age=NR %males=NR); HF prevalence=NR	125	99	NR	NR	NR	NR
			NT-proBNP (rule out) (ELECSY-proBNP Immunoassay)	age >75 (n=NR age=NR %males=NR); HF prevalence=NR	450	99	NR	NR	NR	NR
Steinhart,[73] 2009 Canada	Cohort (IMPROVE-CHF); Ethnicity: NR Comorbidities: NR Reference standard: 2 Cardiologists, Framingham, NHANES	Diagnosis of AHF (to derive and validate a prediction model by using N-terminal pro,ÄìB-type natriuretic peptide NT-proBNP) and clinical variables to improve the diagnosis of acute AHF)	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=483 age=70y, %males=NR HF Prev=NR%	<300	NR	NR	NR	NR	NR
					300-899	NR	NR	NR	NR	NR
					900	NR	NR	NR	NR	NR
					<300	NR	NR	NR	NR	NR
					300-899	NR	NR	NR	NR	NR
					900-2,699	NR	NR	NR	NR	NR
					2,700-8,099	NR	NR	NR	NR	NR
					>8,100	NR	NR	NR	NR	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Tung,[74] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: Caucasian (n=192); Comorbidities: Arrhythmia (n=35), Hypertension (n=101), CAD (n=47), Historical MI (n=18); Reference standard: 2 Cardiologists	To evaluate results from amino-terminal pro-brain natriuretic peptide (NT-proBNP) testing with or without those of clinical judgment for the evaluation of dyspneic patients with previous chronic obstructive pulmonary disease or asthma.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=216 age=(HF) 69(1y; no HF) 59(16)y, %males=44.9 HF Prev=25%; Only 140 echo was taken in whole of PRIDE study; this is a subset analysis	450 pg/mL for patients ages <50 years and 900 pg/mL for patients >=50 years	87	84	5.44	0.15	0.9
					300	94	61	2.41	0.10	NR
				COPD, No h/o HF n=NR age=NR %males=NR HF Prev=13%	>450	82	90	8.20	0.20	0.88
				COPD, HF n=NR age=NR %males=NR HF Prev=63%	>450	91	47	1.72	0.19	0.85
				COPD, No h/o HF n=NR age=NR %males=NR HF Prev=13%	300	90	66	2.65	0.15	NR
				COPD, HF n=NR age=NR %males=NR HF Prev=63%	300	97	21	1.23	0.14	NR

Table H-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the emergency department (continued)

Author Year Country	Study Design (companion study) Ethnicity Comorbidities Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
van Kimmenade,[75] 2006 USA	Cross-Sectional (PRIDE); Ethnicity: NR Comorbidities: Arrhythmia (n=102), Hypertension (n=294), CAD (n=166), Acute MI (n=79), COPD (n=216), Diabetes (n=158), Cardiomyopathy (n=65), Congestive Heart failure (n=148); Reference standard: Study physician	60 day follow up survival, diagnostic accuracy	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea n=599 age=(AHF) 72(13.6)y, %males= no AHF) 56.9(16.3)y HF Prev=35%	NR	NR	NR	NR	NR	0.94
Zaninotto ,[76] 2005 Italy	Case-control (Independent study); Ethnicity: NR Comorbidities: CARD (n=56), Pulmonary Disease (n=23), Pulmonary And Concomitant Cardiac Disease (n=17), Other Disease (n=7), Pulmonary Embolism (n=8), AMI (n=11); Reference standard: European society of cardiology guideline	To verify the usefulness of NT-proBNP in the differential diagnosis of dyspnea in a population of patients presenting in the ER with breathlessness.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Continuous ER patients (Acute-severe dyspnea) n=122 age=78*y, %males=47.5 HF Prev=46%	1,760 ng/L	80	76	3.33	0.26	0.815

Abbreviations: AUC = Area Under the Curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CHF = Congestive Heart Failure; CI = Confidence Interval; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; EPIDASA = Epidemiological study of acute dyspnea in elderly patients; GFR = Glomerular filtration rate; glow = Lower gray zone; gup = Upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = Heart Failure; KD = Kidney disease; kg/m2 = Kilograms per meter squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LVEF = Left Ventricular Ejection Fraction; mg/dL = Milligram per deciliter; mL/min/1.73m2 = Milliliter per minute per 1.73 meters squared; NA = Not applicable; ng/L = Nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = Not reported ; pg/mL = Picograms per milliliter; RCT = Randomized controlled trial; SOB = Shortness of breath; yrs = years

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED

Author Year Companion/ sub-analysis	Study Design	Population	n, Mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Alibay,[1] 2005	Cross-sectional	Dyspnea	160, 80.1(13.5)y, 47.5	38	2 cardiologists	NT-proBNP	280	100	5	1.05	0.00	NR	
						NT-proBNP	600	100	51	2.04	0.00	NR	
						NT-proBNP	1,000	97	63	2.62	0.05	NR	
						NT-proBNP	1,250	87	66	2.56	0.20	NR	
Anwaruddin,[53] 2006 PRIDE	Cross-sectional	Dyspnea	599, (GFR<30) 78.0(7.6)y; (GFR 30-59) 73.1(12.4)y; (GFR60-89) 60.7(15.7)y; (GFR≥90) 51.3(15.7)y, 59.32	35	2 cardiologists	NT-proBNP	450 for patients ages <50 years and 900 for patients ≥ 50 years	NR	NR	NR	NR	NR	Paper says that 140 patients underwent echo. Table 2 lists echo values, but the total is 139 patients
		GFR ≥60 ml/min/1.73 m^2	NR, NR, NR	21	2 cardiologists	NT-proBNP	450 for patients ages <50 years and 900 for patients ≥ 50 years	85	88	7.08	0.17	0.95	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Anwaruddin[53] 2006 PRIDE (cont'd)	Cross-sectional	GFR ≥60 ml/min/1.73 m2	NR, NR, NR	21	2 cardiologists	NT-proBNP	450 for patients ages <50 years and 900 for patients ≥50 years	97	68	3.03	0.04	0.88	
						NT-proBNP	1,200	89	72	3.18	0.15	NR	
		GFR <44 ml/min/1.73 m2	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1,200	92	70	3.07	0.11	0.89	
Bayes-Genıs,[54] 2004	Cross-sectional	Acute dyspnea	89, (Decompensated HF) 71(10)y; (Masked HF) 76(7)y; (Normal) 62(13)y, 60.67	83	2 cardiologists	NT-proBNP	30 pmol/L	98.6	46.7	1.85	0.03	NR	30 cut for ruling out cardiac origin dyspnea;115 to rule in.
						NT-proBNP pmol/L	50 pmol/L	95.7	60	2.39	0.07	NR	
						NT-proBNP	70 pmol/L	94.3	73.3	3.53	0.08	NR	
						NT-proBNP	90 pmol/L	91.4	73.3	3.42	0.12	NR	
						NT-proBNP	115 pmol/L	91.4	93.3	13.64	0.09	0.96	
						NT-proBNP	130 pmol/L	90	93.3	13.43	0.11	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Bayes-Genis,[55] 2007 ICON	Cross-sectional	Lean, BMI lower than 25.0	412, 70.5(15.7)y, 48.8	NR	Cardiologists/ physicians	NT-proBNP	NR	NR	NR	5.34	0.02	NR	
		Overweight, BMI of 25.0 to 29.9	NR, NR, NR	NR	Cardiologists/ physicians	NT-proBNP	NR	NR	NR	13.32	0.03	NR	
		Obese, BMI≥ 30.0	NR, NR, NR	NR	Cardiologists/ physicians	NT-proBNP	NR	NR	NR	7.54	0.08	NR	
Behnes,[56] 2009 MANPRO	Cross-sectional	Acute dyspnea/ peripheral edema	401, 67.4y, 51	30	1 physician	NT-proBNP	100	98	27	1.34	0.07	NR	
						NT-proBNP	200	98	40	1.63	0.05	NR	
						NT-proBNP	300	96	48	1.85	0.08	0.85	
						NT-proBNP	400	94	54	2.04	0.11	NR	
						NT-proBNP	500	92	60	2.30	0.13	NR	
Behnes,[57] 2011 MANPRO	Cross-sectional	Dyspnea	401, 67.4y, 51	30	Diagnoses of AF and CHF were based on clinically assessed final diagnoses of the individual hospital stay of each individual patient according to European Guidelines	NT-proBNP	NR	NR	NR	NR	NR	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Behnes,[57] 2011 MANPRO (cont'd)	Cross-sectional	Dyspnea	NR, NR, NR	27	Diagnoses of AF and CHF were based on clinically assessed final diagnoses of the individual hospital stay of each individual patient according to European Guidelines	NT-proBNP	270	0.95	NR	NR	NR	0.73	
			NR, NR, NR	30	Diagnoses of AF and CHF were based on clinically assessed final diagnoses of the individual hospital stay of each individual patient according to European Guidelines	NT-proBNP	300	NR	NR	NR	NR	0.85	
Berdague,[58] 2006	Cross-sectional	Acute dyspnea,>70y.	254, 81(7)y, 48	56	2 cardiologists	NT-proBNP	1,000	97	49	1.90	0.06	NR	
						NT-proBNP	1,200	97	65	2.77	0.05	NR	
						NT-proBNP	1,630	92	55	2.04	0.15	NR	
						NT-proBNP	2,000	87	72	3.11	0.18	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Berdague,[58] 2006 (cont'd)	Cross-sectional	Acute dyspnea,>70y.	254, 81(7)y, 48	56	2 cardiologists	NT-proBNP	2,300	81	75	3.24	0.25	NR	
						NT-proBNP	3,000	75	80	3.75	0.31	NR	
						NT-proBNP	4,500	64	86	4.57	0.42	NR	
						NT-proBNP	5,500	58	87	4.46	0.48	NR	
Chenevier-Gobeaux,[6] 2005	Cross-sectional	Dyspnea	381, 79(12)y, NR	30	2 urgentists	NT-proBNP	NR	NR	NR	NR	NR	NR	There is mention of echo in the methods or results sections
		eGFR≥90 ml/min/1.73 m^2, CKD Level1	NR, NR, NR	8	2 urgentists	NT-proBNP	NR	NR	NR	NR	NR	NR	
		eGFR 60-89 ml/min/1.73 m^2, CKD Level 2	NR, NR, NR	20	2 urgentists	NT-proBNP	1,360	77	86	5.50	0.27	0.8476	
		eGFR 30-59 ml/min/1.73 m^2, CKD Level 3	NR, NR, NR	34	2 urgentists	NT-proBNP	1,980	62	80	3.10	0.48	0.7314	
		eGFR 15–29 ml/min/1.73 m2; CKD Level 4	NR, NR, NR	49	2 urgentists	NT-proBNP	6,550	82	79	3.90	0.23	0.8025	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Chenvier,[7] 2008	Cohort	Dyspnea (all)	570 (<85 non CHF), 75(6)y; (<85 CHF) 77(6)y; (≥85 non CHF) 91(4)y; (≥85 CHF) 90(4)y, males 47.89	44	2 emergency physicians or a pulmonologist and cardiologist	NT-proBNP	NR	NR	NR	NR	NR	NR	Echo performed in patients adjudicated by pulmono-logist and cardiologist
						NT-proBNP	1,700	74	77	3.22	0.34	0.786	
						NT-proBNP	1,750	85	59	2.07	0.25	NR	
						NT-proBNP	2,100	82	63	2.22	0.29	NR	
						NT-proBNP	2,800	74	70	2.47	0.37	NR	
						NT-proBNP	3,300	69	75	2.76	0.41	NR	
						NT-proBNP	4,900	57	80	2.85	0.54	NR	
						NT-proBNP	6,000	53	85	3.53	0.55	NR	
Chenevier-Gobeaux,[8] 2010	Cross-sectional	Dyspnea (age 60+)	378, 78(12)y, 50.26	30	2 emergency physicians	NT-proBNP	300 ng/L	100	27	1.37	0.00	NR	Population age 60y or more
		Tertile 3 (eGFR ≥ 58.6 mL/min/1.73 m^2)	NR, NR, NR	17	2 emergency physicians	NT-proBNP	>1,500 ng/L	82	82	4.56	0.22	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Chenevier-Gobeaux,[8] 2010 (cont'd)	Cross-sectional	Tertile 2 (eGFR between 44.3 and 58.5 mL/min/1.73m2)	NR, NR, NR	34	2 emergency physicians	NT-proBNP	>1,700 ng/L	88	71	3.03	0.17	NR	
		Tertile 1 (eGFR<44.3 mL/ min/1.73 m2)	NR, NR, NR	39	2 emergency physicians	NT-proBNP	>4,000 ng/L	79	60	1.98	0.35	NR	
deFilippi,[15] 2007	Cohort	Dyspnea	831, (eGFR<60) 69.3(13.1)y; (eGFR≥60) 63.5(16)y, 45.7	53	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
		eGFR<60	NR, NR, NR	61	2 cardiologists	NT-proBNP	1,200 ng/L	81	49	1.59	0.39	NR	
		eGFR≥60	NR, NR, NR	45	2 cardiologists	NT-proBNP	900 ng/L for age ≥50, 450 ng/L for age<50	81	52	1.70	0.36	NR	
Gorrisen,[17] 2007	Cross-sectional	Dyspnea	80, 74(10)y, 55	50	1 cardiologist, 1 pulmonologist	NT-proBNP	1,550 ng/L	80	65	2.29	0.31	0.774	
		<65y	NR, NR, NR	NR	1 cardiologist, 1 pulmonologist	NT-proBNP	591 ng/L	55	100	NA	0.45	0.614	
		65 to 75y	NR, NR, NR	NR	1 cardiologist, 1 pulmonologist	NT-proBNP	1,922 ng/L	75	73	2.78	0.34	0.75	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Gorrisen,[17] 2007 (cont'd)	Cross-sectional	>75y	NR, NR, NR	NR	1 cardiologist, 1 pulmonologist	NT-proBNP	1,737 ng/L	71	84	4.44	0.35	0.831	
		GFR >60 mL/min/1.73 m^2	NR, NR, NR	NR	1 cardiologist, 1 pulmonologist	NT-proBNP	1,118 ng/L	85	73	3.15	0.21	0.781	
		GFR ≤60 mL/min/1.73 m^2	NR, NR, NR	NR	1 cardiologist, 1 pulmonologist	NT-proBNP	2,592 ng/L	70	64	1.94	0.47	0.702	
Gruson,[18] 2008	Cohort	Dyspnea (CHF)	137, 69y, 56.2	23	1 cardiologist	NT-proBNP	NR	NR	NR	NR	NR	O.91	0.91 AUC is for diagnosis of CHF
Gruson,[20] 2012	Cohort	Dyspnea and/or chest pain, all	156 67y 54.5	29.5	Clinicians	NT-proBNP	100 ng/L	NR	NR	NR	NR	0.92	Independent Study
Green,[59] 2008 PRIDE	Cohort	Dyspnea	592, (Clinical uncertainty present) 69(14)y; (Clinical uncertainty absent) 59(18)y, 50.51	34	2 cardiologists	NT-proBNP	450 for patients ages <50y and 900 for patients 50-75y; 1,800 in >75y	NR	NR	NR	NR	NR	
		Clinical certainty group	NR, NR, NR	24	2 cardiologists	NT-proBNP	450 for patients ages <50y and 900 for patients 50-75; 1,800 in >75y	92	86	6.57	0.09	0.88	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Green,[59] 2008 PRIDE (cont'd)	Cohort	Clinical uncertainty group	NR, NR, NR	56	2 cardiologists	NT-proBNP	450 for patients ages <50y and 900 for patients 50-75y; 1,800 in >75y	90	84	5.63	0.12	NR	
Januzzi,[60] 2005 PRIDE	Cross-sectional	All patients	599, (Acute CHF) 72.8(13.6)y; (No acute CHF) 56.9(16.3)y, 51	35	2 cardiologists	NT-proBNP	300	99	68	3.09	0.01	NR	
						NT-proBNP	450	98	76	4.08	0.03	NR	
						NT-proBNP	600	96	81	5.05	0.05	NR	
		Dyspnea	NR, NR, NR	35	2 cardiologists	NT-proBNP	900	90	85	6.00	0.12	0.94	
		All patients	599, (Acute CHF) 72.8(13.6)y; (No acute CHF) 56.9(16.3)y, 51	35	2 cardiologists	NT-proBNP	1,000	87	86	6.21	0.15	NR	
		<50y old	NR, NR, NR	NR	2 cardiologists	NT-proBNP	450	93	95	18.60	0.07	0.98	
		≥50y old	NR, NR, NR	NR	2 cardiologists	NT-proBNP	900	91	80	4.55	0.11	0.93	
		<50y old	NR, NR, NR	NR	2 cardiologists	NT-proBNP	900	73	96	18.25	0.28	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Januzzi,[61] 2006 PRIDE	Cross-sectional	Dyspnea	1256, 68.3(15.9)y, 51	57	Cardiologists	NT-proBNP	300	99	60	2.48	0.02	NR	
						NT-proBNP	Age specific cutpoint	90	84	5.63	0.12	NR	
		<50y old	NR, NR, NR		Cardiologists	NT-proBNP	450	97	93	13.86	0.03	0.99	
		50-75y old	NR, NR, NR		Cardiologists	NT-proBNP	900	90	82	5.00	0.12	0.93	
		>75y old	NR, NR, NR		Cardiologists	NT-proBNP	1,800	85	73	3.15	0.21	0.86	
Krauser,[62] 2006 PRIDE	Cross-sectional	Dyspnea	599, (men) 61.7(16)y, (women) 63.2(17)y, 51	35	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
		African American	NR, NR, NR	30	2 cardiologists	NT-proBNP	Optimal diagnostic cutpoints of 450 (age <50y), 900 (age 50 to 75y) and 1,800 (age >75y)	100	90	10.00	0.00	0.96	
		Non-African-American	NR, NR, NR	35	2 cardiologists	NT-proBNP	NR	NR	NR	NA	NA	0.94	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Krauser[62] 2006 PRIDE (cont'd)	Cross-sectional	Female	NR, NR, NR	35	2 cardiologists	NT-proBNP	Optimal diagnostic cutpoints of 450 (age <50y), 900 (age 50 to 75y) and 1,800 (age >75y)	89	90	8.90	0.12	0.95	
		Male	NR, NR, NR	35	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	0.94	
Lainchbury,[25] 2003	Cross-sectional	Acute dyspnea	205, 70(14)y, 49	34	2 cardiologists	NT-proBNP	140	87	71	3.00	0.18	0.76	Echo performed in 171 patients.
						NT-proBNP	240	83	82	4.61	0.21	0.83	
						NT-proBNP	340	80	87	6.15	0.23	0.85	
						NT-proBNP	440	74	90	7.40	0.29	0.85	
						NT-proBNP	540	68	92	8.50	0.35	0.84	
Liteplo,[63] 2009	Cross-sectional	Dyspnea	94, 74(14)y, 59	43	2 emergency physicians.	NT-proBNP	450/900/ 1,800	85	62.96	2.29	0.24		

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Martinez-Rumayor,[64] 2010 PRIDE	Cross-sectional	Suspected AHF	599, (Normal CXR) 59y*, (Abnormal CXR) 71y*, 51.25	35	2 cardiologists	NT-proBNP	'Rule in cut-off points' (450/900/ 1,800 for ages <50/50–75/>75y)	90	86	6.43	0.12	NR	
		Normal CXR	NR, NR, NR	21	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	0.94	
		Abnormal CXR	NR, NR, NR	56	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	0.92	
Moe,[65] 2007 BACH	Cross-sectional	Dyspnea	500, 70y, 51.6	46	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	0.86	
		NT-proBNP	NR, NR, NR	NR	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
		Usual care	NR, NR, NR	NR	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
Mueller,[35] 2005 & Gegenhuber,[36] 2006	Cross-sectional	Dyspnea	251, (HF) 76y, (No CHF) 69y, 93.2	55	1 internist, Framingham criteria	NT-proBNP	292 ng/L	95	53	2.02	0.09	NR	
						NT-proBNP	125/450 ng/L	94	46	1.74	0.13	NR	
						NT-proBNP	476 ng/L	90	65	2.57	0.15	NR	
						NT-proBNP	825 ng/L	87	81	4.58	0.16	NR	
Nazerian,[66] 2010	Cohort	Acute dyspnea	145, (HF) 81(8)y, (non HF) 75(12)y, 48.9	44	2 cardiologists, 1 respiratory physician, Boston criteria for CHF.	NT-proBNP	≤300	98	22	1.26	0.09	NR	
						NT-proBNP	≥2,200	83	70	2.77	0.24	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
O'Donoghue,[67] 2007 PRIDE	Cross-sectional	Dyspnea	599, NR, 50.58	35	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
		With DM	NR, NR, NR	56	2 cardiologists	NT-proBNP	Optimal diagnostic cutpoints of 450 (age <50y), 900 (age 50 to 75y) and 1,800 (age >75y)	92	90	9.20	0.09	0.94	
		No DM	NR, NR, NR	27	2 cardiologists	NT-proBNP	NR	NR	NR	NR	NR	NR	
Oh,[68] 2009	Cross-sectional	Clinical diagnosis of AHF	100, 64.3(13.1)y, 60	44	ECHO - blinded analysis	NT-proBNP	NR	NR	NR	NR	NR	NR	
		RDW tertile 1	NR, NR, NR	NR	ECHO - blinded analysis	NT-proBNP	NR	NR	NR	NR	NR	NR	
		RDW tertile 2	NR, NR, NR	NR	ECHO - blinded analysis	NT-proBNP	NR	NR	NR	NR	NR	NR	
		RDW tertile 3	NR, NR, NR	NR	ECHO - blinded analysis	NT-proBNP	NR	NR	NR	NR	NR	NR	
Potocki,[40] 2010	Cross-sectional	Acute dyspnea	287, 77y*, 52	54	2 cardiologists	NT-proBNP	1,560	85	85	5.67	0.18	0.92	
Prosen,[69] 2011	Cohort	Dyspnea	218, (HF) 70.9(11.7)y; (Pulmonary edema) 52.3(15.3)y, 70	NR	Cardiologists,ICU physicians,Boston, Framingham	NT-proBNP	1,000	92	89	8.36	0.09	0.9	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Ray,[41] 2005 EPIDASA study	Cross-sectional	Acute dyspnea	202, 80(9)y, 49.5	44	Pulmonologist, cardiologist,emergency physician,or geriatric or internal medicine	NT-proBNP	≥1,500	75	76	3.13	0.33	0.8	Echo done in only 45%, population selected for age 65 and over
Robaei,[70] 2011	RCT	Dyspnea	68, 73(16)y, 44.12	40	1 cardiologist	NT-proBNP	450 for patients ages <50y and 900 for patients 50-75; 1,800 in >75y	81	66	2.38	0.29	NR	
Sanz,[46] 2006	Cross-sectional	Acute dyspnea	75, 75(14.8)y, 67	60	Clinicians	NT-proBNP	817	97.7	93.5	15.03	0.02	0.979	
						NT-proBNP	300	100	50	2.00	0.00	NR	Echo not performed in many patients - doesn't report how many
Shah,[47] 2009a	Cohort	for the diagnosis of LVEF ≤40%	NR, NR, NR	37	Panel of physicians	NT-proBNP	300	NR	NR	NR	NR	0.86	
		For the diagnosis of diastolic dysfunction	NR, NR, NR	NR	Panel of physicians	NT-proBNP	300	NR	NR	NR	NR	0.67	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Shah,[47] 2009a (cont'd)	Cohort	For the diagnosis of diastolic dysfunction in patients with preserved systolic function (LVEF≥50 %)	NR, NR, NR	NR	Panel of physicians	NT-proBNP	300	NR	NR	NR	NR	0.6	
Shah[48] 2009b	Cohort	Acute dyspnea	412, 58(14)y, 61	36	Panel of physicians	NT-proBNP	NR	NR	NR	NR	NR	0.86	
Shaikh,[72] 2011	Cohort	Dyspnea(all patients)	100 61±14y 48	79	NR	NT-proBNP (rule out)	300	100	42.85	1.75	0.00	NR	
						NT-proBNP	900	96.2	80.95	5.05	0.05	NR	
		Age<50y	22 NRy NR	NR	NR	NT-proBNP	450	100	33.33	1.50	0.00	NR	
		Age>50y	78 NRy NR	NR	NR	NT-proBNP (rule in)	900	96.82	86.66	7.26	0.04	NR	
		Age<75y	NR	NR	NR	NT-proBNP (rule out)	125	99	NR	NR	NR	NR	
		Age>75y	NR	NR	NR	NT-proBNP (rule out)	450	99	NR	NR	NR	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
Steinhart,[73] 2009 IMPROVE-CHF	Cohort	Dyspnea	483, 70y, NR	NR	2 cardiologists, Framingham, NHANES	NT-proBNP	<300	NR	NR	NR	NR	NR	
						NT-proBNP	300-899	NR	NR	NR	NR	NR	
						NT-proBNP	900	NR	NR	NR	NR	NR	
						NT-proBNP	<300	NR	NR	NR	NR	NR	
						NT-proBNP	300-899	NR	NR	NR	NR	NR	
						NT-proBNP	900-2,699	NR	NR	NR	NR	NR	
						NT-proBNP	2,700-8,099	NR	NR	NR	NR	NR	
						NT-proBNP	>8,100	NR	NR	NR	NR	NR	
Tung,[74] 2006 PRIDE	Cross-sectional	Dyspnea	216, (HF) 69(11)y; (No HF) 59(16)y, 44.9	25	2 cardiologists	NT-proBNP	450 for patients ages <50 years and 900 for patients ≥ 50 years	87	84	5.44	0.15	0.9	Only 140 echo was taken in whole of PRIDE study; this is a subset analysis
						NT-proBNP	300	94	61	2.41	0.10	NR	
		COPD, No HF history	NR, NR, NR	13	2 cardiologists	NT-proBNP	>450	82	90	8.20	0.20	0.88	
		COPD, HF	NR, NR, NR	63	2 cardiologists	NT-proBNP	>450	91	47	1.72	0.19	0.85	
		COPD, No HF history	NR, NR, NR	13	2 cardiologists	NT-proBNP	300	90	66	2.65	0.15	NR	
		COPD, HF	NR, NR, NR	63	2 cardiologists	NT-proBNP	300	97	21	1.23	0.14	NR	

Table H-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the ED (continued)

Author Year Companion/ sub-analysis	Study Design	Population	n, mean age (SD), %male	Prevalence of HF (%)	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC	Comments
van Kimmenade,[75] 2006 PRIDE	Cross-sectional	Dyspnea	599, (AHF) 72(13.6)y, (No AHF) 56.9(16.3)y, 51.25	35	Study physician	NT-proBNP	NR	NR	NR	NR	NR	0.94	
Zaninotto,[76] 2005	Case-control	Continuous ER patients (Acute-severe dyspnea)	122, 78*y, 47.5	46	European society of cardiology guideline	NT-proBNP	1,760 ng/L	80	76	3.33	0.26	0.815	

Abbreviations: AHF = acute heart failure; AUC = area under the curve; BACH = Biomarkers in Acute Heart Failure; BASEL = B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation; BMI = body mass index; BNP = B-type natriuretic peptide; CHF = congestive heart failure; CI = confidence interval; CXR = chest x-ray; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EPIDASA = Epidemiological Study of Acute Dyspnea in Elderly Patients; GFR = glomerular filtration rate; glow = lower gray zone; gup = upper gray zone; HEARD-IT = Heart Failure and Audicor technology for Rapid Diagnosis and Initial Treatment; HF = heart failure; KD = kidney disease; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVEF = left ventricular ejection fraction; mg/dL = milligram per deciliter; mL/min/m2 = milliliter per minute per meters squared; NA = not applicable; ng/L = nanogram per liter; NHANES = National Health and Nutrition Examination Survey; NR = not reported ; pg/mL = picograms per milliliter; RCT = randomized controlled trial; SOB = shortness of breath; y = years

Figure H-13. Summary forest plot of sensitivity and specificity (ED NTProBNP, manufacturer cut-point), bivariate mixed effect model

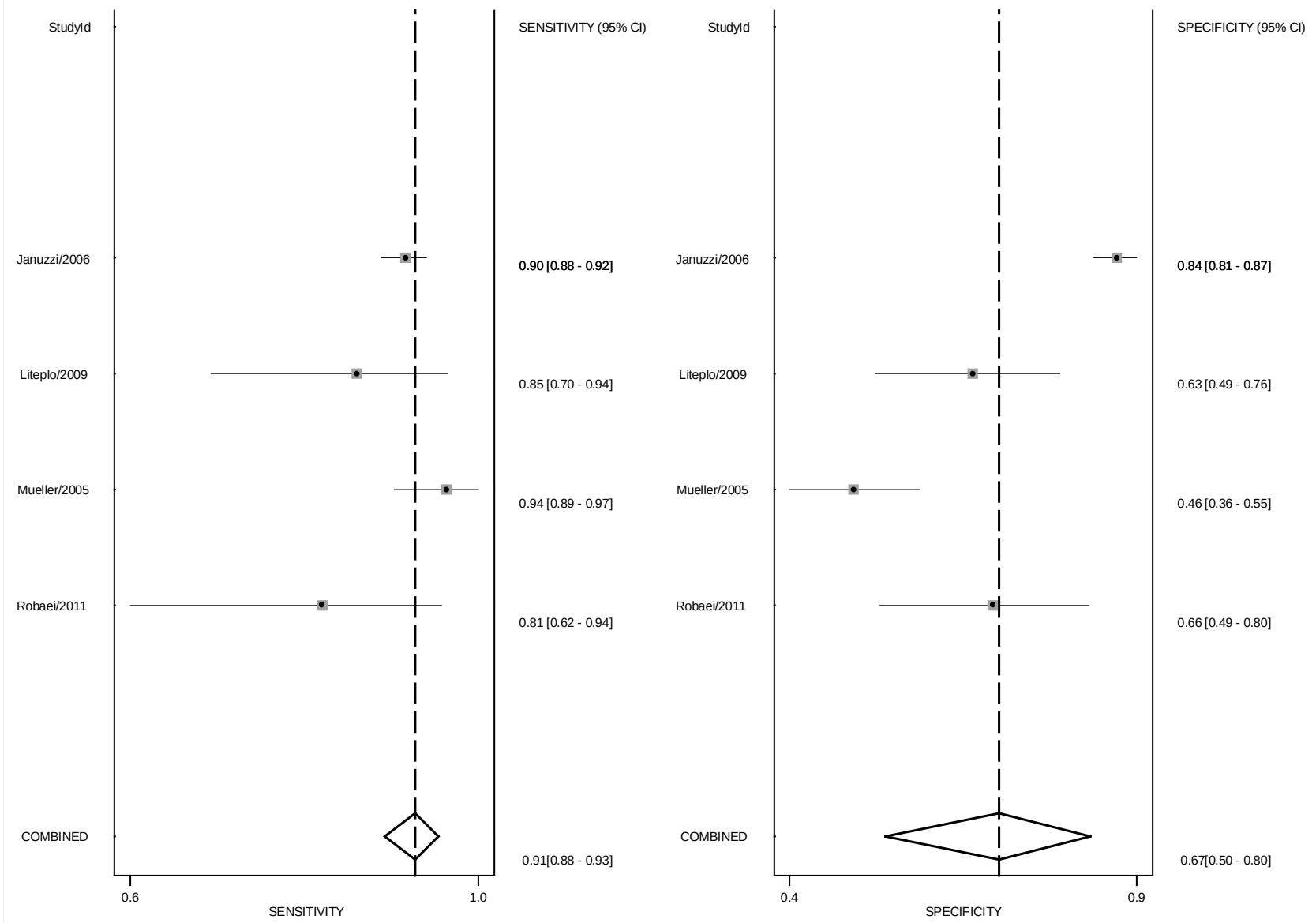


Figure H-14. Summary forest plot of sensitivity and specificity (ED NTProBNP, optimum cut-point), bivariate mixed effect model

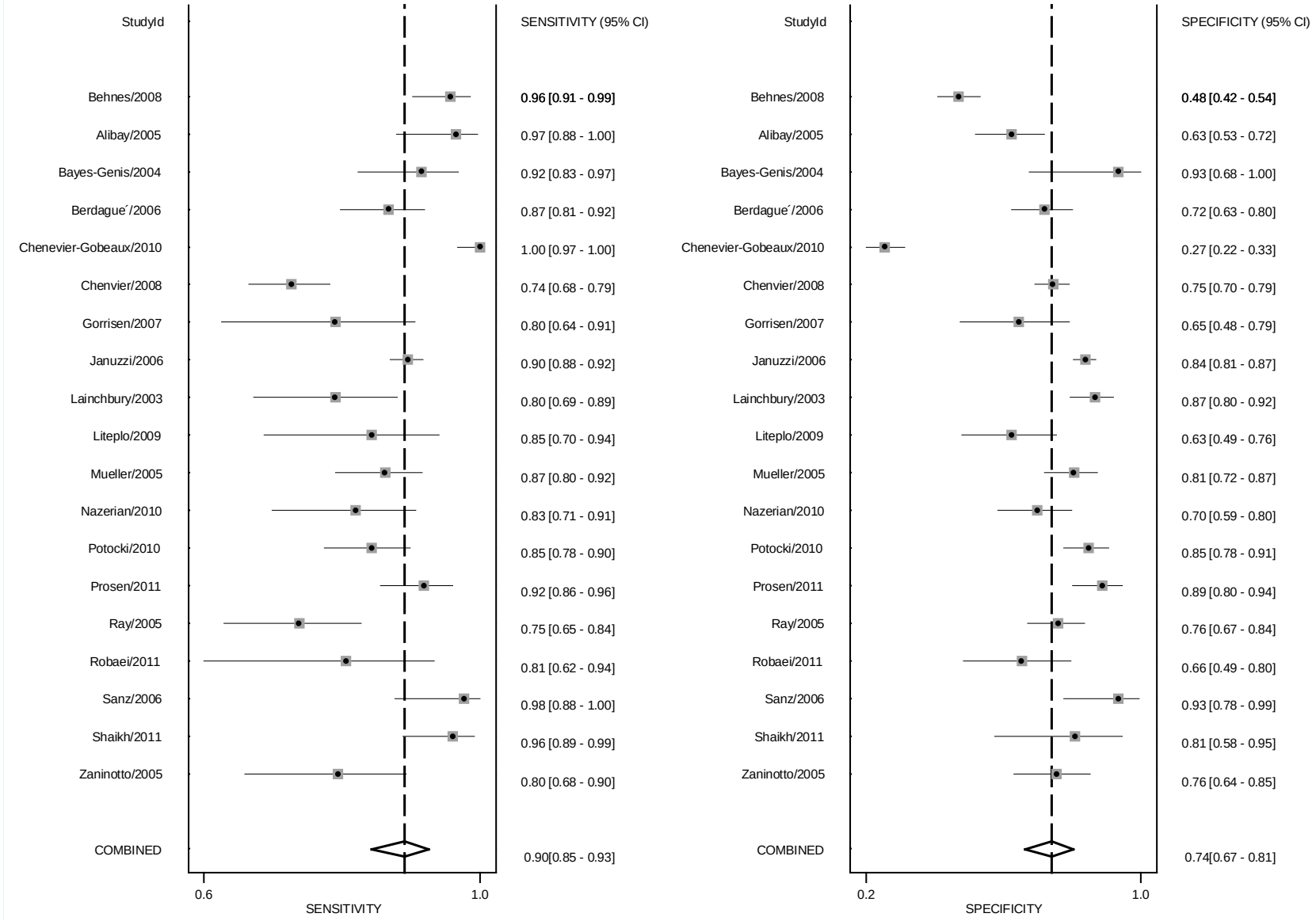


Figure H-15. Summary forest plot of sensitivity and specificity (ED NTProBNP, lowest cut-point), bivariate mixed effect model

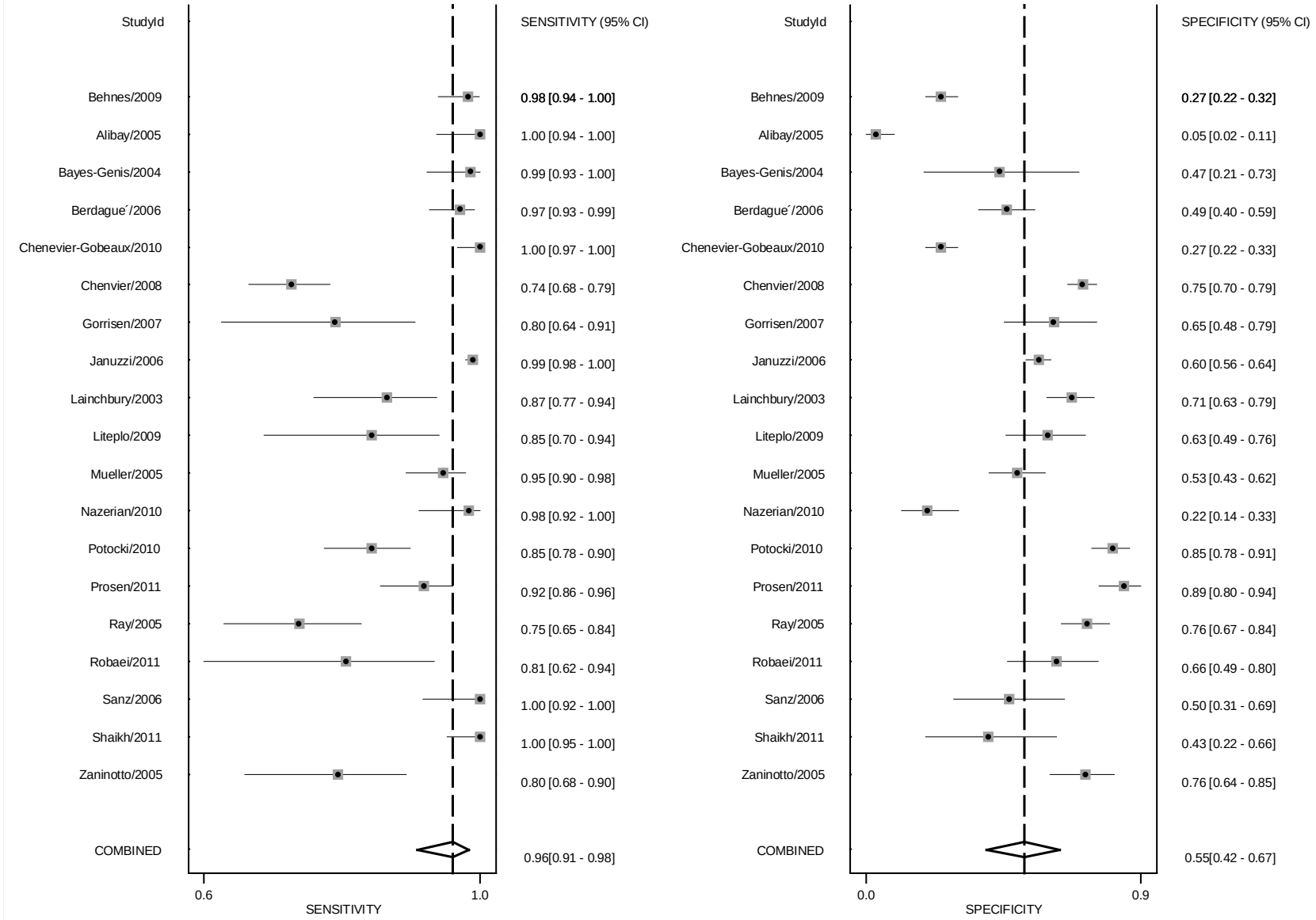


Figure H-16. Summary forest plot of LR+ and LR- (ED NTProBNP, manufacturer cut-point), bivariate mixed effect model

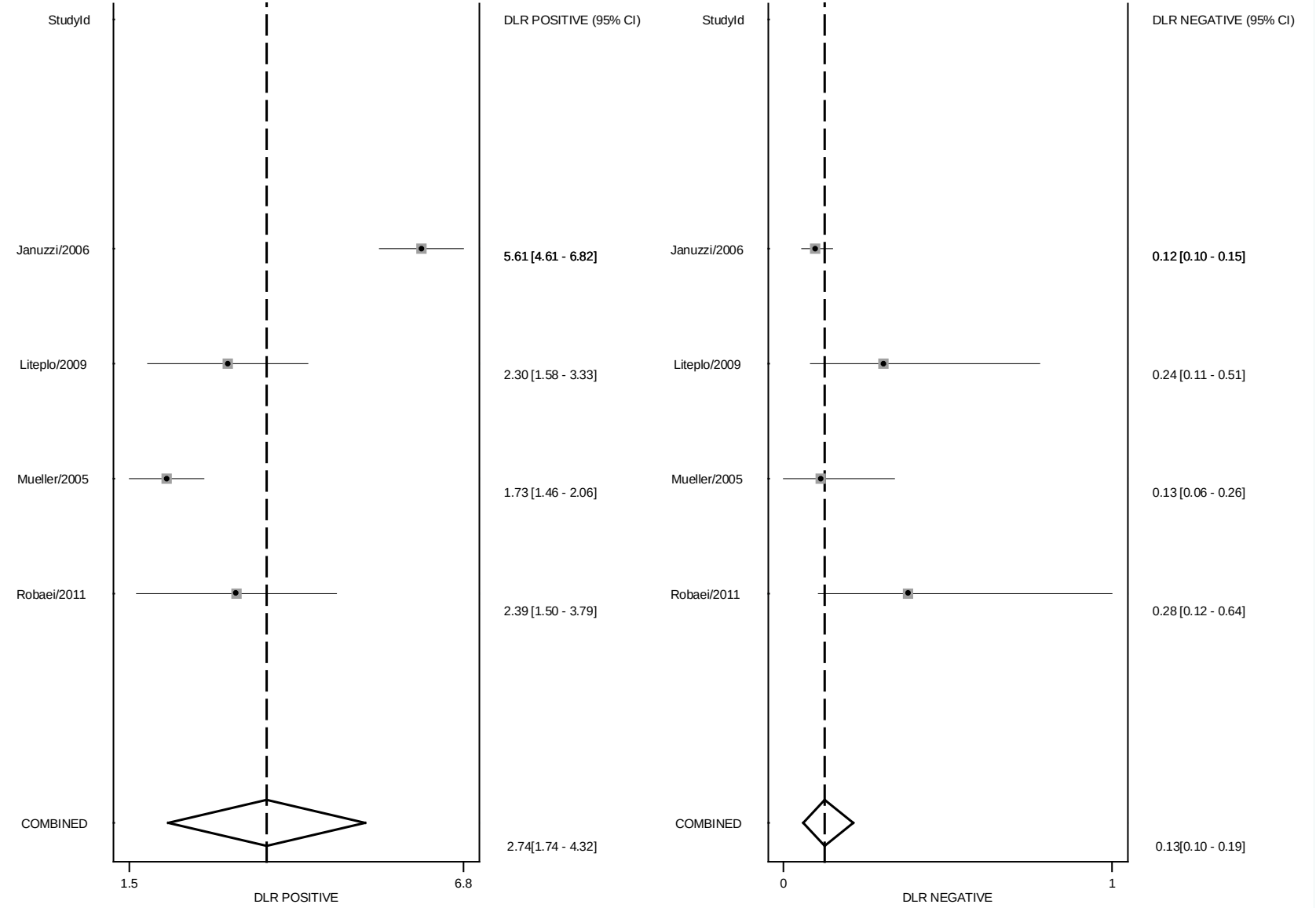


Figure H-17. Summary forest plot of LR+ and LR- (ED NTProBNP, optimum cut-point), bivariate mixed effect model

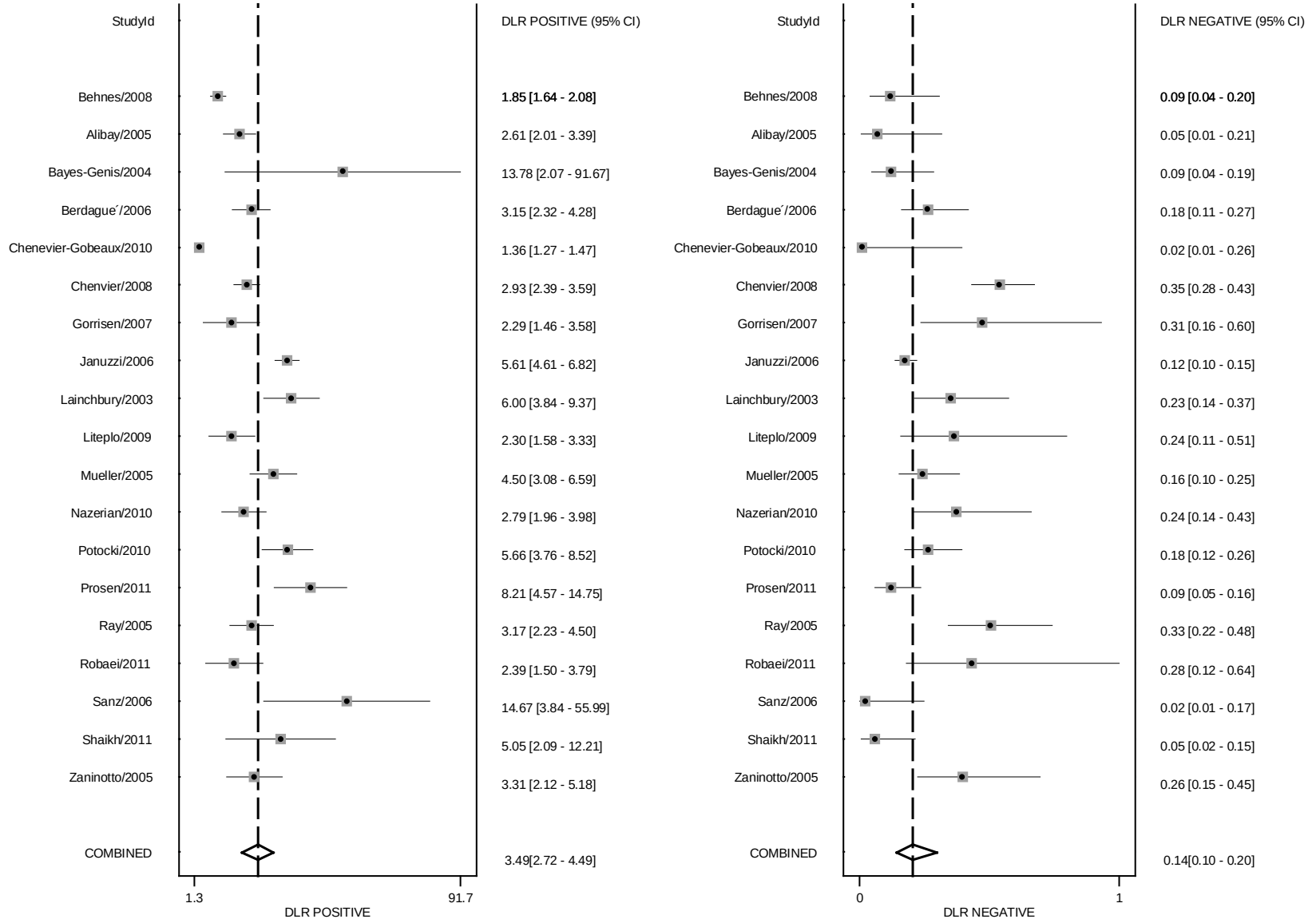


Figure H-18. Summary forest plot of LR+ and LR- (ED NTProBNP, lowest cut-point), bivariate mixed effect model

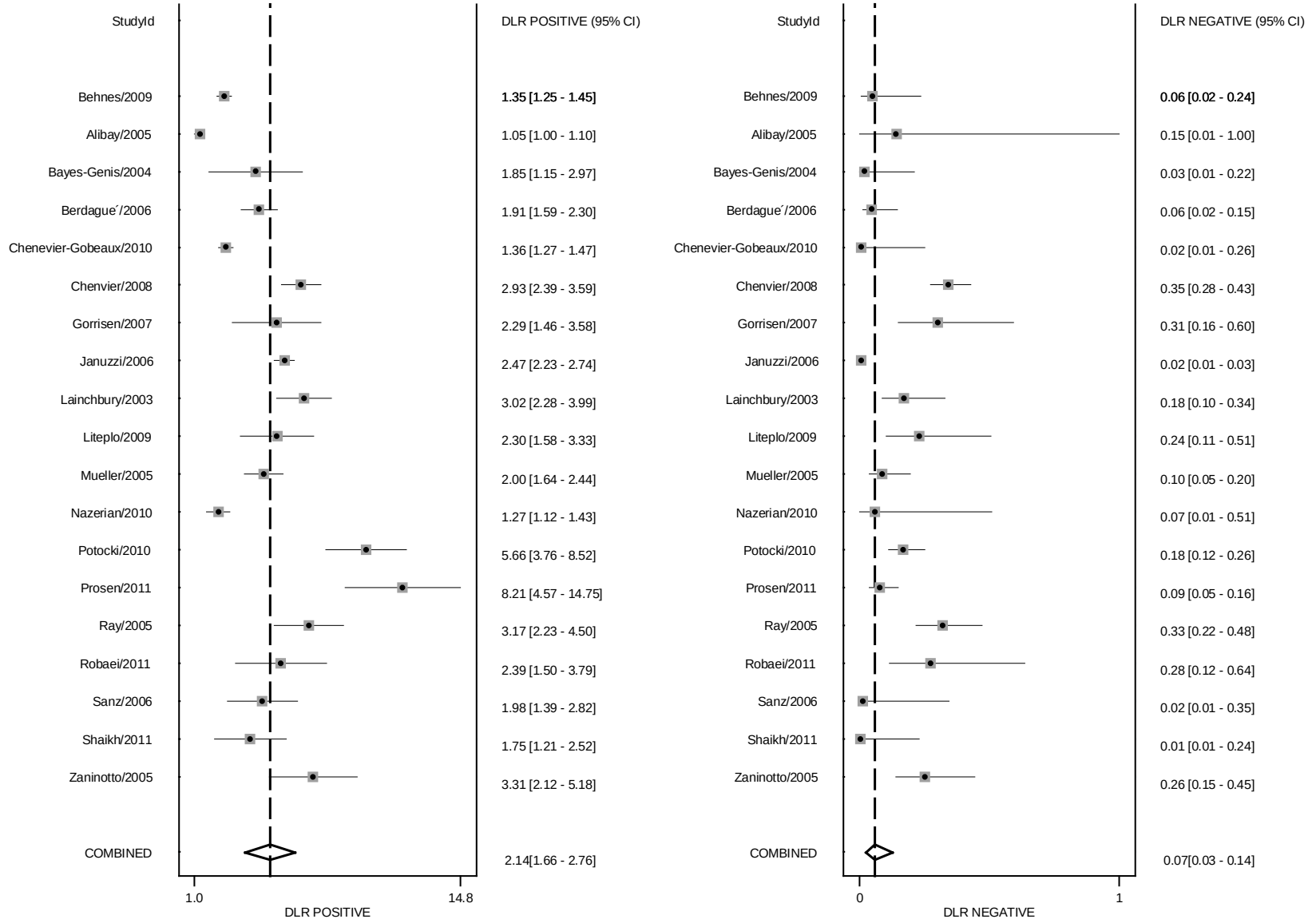


Figure H-19. Summary forest plot of LogDOR and DOR (ED NTProBNP, manufacturer cut-point), bivariate mixed effect model

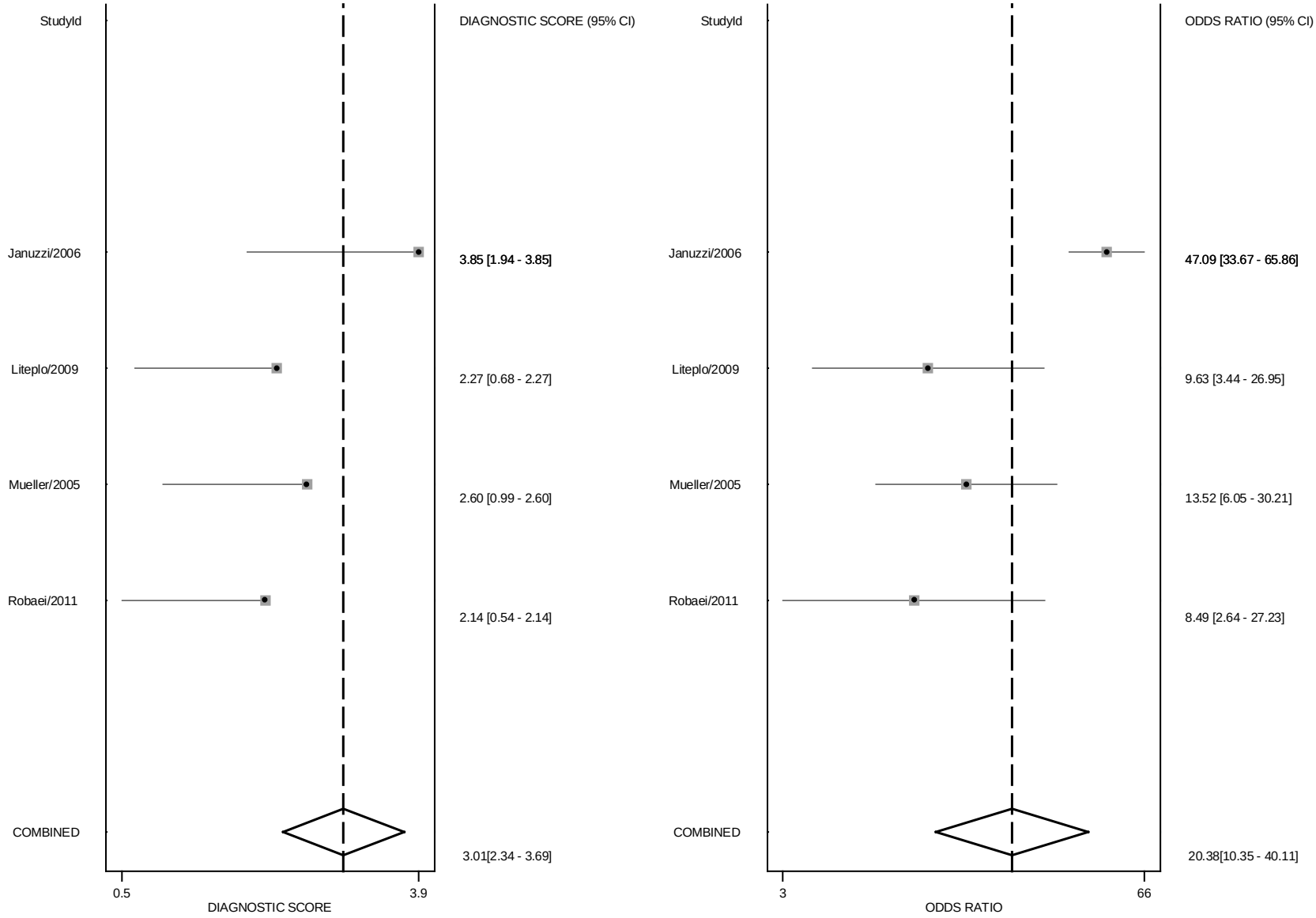


Figure H-20. Summary forest plot of LogDOR and DOR (ED NTProBNP, optimum cut-point), bivariate mixed effect model

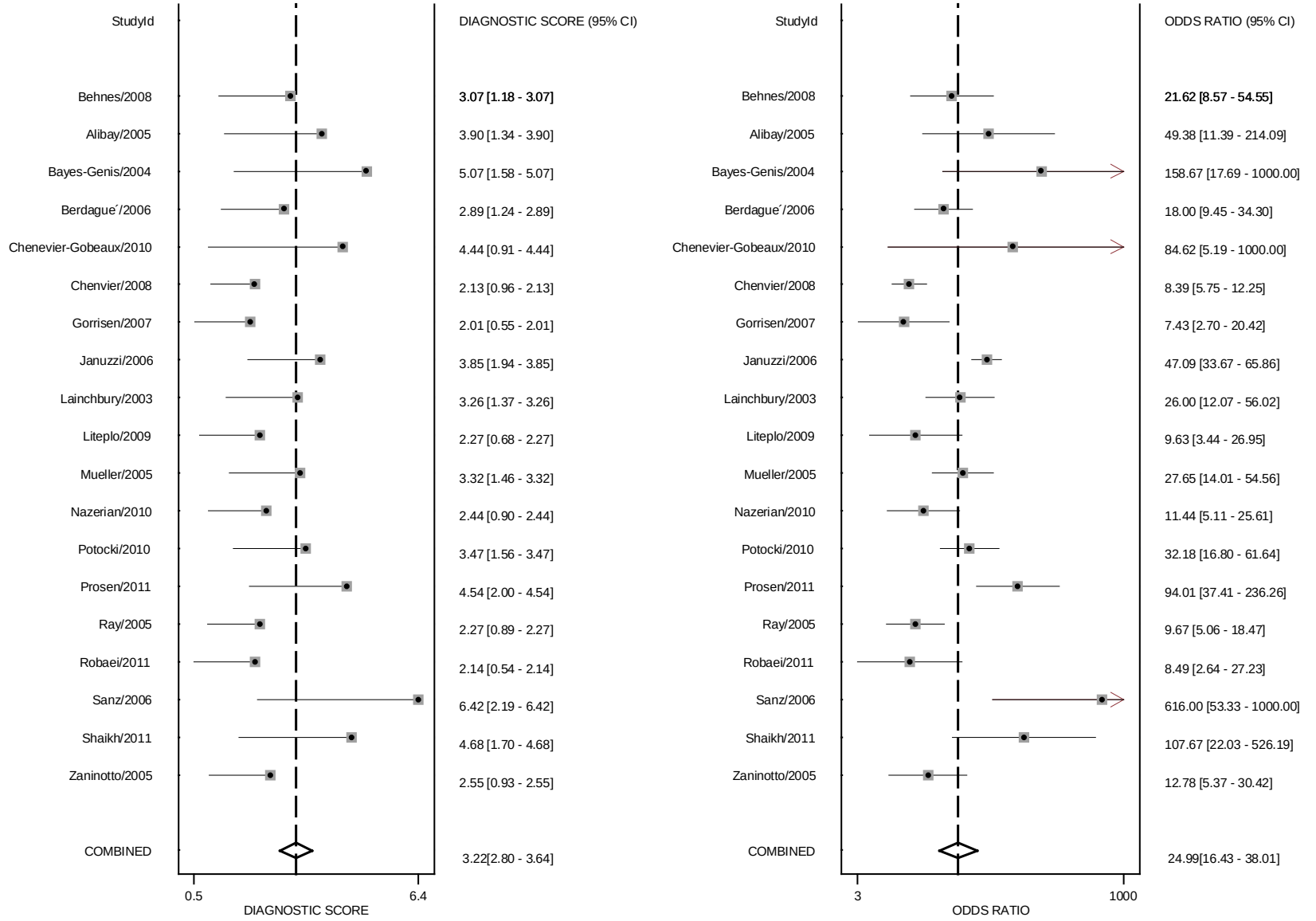


Figure H-21. Summary forest plot of LogDOR and DOR (ED NTProBNP, lowest cut-point), bivariate mixed effect model

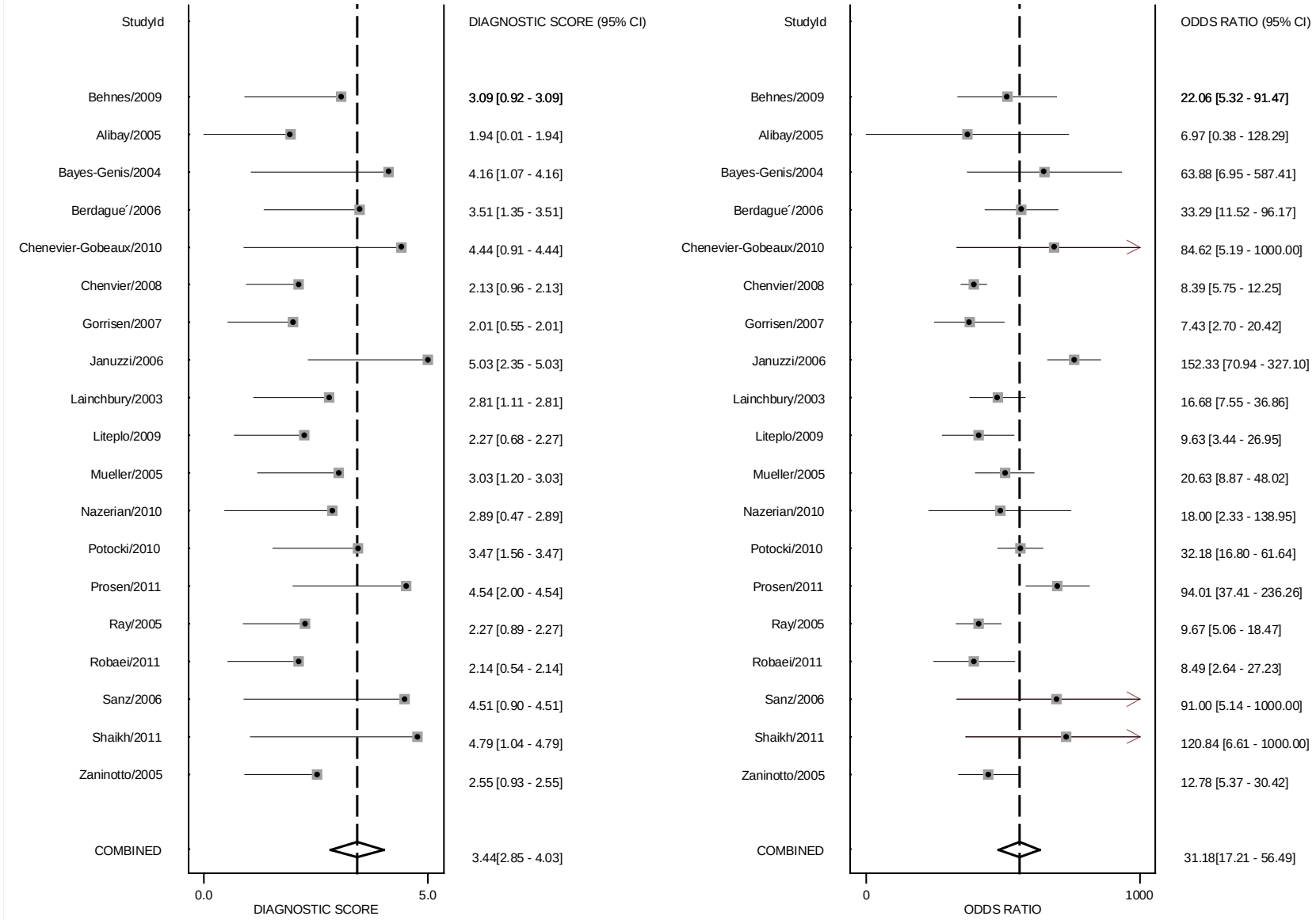


Figure H-22. Summary ROC-curve (ED NTProBNP, manufacturer cut-point), bivariate mixed effect model

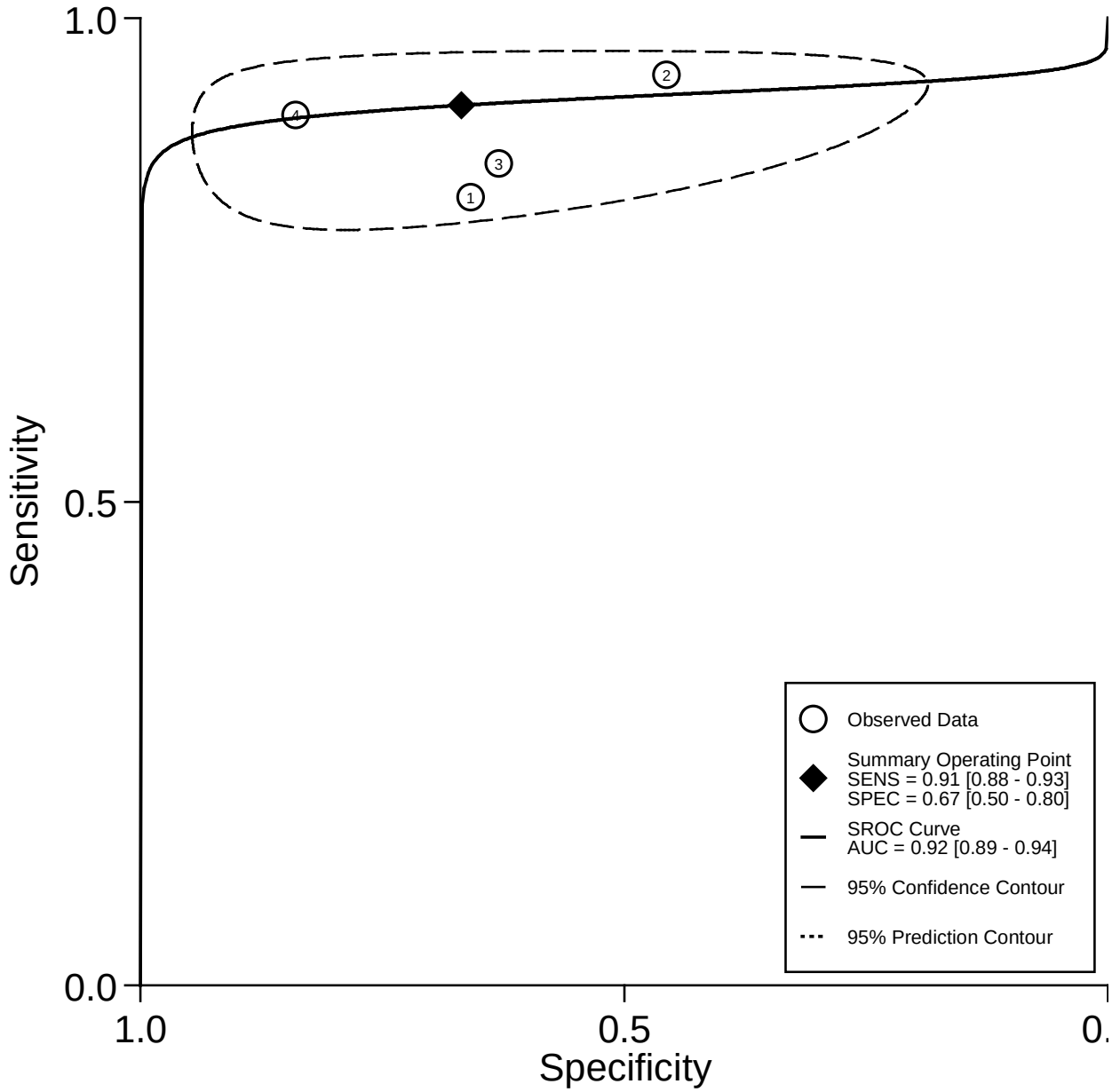


Figure H-23. Summary ROC-curve (ED NTProBNP, optimum cut-point), bivariate mixed effect model

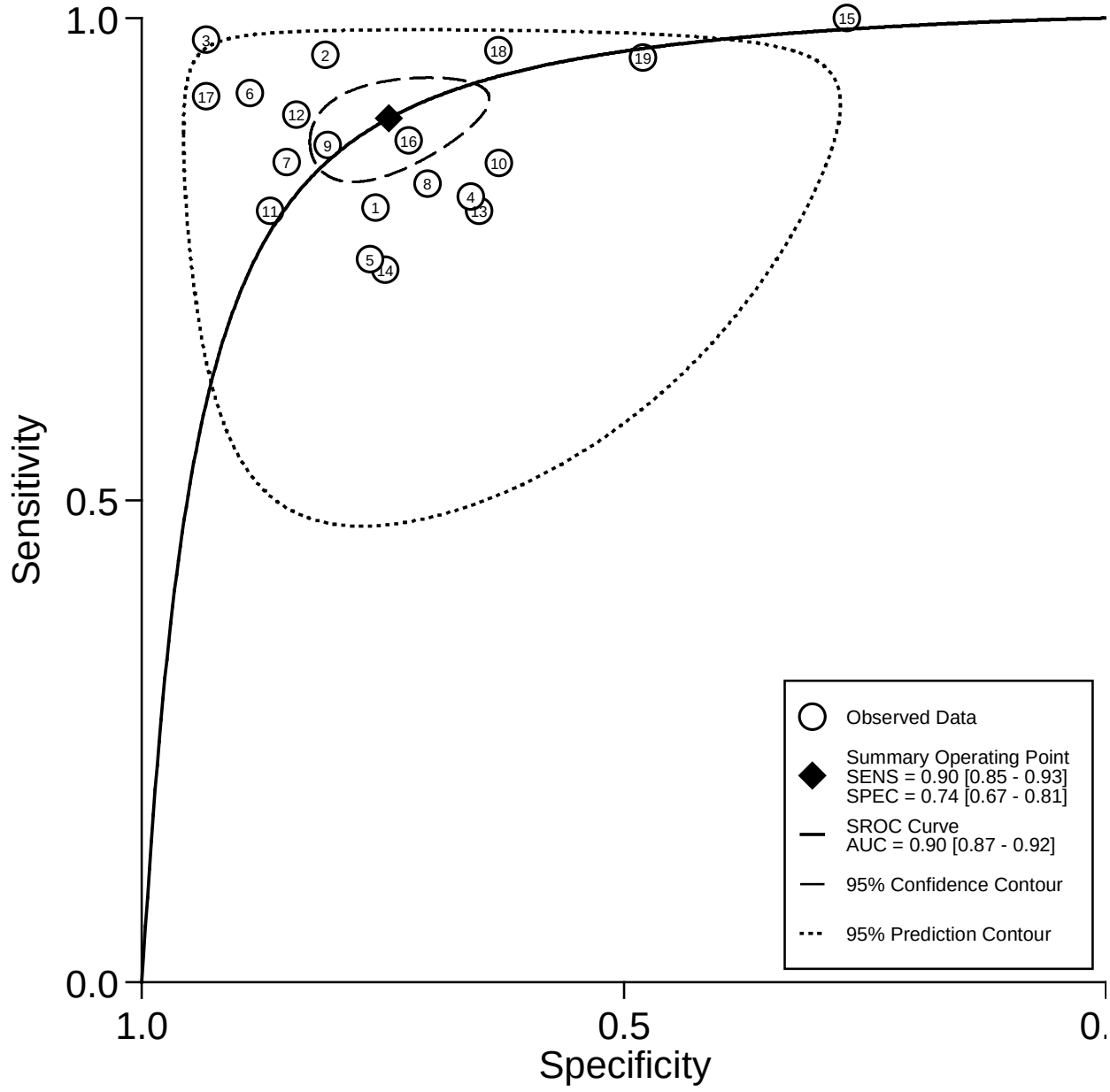


Figure H-24. Summary ROC-curve (ED NTProBNP, lowest cut-point), bivariate mixed effect model

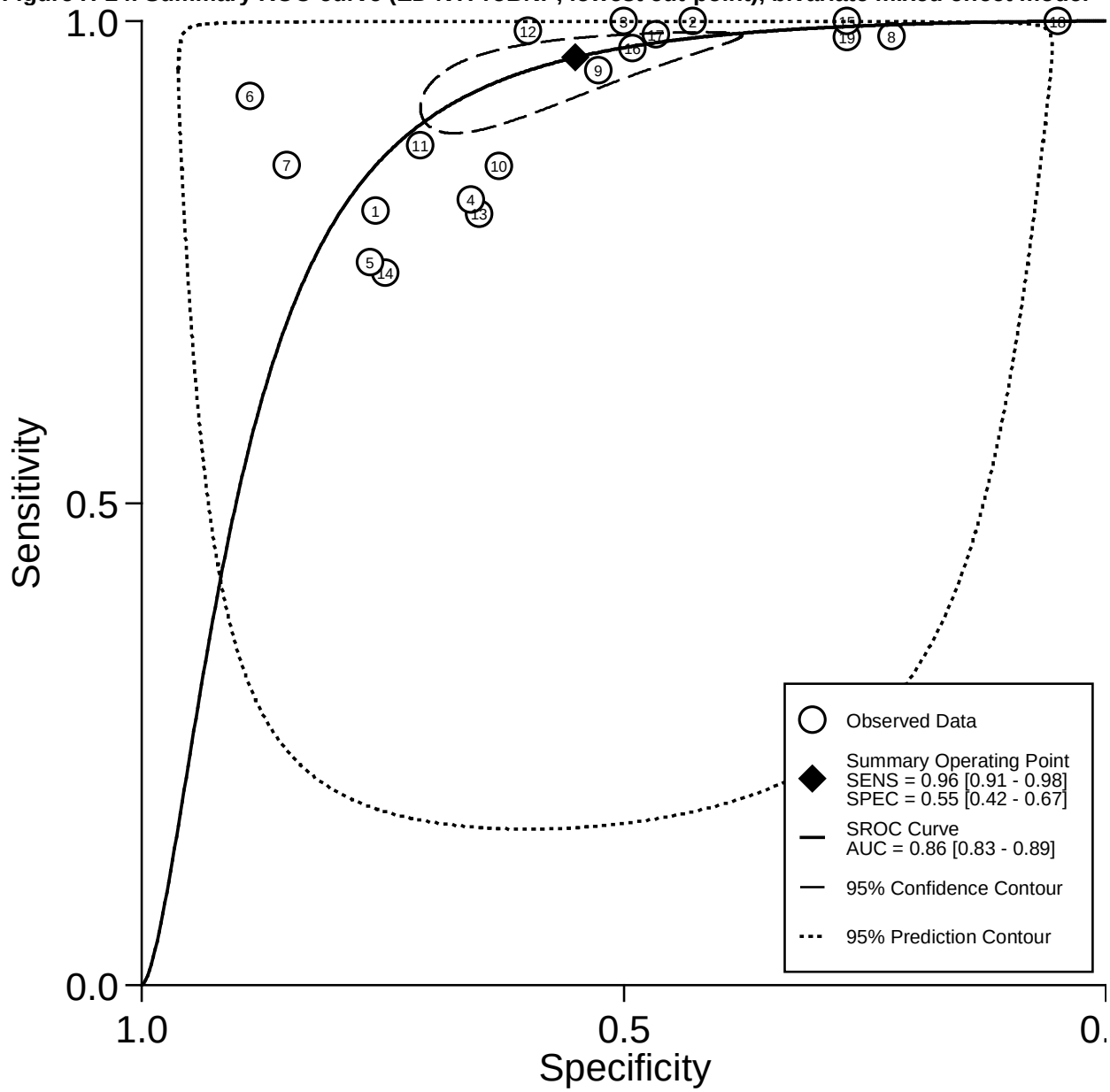


Table H-5. Risk of bias and applicability in all diagnostic studies using BNP in emergency department, results of QUADAS 2 quality assessment

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Alibay,[1] 2005	?	✔	✔	✔	✔	✔	✔
Arenja,[2] 2012	?	?	✔	?	✔	✔	✔
Arques,[3] 2007	✔	✔	✔	✔	✔	✔	✔
Barcarse,[4] 2004	✘	✘	✔	✔	✘	✔	✔
Boldanova,[5] 2010	✔	✘	✔	✔	✔	✔	✔
Chenevier-Gobeaux,[7] 2008	✘	✘	✔	?	✘	✔	✔
Chenevier-Gobeaux,[6] 2005	✘	✘	✔	✔	✔	✔	✔
Chenevier-Gobeaux,[8] 2010	✘	✘	✔	✘	✔	✔	✔
Choi,[9] 2007	?	✘	✔	✔	✘	✔	✔
Chung,[10] 2006	?	✘	✘	✔	✘	✘	✘
Collins,[11] 2006	✘	✘	✔	✘	✔	✔	✔
Coste,[12] 2006	✔	✘	✔	✔	✘	✘	✘
Daniels,[13] 2006	?	✘	✔	✔	✔	✔	✔
Dao,[14] 2001	✘	✘	✔	✔	✘	✔	✔
Defilippi,[15] 2007	✔	✘	✔	✔	✔	✔	✔
Dieplinger,[16] 2009	?	✘	✔	✔	✔	✔	✔
Gorissen,[17] 2007	✔	✔	✔	✘	✔	✔	✔
Gruson,[19] 2009	✔	?	?	✔	✘	✘	✘
Gruson,[18] 2008	?	✘	✔	?	✔	✔	✔
Gruson,[20] 2012	✔	✘	✔	?	✔	✔	✔
Havelka,[21] 2011	✘	✘	✘	✔	✔	✔	✔
Rogers,[44] 2009	✘	✘	✔	✘	✔	✔	✔
Knudsen,[22] 2004	✔	✘	✔	✔	✔	✔	✔
Knudsen,[24] 2005	?	✘	✔	✔	✔	✔	✔
Knudsen,[23] 2004	?	✔	✔	✘	✔	✔	✔
Lainchbury,[25] 2003	?	✘	✔	✔	?	✔	✔
Logeart,[26] 2002	✔	✘	✔	✔	✔	✔	✔

Table H-5. Risk of Bias and Applicability in all Diagnostic Studies using BNP in emergency department, results of QUADAS 2 quality assessment (continued)

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Lokuge,[27] 2010	?	✗	✓	✓	✓	✓	✓
Maisel,[30] 2004	?	✗	✓	✓	✓	✓	✓
Maisel,[31] 2010	✓	✗	✓	✓	✓	✓	✓
Maisel,[29] 2003	?	✗	✓	✓	?	✓	✓
Maisel,[28] 2002	?	✗	✓	✓	✓	✓	✓
McCullough,[32] 2003	?	✓	✓	✓	?	✓	✓
McCullough,[33] 2002	?	✗	✓	✗	✓	✓	✓
Morrison,[34] 2002	✗	✗	✓	✓	✗	✓	✓
Mueller,[35] 2005	?	✗	✓	✗	✗	✗	✗
Noveanu,[37] 2009	?	?	✓	✓	✓	?	✓
Pahle,[38] 2009	?	✗	✓	✗	✗	✗	✗
Parrinello,[39] 2008	?	✗	✓	✓	✓	✓	✓
Potocki,[40] 2010	✓	✗	✓	✓	✓	✓	✓
Ray,[42] 2004	?	✗	✓	✗	✗	✓	✓
Ray,[41] 2005	?	✗	✓	✓	✗	✗	✗
Ro,[43] 2011	✓	✓	✓	?	✓	✓	✓
Rogers,[45] 2009	?	✗	✓	✓	✗	✗	✗
Sanz,[46] 2006	?	?	✓	?	✗	✗	✗
Shah,[47] 2009	?	✓	✓	✓	✗	✗	✗
Shah,[48] 2009	✗	✓	✓	✓	✗	✗	✗
Steg,[49] 2005	?	?	✓	✓	✗	✗	✗
Villacorta,[50] 2002	✓	✗	✓	✓	✓	✓	✓
Wang,[51] 2010	?	✓	✓	✗	?	✓	✓
Wu,[52] 2004	?	✓	✓	✓	?	✓	✓

✓ = Low Risk ✗ = High Risk ? = unclear

Table H-6. Risk of bias and applicability in all diagnostic studies using NT-ProBNP in emergency department, results of QUADAS 2 quality assessment

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Alibay,[1] 2005	?	✔	✔	✔	✔	✔	✔
Anwaruddin,[53] 2006	✘	✔	✔	✔	✔	✔	✔
Bayes-Genis,[55] 2007	✘	✔	✘	✔	✔	✔	✔
Bayes-Genis,[54] 2004	✔	✘	✘	✔	✔	✔	✔
Behnes,[57] 2011	✔	✘	✔	✔	✔	✔	✔
Behnes,[56] 2009	✔	✘	✔	✔	✘	✘	✘
Berdague,[58] 2006	?	✘	✘	✔	✘	✔	✔
Chenevier-Gobeaux,[7] 2008	✘	✘	?	✔	✘	✔	✔
Chenevier-Gobeaux,[6] 2005	✘	✘	✔	✔	✔	✔	✔
Chenevier-Gobeaux,[8] 2010	✘	✘	✘	✔	✔	✔	✔
Defilippi,[15] 2007	✔	✘	✔	✔	✔	✔	✔
Gorissen,[17] 2007	✔	✔	✘	✔	✔	✔	✔
Green,[59] 2008	✘	✘	✔	✔	✔	✔	✔
Gruson,[18] 2008	?	✘	?	✔	✔	✔	✔
Gruson,[20] 2012	✔	✘	✔	?	✔	✔	✔
Januzzi,[61] 2006	?	✘	✘	✔	✔	✔	✔
Januzzi,[60] 2005	✘	✘	✔	✔	✔	✔	✔
Krauser,[62] 2006	✘	✔	✔	✔	✘	✘	✘
Lainchbury,[25] 2003	?	✘	✔	✔	?	✔	✔
Liteplo,[63] 2009	✘	?	✔	✔	✘	✘	✘
Martinez-Rumayor,[64] 2010	✘	✘	✔	✔	✔	✔	✔
Moe,[65] 2007	✘	✘	✘	✔	✔	✔	✔
Mueller,[35] 2005	?	✘	✘	✔	✘	✘	✘
Nazerian,[66] 2010	✘	✔	✔	✔	✘	✔	✔
O'Donoghue,[67] 2007	✘	✔	✔	✔	✔	✔	✔
Oh,[68] 2009	?	?	✔	✔	✔	✔	✔
Potocki,[40] 2010	✔	✘	✔	✔	✔	✔	✔

Table H-6. Risk of bias and applicability in all diagnostic studies using NT-ProBNP in emergency department, results of QUADAS 2 quality assessment (continued)

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Prosen,[69] 2011	✔	✔	✔	✔	✔	✔	✔
Ray,[41] 2005	?	✘	✔	✔	✘	✘	✘
Robaei,[70] 2011	✔	?	?	✔	✔	✔	✔
Sakhuja,[71] 2005	✘	✔	✔	✔	✔	✔	✔
Shaikh,[72] 2011	✔	?	?	?	✔	?	?
Sanz,[46] 2006	?	?	?	✔	✘	✘	✘
Shah,[47] 2009	?	✔	✔	✔	✘	✘	✘
Shah,[48] 2009	✘	✔	✔	✔	✘	✘	✘
Steinhart,[73] 2009	✘	?	✘	✔	✘	✘	✘
Tung,[74] 2006	✘	✘	✔	✔	✔	✔	✔
van Kimmenade,[75] 2006	✘	✘	✔	✔	✘	✘	✘
Zaninotto,[76] 2005	✔	✘	?	✔	✔	✔	✔

✔ = Low Risk ✘ = High Risk ? = unclear

Table H-7a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Sensitivity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,459	0.9 (0.88-0.92)	High	High

Table H-7a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing BNP in emergency department settings (continued)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay[1] 2005 Arques[3] 2007 Boldanova[5] 2010 Chenevier-Gobeaux[8] 2010 Chenevier-Gobeaux[7] 2008 Choi[9] 2007 Chung[10] 2006 Dao[14] 2001 Defilippi[15] 2007 Dieplinger[16] 2009 Gorissen[17] 2007 Gorissen[17] 2007 Knudsen[22] 2004 Lainchbury[25] 2003 Logeart[26] 2002 Lokuge[27] 2010 Maisel[28] 2002 Maisel[31] 2010 Morrison[34] 2002 Mueller[35] 2004 Parrinelo[39] 2008 Ray[42] 2006 Ray[41] 2005 Rogers[45] 2009 Sanz[46] 2006 Sanz[46] 2006 Steg[49] 2005 Villacorta[50] 2002 Wang[51] 2010	Specificity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,459	0.77 (0.72-0.83)	Moderate	Moderate

Table H-7b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Gruson,[19] 2009 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Sensitivity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	Consistent – range of estimates is small	n=11,556	0.94 (0.93-0.96)	High	High

Table H-7b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing BNP in emergency department settings (continued)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Arques,[3] 2007 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Chenevier-Gobeaux,[7] 2008 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Defilippi,[15] 2007 Dieplinger,[16] 2009 Gorissen,[17] 2007 Gorissen,[17] 2007 Gruson,[19] 2009 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ray,[41] 2005 Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Villacorta,[50] 2002 Wang,[51] 2010	Specificity	Cross-sectional (n=26), cohort (n=2), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=11,556	0.64 (0.57-0.72)	Moderate	Moderate

Table H-7c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoints for diagnostic studies utilizing BNP in emergency department settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ro,[43] Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Wang,[51] 2010	Sensitivity	Cross-sectional (n=21), RCT (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	Consistent – range of estimates is small	n=9,584	0.95 (0.93-0.96)	High	High

Table H-7c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoints for diagnostic studies utilizing BNP in emergency department settings (continued)

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Boldanova,[5] 2010 Chenevier-Gobeaux,[8] 2010 Choi,[9] 2007 Chung,[10] 2006 Dao,[14] 2001 Knudsen,[22] 2004 Lainchbury,[25] 2003 Logeart,[26] 2002 Lokuge,[27] 2010 Maisel,[28] 2002 Maisel,[31] 2010 Morrison,[34] 2002 Mueller,[35] 2004 Parrinelo,[39] 2008 Ray,[42] 2006 Ro,[43] Rogers,[45] 2009 Sanz,[46] 2006 Sanz,[46] 2006 Steg,[49] 2005 Wang,[51] 2010	Specificity	Cross-sectional (n=21), RCT (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – CI is small, but hetero-geneity is large	No evidence to suggest	n=9,584	0.64 (0.57-0.71)	Moderate	Moderate

Abbreviations: CI = confidence interval; RCT = randomized controlled trial

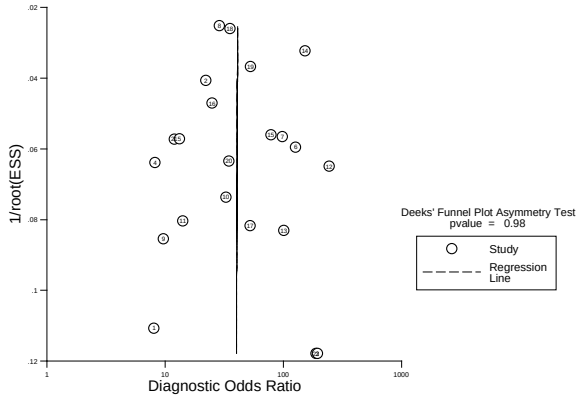
Table H-8. Summary test statistics of publication bias using log diagnostic odds ratios (logDOR), presented separately for different cut points.

Assay	Groups	n study	Deeks'	
			Coef.	P value
Emergency department				
BNP	Manufacturer cut point	22	-0.26	0.977
	Lowest cut point	31	-0.35	0.968
	Optimum cut point	29	8.94	0.266
NT-proBNP	Manufacturer cut point	4	-22.05	0.053
	Lowest cut point	19	-19.57	0.053
	Optimum cut point	19	-0.83	0.920

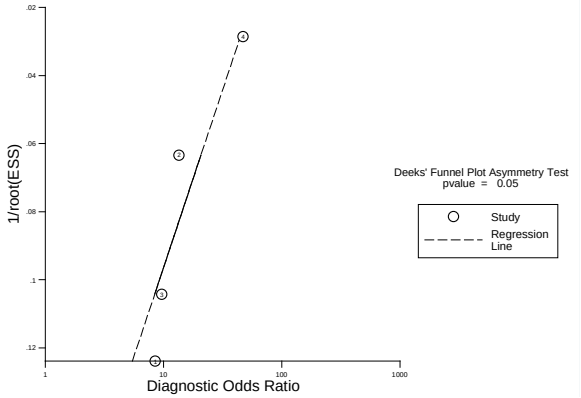
Background: The Deeks' method [77]assesses the publication bias by performing linear regression of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry in diagnostic meta-analyses and a non-zero slope coefficient is suggestive of significant small study bias (p-value < 0.10). Based on the information provided in the attached table, the publication bias was significant for NT-proBNP (ED- Manufacturers cut-point, p=0.053) and NT-proBNP (ED- lowest cut-point, p=0.053). But there were only 4 studies in NT-proBNP (ED- Manufacturers cut-point), so information on publication bias is unreliable.

Figure H-25. Emergency department publication bias: BNP and NT-proBNP

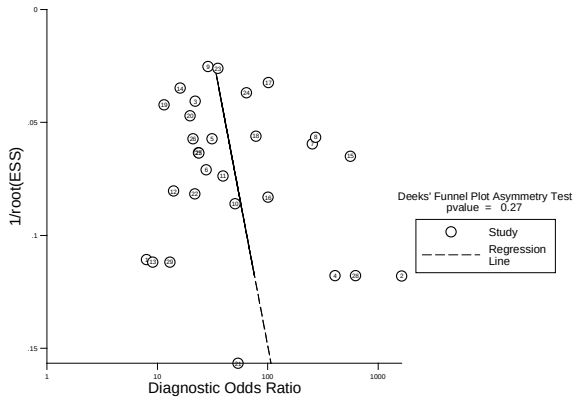
BNP

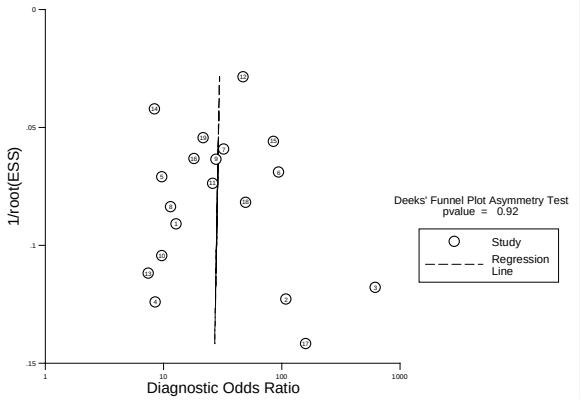


NT-ProBNP

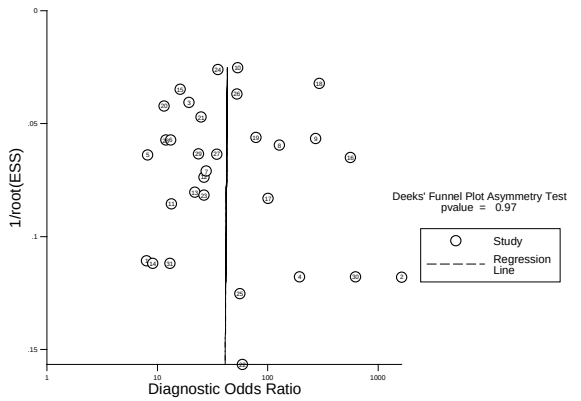


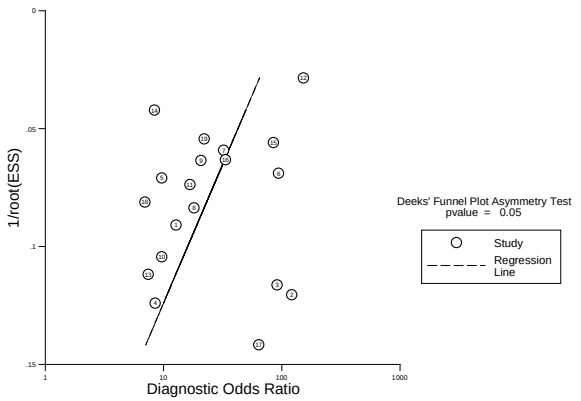
Manufacturer cut point





Optimum cut point





Lowest cut point

Table H-9a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Shaikh,[72] Zaninotto,[76] 2005	Sensitivity	Cross-sectional (n=14), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=4,955	0.9 (0.87-0.94)	High	High

Table H-9a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings (continued)

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005	Specificity	Cross-sectional (n=13), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=4,855	0.95 (0.44-0.86)	Moderate	Moderate

Table H-9b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005	Sensitivity	Cross-sectional (n=13), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=4,855	0.92 (0.90-0.95)	High	High

Table H-9b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoints for diagnostic studies utilizing NT-proBNP in emergency department settings (continued)

No. of studies	Outcome	Study design	GRADE Risk of Bias	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Alibay,[1] 2005 Bayes-Genis,[54] 2004 Behnes,[56] 2009 Berdague,[58] 2006 Chenevier-Gobeaux,[8] 2010 Chenvier-Gobeaux,[7] 2008 Gorrisen,[17] 2007 Januzzi,[61] 2006 Lainchbury,[25] 2003 Liteplo,[63] 2009 Mueller,[35] 2005 Nazerian,[66] 2010 Potocki,[40] 2010 Prosen,[69] 2011 Ray,[41] 2005 Robaei,[70] 2011 Sanz,[46] 2006 Zaninotto,[76] 2005 Shaikh,[72] 2011	Specificity	Cross-sectional (n=14), Cohort (n=3), Case-control (n=1), Unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=4,955	0.56 (0.43-0.96)	Moderate	Moderate

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Appendix I. Key Question 2 Evidence Set

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Arques,[1] 2005 (country unreported)	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=36), CAD (n=23), COPD (n=36), Diabetes (n=18), HF (n=12), Reference standards: 2 Cardiologists, 1 Chest physician, Framingham criteria	Diagnosis of either decompensated HF or respiratory disease as the primary cause of SOB	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Acute/recently aggravated dyspnea n=70 mean age= HF: 77y (12); noHF: 74y (12) %males=50 HF Prev=45.7%	>100	97	63	2.63	0.05	NR
					>146	91	76	3.82	0.12	0.875
					>402	59	90	5.66	0.45	NR
Aspromonte,[2] 2006 Italy	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=91), AF(n=36), COPD (n=28), Diabetes (n=17),IHD (n=60), Renal disease (n=13) Reference standards: Cardiologists, Framingham	Diagnostic accuracy and cost analysis for HF	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected CHF referred by GPs (all) n=357 mean age= (HF) 76y (10); (no HF) 71y (11) %males=50 HF Prev=67%	30	99	71	3.41	0.01	NR
					50	93	85	6.20	0.08	NR
					70	87	89	7.91	0.15	NR
					80	84	90	8.40	0.18	NR
					100	80	91	8.89	0.22	NR
					120	76	92	9.50	0.26	NR
					200	86	60	2.15	0.23	NR
					300	86	69	2.77	0.20	NR
					400	86	77	3.74	0.18	0.85
					470	86	81	4.53	0.17	NR
					500	86	81	4.53	0.17	NR
Barrios,[3] 2011 Spain	Cross-sectional (PANAMA) Ethnicity: NR Comorbidities: Dyslipidemia (n=39), HBP (n=54), Diabetes (n=21), IHD(n=15) Reference Standard: Framingham	Clinical applicability of BNP in suspected HF primary care patients	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Clinical diagnosis of HF≥18 n=72 mean age= 75.1y (8.7), %males=25.4 HF Prev=61%	>100	25	81	1.30	0.93	0.72

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Christenson,[4] 2010 United States	Cross-sectional (INDEPENDENT STUDY) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF(n=147), Diabetes (n=245), Prior HF (n=236) Reference standards: 1 Cardiologist	Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Dyspnea, Suspected HF n=675 mean age= NR %males=48 HF Prev=35%	100	NR	NR	NA	NA	0.73
				Dyspnea (decompensated HF, Normal Weight, BMI <25 kg/m2) n=212 mean age= 69.8y (15.5) %males=52.4 HF Prev=36.3%	100	89	38	1.44	0.29	0.78
				Dyspnea (decompensated HF, Over Weight, BMI 25-30 kg/m2) n=193 mean age= 66.6y (13.8) %males=57.5 HF Prev=37.3%	100	85	38	1.37	0.39	0.62
				Dyspnea (decompensated HF, Obese, BMI >30 kg/m2) n=280 mean age= 62.5y (14.6) %males=37.8 HF Prev=32.2%	100	81	49	1.59	0.39	0.72

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Fuat,[5] 2006 United Kingdom	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=102), AF, (n=56), COPD (n=69), Diabetes (n=27), Historical MI (n=39),IHD (n=87) Reference standards: GPs,15% of ECHO verified by cardiologists	To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT proBNP) in diagnosing HF due to left ventricular systolic dysfunction	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs n=297, mean age= (patients with LVSD) 73.5y; (patients with no LVSD) 74y %males=37 HF Prevalence=38%	40	92	38	1.48	0.21	0.79
Jeyaseelan,[6] 2007 United Kingdom	Cross-sectional (INDEPENDENT STUDY); Ethnicity: NR Comorbidities: HBP (n= 218), Previous Revascularization (n=35), Prior AMI/Angina (n=176), AF(n=42), Myocardial Infarction (n=89), Valvular Disease (n=209), LVSD (n=37), Clinical HF (n=57), LV Hypertrophy (n=44) Reference Standards:1 Cardiologist, 1 Physician, 1 Cardiologist fellow	Diagnostic adequacy of ECG and BNP as screening for LVSD and HF	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GP (all) n=458 mean age= 72.6y %males=40.2 HF Prev=8%	>100	NR	NR	NA	NA	NR
				LVSD n=458 mean age= 72.6y %males=40.2 HF Prev=8.1%	>100	86	74	3.31	0.19	NR
				Clinical HF (LVSD + other) n=458 mean age= 72.6y %males=40.2 HF Prev=13%	>100	82	76	3.42	0.24	NR
				Left ventricular hypertrophy n=458 mean age= 72.6y %males=40.2 HF Prev=10%	>100	59	73	2.19	0.56	NR

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Jeyaseelan,[6] 2007 (cont'd)				Valvular disease n=458 mean age= 72.6y %males=40.2 HF Prev=46%	>100	48	84	3.00	0.62	NR
Kelder,[7] 2011 Netherlands	Cross-sectional (UHFO-IA) Ethnicity: NR Comorbidities: HBP (n=88), AF(n=8), COPD (n=47), Diabetes (n=29), Stroke Or TIA (n=15), MI/PCI/CABG (n=9) Reference Standard: 1 Cardiologist, 1 Pulmonologist, I GP	Data on the comparative performance of 3 popular automated assays in patients suspected of new slow onset HF	BNP (Abbott AxSYM® B-Type Natriuretic Peptide Microparticle Enzyme Immunoassay (MEIA), ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Suspected HF referred by GPs n=172 mean age=70.2y (11.3) %males=34.3 HF Prev=29.7%	NR	NR	NR	NA	NA	NR
				Intermediate risk of HF n=111 mean age=74.4y (8.3) %males=36 HF Prev=34.2%	NR	NR	NR	NA	NA	0.85
Macabasco-O'Connell,[8] 2010 United States	Cross-sectional (INDEPENDENT STUDY) Ethnicity: Caucasian (n=9), African-American (n=4), Hispanic (n=34), Asian= (n=4), Other (n=2) Comorbidities: Dyslipidemia (n=12), HBP (n=39), Diabetes (n=27), Obesity (n=48), Metabolic syndrome (n=25); Reference Standard: ECHO	to describe BNP levels in asymptomatic low-income, uninsured individuals with multiple CRFs and determine the correlation between BNP levels and echocardiography for identifying ALVD	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Low-Income, uninsured Patients. age ≥30 years and a history of three or more CRFs with no prior history of HF or LVSD n=53 mean age= 55y (10) %males=36 HF Prev=57%	50	88	67	2.67	0.18	0.82
Mak,[9] 2008 United Kingdom	Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=174), AF(n=71), COPD (n=44), Diabetes (n=41),IHD (n=55) Reference standards: 1 Cardiologist, Framingham	To determine the diagnostic value of BNP in HF referrals by GPs	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs n=327 mean age= 75y(10) %males=49 HF Prev=39%	100	84	23	1.09	0.70	NR

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Murtagh,[10] 2012 Finland	Cross-Sectional Design (STOP-HF); Ethnicity: NR; Comorbidities: dyslibide (n=563), hypertension (n=539), CAD (n=159), vascular disease/ claudication/perpheral arterial anloplastry (n=21), Diabetes (n=121); Reference Standard: NR	Using the STOP-HF population (ClinicalTrials.gov identifier: NCT00921960), we assessed the significance of ALVDD in explaining the false-positive burden when using BNP to screen for ALVSD. Secondly, we determined the effectiveness of BNP as a screen in defining PCVD. Both assessments were made with or without the addition of ECG to the screening strategy, as it is well described that this investigation can be an effective rule out for ALVSD.	BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)	patients over 40 with at least one risk factor for venticular dysfuncton (n= 814, age=67±10y, %males= 48); HF prevalance= 4.05%	>20	88	46	1.63	0.26	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>50	70	77	3.04	0.39	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>100	45	90	4.50	0.61	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>50	70	77	3.04	0.39	NR
			BNP (TRIAGE -B-Type Natriuretic Peptide (BNP) Test)		>100	45	90	4.50	0.61	NR

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea	Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259),IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Dyspnea or chest discomfort (0verall) n=1032 mean age= 62y(13) %males=53.8 HF Prev=NR%	NR	NR	NR	NA	NA	NR
				Men, LVSD n=555 mean age=NR %males=100 HF Prev=9.5%	111	81	79	3.84	0.24	0.892
				Men, advanced DD n=555, mean age= NR %males=100 HF Prev=7.2%	99	80	80	4.08	0.25	0.89
				Women, LVSD n=477, mean age= NR, %males=100); HF Prev=9.8%	209	85	85	5.67	0.18	0.929
				Women, advanced DD n=477 mean age=NR %males=100 HF Prev=6.9%	166	85	85	5.51	0.18	0.907
				Age ≥ 65, LVSD n=NR mean age=NR %males= NR HF Prev=NR%	250	84	84	5.15	0.19	0.903
				Age ≥ 65, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	236	84	84	5.28	0.19	0.9

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	(repeated data) Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Age < 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	82	84	84	5.32	0.19	0.916
				Age < 65, advanced DD n=NR mean age= NR, %males= NR HF Prev=NR%	70	83	83	4.99	0.20	0.912
				BMI ≥ 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	151	85	85	5.67	0.18	0.933
				BMI ≥ 25, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	82	80	80	4.02	0.25	0.841
				BMI < 25, LVSD n=NR, mean age= NR, %males= NR); HF Prev=NR%	154	81	81	4.35	0.23	0.897
				BMI<25, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	140	83	83	4.91	0.20	0.916
				Hb ≥ 12, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	110	82	82	4.49	0.22	0.909

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-sectional (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), IHD (n=664), Valvular Disease (n=22), Hypothyroidism (n=155), Cardiomyopathy (n=90) Reference standards: 1 Cardiologist	(repeated data) Detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) BNP (ADIVA - Centaur® B -Type Natriuretic Peptide Assay)	Hb ≥ 12, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	80	81	81	4.24	0.24	0.901
				Hb < 12, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	345	80	81	4.15	0.25	0.882
				Hb < 12, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	338	81	79	3.87	0.24	0.872
				eGFR ≥ 60, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	89	82	82	4.62	0.22	0.915
				eGFR ≥ 60, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	70	83	82	4.50	0.20	0.894
				eGFR < 60, LVSD n=NR mean age= NR, %males= NR HF Prev=NR%	264	78	78	3.55	0.28	0.866

Table I-1. Summary of diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year Country	Study Design (companion study); Ethnicity; Comorbidities; Reference Standard(s)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity %	Specificity %	LR+	LR-	AUC
				eGFR < 60, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	247	78	78	3.60	0.28	0.876
Zaphiriou,[12] 2005 United Kingdom	Cross-sectional (INDEPENDENT STUDY); Ethnicity: NR Comorbidities: Dyslipidemia (n=67), HBP (n=168), Stroke (n=35), COPD (n=58), Diabetes (n=58), MI(n=42), PVD (n=20), Angina (n=80), CABG(n=18) Percutaneous Coronary Intervention (n=7) Reference standards: 1 Cardiologist	Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios for BNP, NTproBNP and the ECG for the diagnosis of HF. Area under the receiver operating characteristics (ROC) curves for the two natriuretic peptides	BNP (TRIAGE -B-Type Natriuretic Peptide Test)	Suspected HF referred by GPs (all) n=306, mean age= 74y (52-87)* %males=42 HF Prev=34%	100	79	72	2.82	0.29	0.84
					65	87	57	2.02	0.23	NR
					30	95	35	1.46	0.14	NR

Abbreviations: AF = Atrial Fibrillation; AMI = Acute myocardial infarction; AUC = Area Under the Curve; AVLD = Asymptomatic Left Ventricular Dysfunction; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CAD = Coronary Artery Disease; CABG = Coronary Artery Bypass Graft; CHF = Congestive Heart Failure; COPD = Chronic obstructive pulmonary disease; CRF = Chronic renal failure; DD = Diastolic dysfunction; ECHO = Echocardiogram; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; GP = General practitioner; Hb = Hemoglobin; HF = Heart Failure; IHD = Ischemic Heart Disease; kg/m2 = Kilograms per metre squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LV = Left ventricle; LVSD = Left ventricular systolic dysfunction ; LVDD = Left ventricular diastolic dysfunction ; MI = Myocardial Infarction; NA = Not applicable; NPV = Negative predictive value; NR = Not reported ; NT-proBNP = N-Terminal proBNP; PANAMA = Patients with suspected heart failure in primary care; PCI = Percutaneous coronary intervention; pg/mL = Picograms per millilitre; PPV = Positive predictive value ; ROC = Receiver operating characteristic ; SD = standard deviation; SOB = shortness of breath;TIA = Transient ischemic attack; UHFO-IA = Utrecht Heart Failure Organisation–Initial Assessment; USA = United States of America; y = years

Table I-2. Detailed diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings

Author Year Companion/ Sub-analysis	Study Design	Population	n, Mean Age (SD), %Males	Prevalence of HF	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Arques[1] 2005	Cross-sectional	Acute/recently aggravated dyspnea	70, (HF) 77(12)y; (noHF) 74 (12)y, 50	46	2 cardiologists, 1 chest physician, Framingham criteria	BNP	>100	97	63	2.63	0.05	NR
						BNP	>146	91	76	3.82	0.12	0.87
						BNP	>402	59	90	5.66	0.45	NR
Aspromonte,[2] 2006	Cross-sectional	Suspected CHF referred by GPs (all)	357, (HF) 76(10)y; (no HF) 71(11), 50	67	Cardiologists, Framingham	BNP	30	99	71	3.41	0.01	NR
						BNP	50	93	85	6.20	0.08	NR
						BNP	70	87	89	7.91	0.15	NR
						BNP	80	84	90	8.40	0.18	NR
						BNP	100	80	91	8.89	0.22	NR
						BNP	120	76	92	9.50	0.26	NR
						BNP	200	86	60	2.15	0.23	NR
						BNP	300	86	69	2.77	0.20	NR
						BNP	400	86	77	3.74	0.18	0.85
						BNP	470	86	81	4.53	0.17	NR
						BNP	500	86	81	4.53	0.17	NR
Barrios,[3] 2011 PANAMA	Cross-sectional	Clinical diagnosis of HF,≥18y (all)	72, 75.1(8.7)y, 25.4	61	Framingham	BNP	>100	25	81	1.30	0.93	0.72
Christenson,[4] 2010	Cross-sectional	Dyspnea, suspected HF	675, NR, 48	35	1 cardiologist	BNP	100	NR	NR	NA	NA	0.73
		Dyspnea (decompensated HF, normal weight, BMI <25 kg/m^2)	212, 69.8(15.5)y, 52.4	36	1 cardiologist	BNP	100	89	38	1.44	0.29	0.78
		Dyspnea (decompensated HF, overweight, BMI 25-30 kg/m^2)	193, 66.6(13.8)y, 57.5	37	1 cardiologist	BNP	100	85	38	1.37	0.39	0.62
		Dyspnea (decompensated HF, obese, BMI >30 kg/m^2)	280, 62.5(14.6)y, 37.8	32	1 cardiologist	BNP	100	81	49	1.59	0.39	0.72

Table I-2. Detailed diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year companion/ Sub-analysis	Study Design	Population	n, Mean Age (SD), %Males	Prevalence of HF	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Fuat,[5] 2006	Cross-sectional	Suspected HF referred by GPs	297, (patients with LVSD) 73.5y; (patients with no LVSD) 74y, 37	38	GPs ,15% of ECHO verified by cardiologists	BNP	40	92	38	1.48	0.21	0.79
Jeyaseelan,[6] 2007	Cross-sectional	Suspected HF referred by GP (all)	458, 72.6y, 40.2	8	1 cardiologist, 1 Physician, 1 cardiologist fellow	BNP	>100	NR	NR	NA	NA	NR
		LVSD	458, 72.6y, 40.2	8	1 cardiologist, 1 Physician, 1 cardiologist fellow	BNP	>100	86	74	3.31	0.19	NR
		Clinical HF (LVSD + other)	458, 72.6y, 40.2	13	1 cardiologist, 1 Physician, 1 cardiologist fellow	BNP	>100	82	76	3.42	0.24	NR
		Left ventricular hypertrophy	458, 72.6y, 40.2	10	1 cardiologist, 1 Physician, 1 cardiologist fellow	BNP	>100	59	73	2.19	0.56	NR
		Valvular disease	458, 72.6y, 40.2	46	1 cardiologist, 1 Physician, 1 cardiologist fellow	BNP	>100	48	84	3.00	0.62	NR
Kelder,[7] 2011 UHFO-IA	Cross-sectional	Suspected HF referred by GPs	172, 70.2(11.3)y, 34.3	30	1 cardiologist, 1 pulmonologist, 1 GP	BNP	NR	NR	NR	NA	NA	NR
		Intermediate risk of HF	111, 74.4 (8.3)y, 36	34	1 cardiologist, 1 pulmonologist, 1 GP	BNP	NR	NR	NR	NA	NA	0.85

Table I-2. Detailed diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year companion/ Sub-analysis	Study Design	Population	n, Mean Age (SD), %Males	Prevalence of HF	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Macabasco-O'Connell,[8] 2010	Cross-sectional	Low-income, uninsured Patients ≥30y and a history of three or more CRFs with no prior history of HF or LVSD	53, 55(10)y, 36	57	ECHO	BNP	50	88	67	2.67	0.18	0.82
Mak,[9] 2008	Cohort	Suspected HF referred by GPs	327, 75(10)y, 49	39	1 cardiologist, Framingham	BNP	100	84	23	1.09	0.70	NR
Murtagh,[10] 2012 STOP-HF"	Cross-sectional	Patients over 40 with at least one risk factor for ventricular dysfunction	814 67±10y 48	4.05	NR	BNP	>20	88	46	1.63	0.26	NR
							>50	70	77	3.04	0.39	NR
							>100	45	90	4.50	0.61	NR
							>50	70	77	3.04	0.39	NR
							>100	45	90	4.50	0.61	NR
Park,[11] 2010	Cross-sectional	Dyspnea or chest discomfort (Overall)	1032, 62(13)y, 53.8	NR	1 cardiologist	BNP	NR	NR	NR	NA	NA	NR
		Men, LVSD	555, NR, 100	10	1 cardiologist	BNP	111	81	79	3.84	0.24	0.892
		Men, advanced DD	555, NR, 100	7	1 cardiologist	BNP	99	80	80	4.08	0.25	0.89
		Women, LVSD	477, NR, 100	10	1 cardiologist	BNP	209	85	85	5.67	0.18	0.929
		Women, advanced DD	477, NR, 100	7	1 cardiologist	BNP	166	85	85	5.51	0.18	0.907
		Age ≥ 65y, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	250	84	84	5.15	0.19	0.903
		Age ≥ 65y, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	236	84	84	5.28	0.19	0.9
		Age <65y, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	82	84	84	5.32	0.19	0.916
		Age <65y, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	70	83	83	4.99	0.20	0.912
		BMI ≥ 25 kg/m^2, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	151	85	85	5.67	0.18	0.933
		BMI ≥ 25 kg/m^2, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	82	80	80	4.02	0.25	0.841

Table I-2. Detailed diagnostic properties of studies evaluating BNP in patients with symptoms suggestive of HF at primary care settings (continued)

Author Year companion/ Sub-analysis	Study Design	Population	n, Mean Age (SD), %Males	Prevalence of HF	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park[11] 2010 (cont'd)	Cross-sectional	BMI <25 kg/m^2, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	154	81	81	4.35	0.23	0.897
		BMI<25 kg/m^2, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	140	83	83	4.91	0.20	0.916
		Hb ≥ 12, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	110	82	82	4.49	0.22	0.909
		Hb ≥ 12, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	80	81	81	4.24	0.24	0.901
		Hb <12, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	345	80	81	4.15	0.25	0.882
		Hb <12, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	338	81	79	3.87	0.24	0.872
		eGFR ≥ 60, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	89	82	82	4.62	0.22	0.915
		eGFR ≥ 60, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	70	83	82	4.50	0.20	0.894
		eGFR <60, LVSD	NR, NR, NR	NR	1 cardiologist	BNP	264	78	78	3.55	0.28	0.866
		eGFR <60, advanced DD	NR, NR, NR	NR	1 cardiologist	BNP	247	78	78	3.60	0.28	0.876
Zaphiriou,[12] 2005	Cross-sectional	Suspected HF referred by GPs (all)	306, 74 (52-87)*y, 42	34	1 cardiologist	BNP	100	79	72	2.82	0.29	0.84
						BNP	65	87	57	2.02	0.23	NR
						BNP	30	95	35	1.46	0.14	NR

Abbreviations: AUC = area under the curve; BMI = body mass index; BNP=B-type natriuretic peptide; CHF = congestive heart failure; CRF = chronic renal failure; DD = diastolic dysfunction; ECHO = echocardiogram; eGFR = estimated glomerular filtration rate; GP = general practitioner; Hb = hemoglobin; HF = heart failure; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVSD = left ventricular systolic dysfunction ; NA = not applicable ; NR = not reported; pg/mL = picograms per milliliter; SD = standard deviation; UHFO-IA = Utrecht Heart Failure Organisation – Initial Assessment

Figure I-1. Summary forest plot of sensitivity and specificity (PC BNP, manufacturer cut-point), bivariate mixed effect model

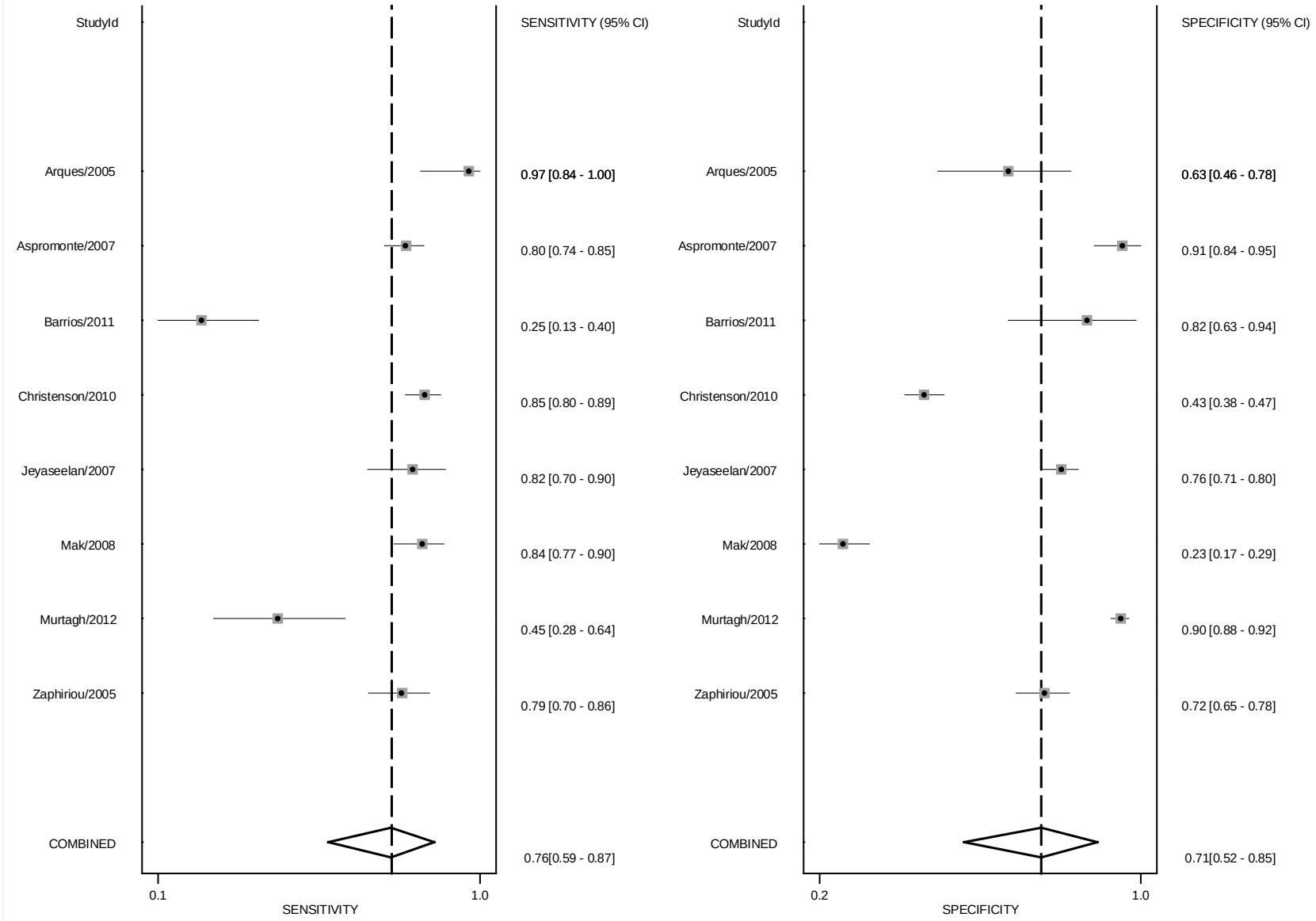


Figure I-2. Summary forest plot of sensitivity and specificity (PC BNP, optimum cut-point), bivariate mixed effect model

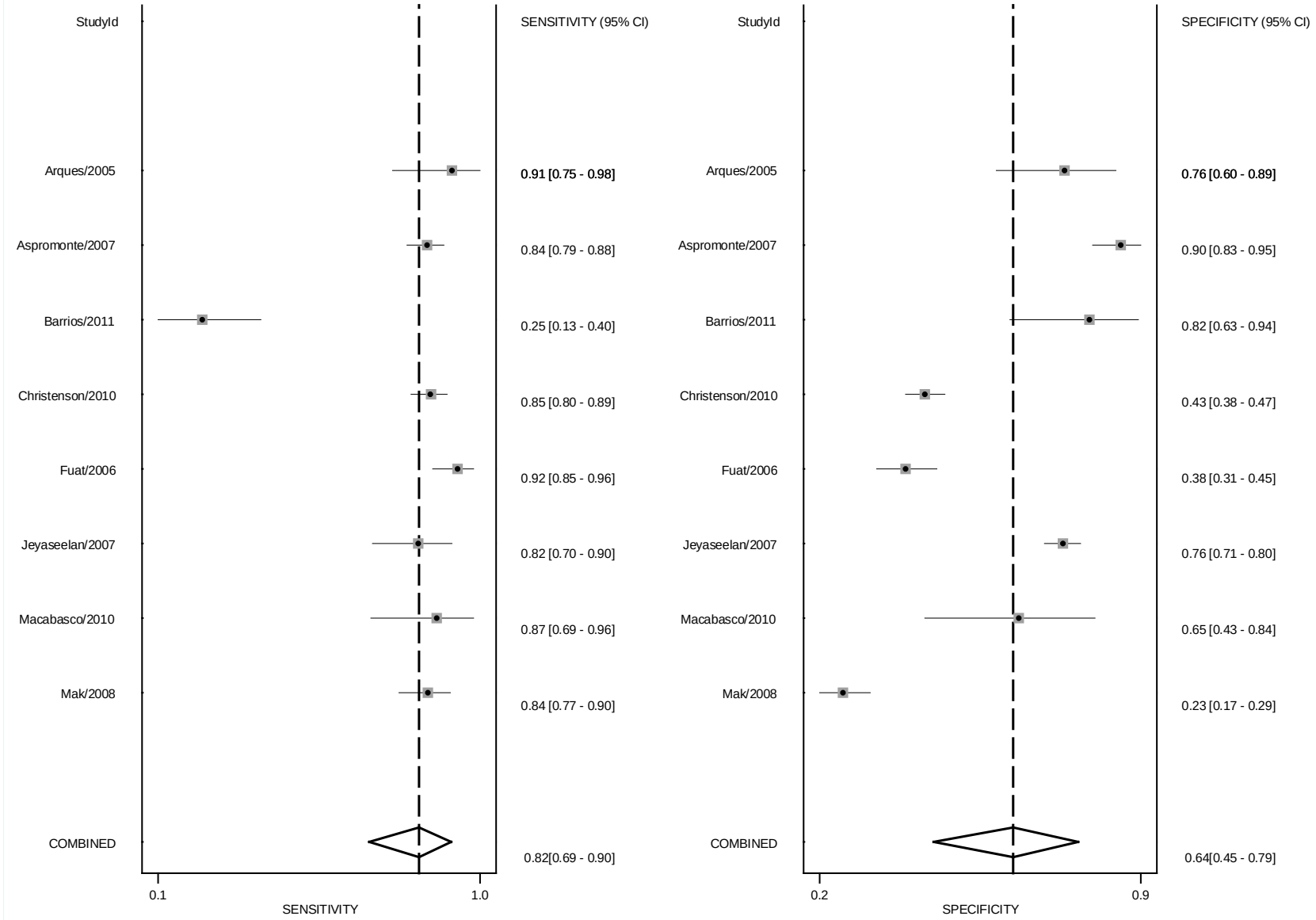


Figure I-3. Summary forest plot of sensitivity and specificity (PC BNP, lowest cut-point), bivariate mixed effect model

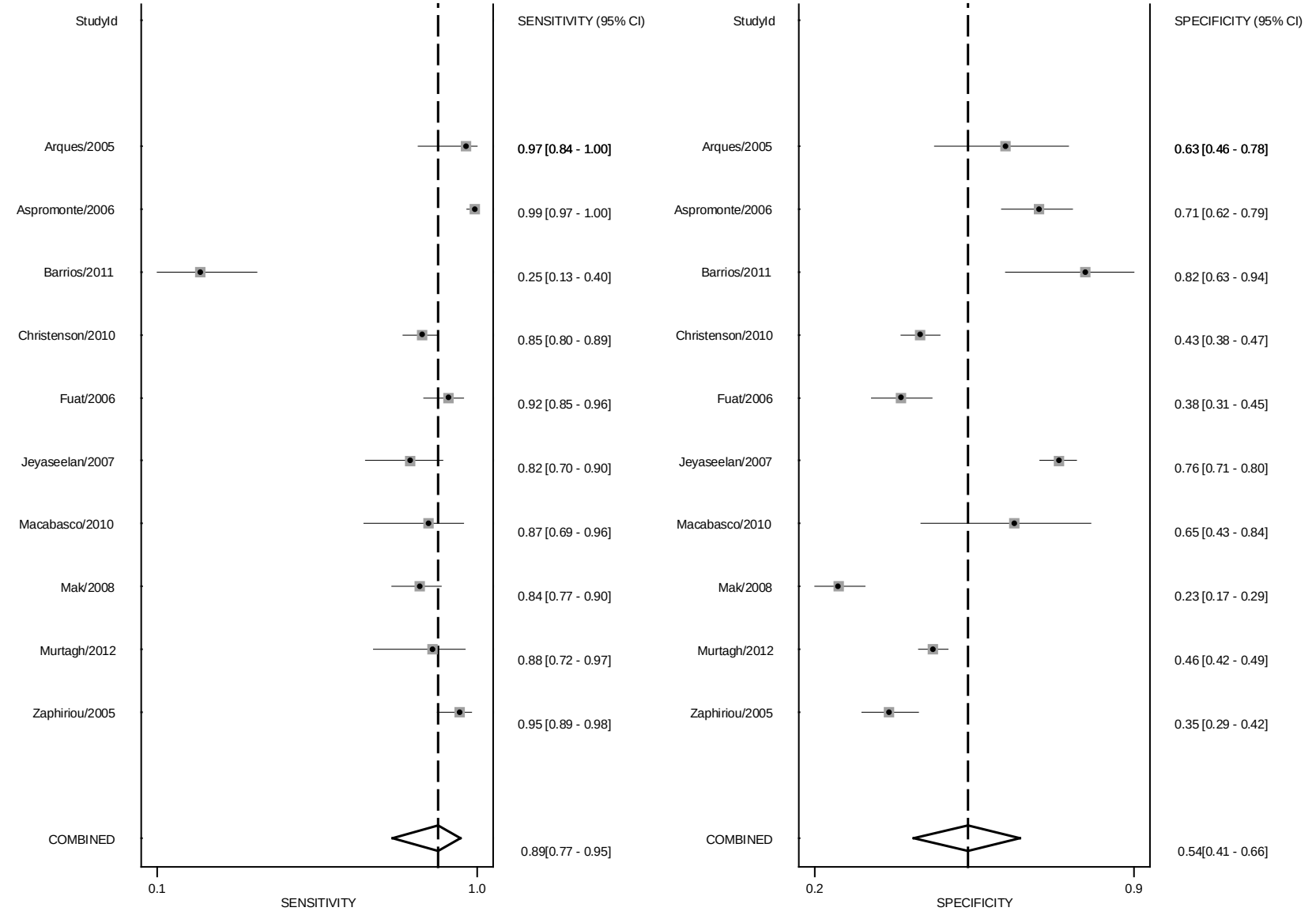


Figure I-4. Summary forest plot of LR+ and LR- (PC BNP, manufacturer cut-point), bivariate mixed effect model

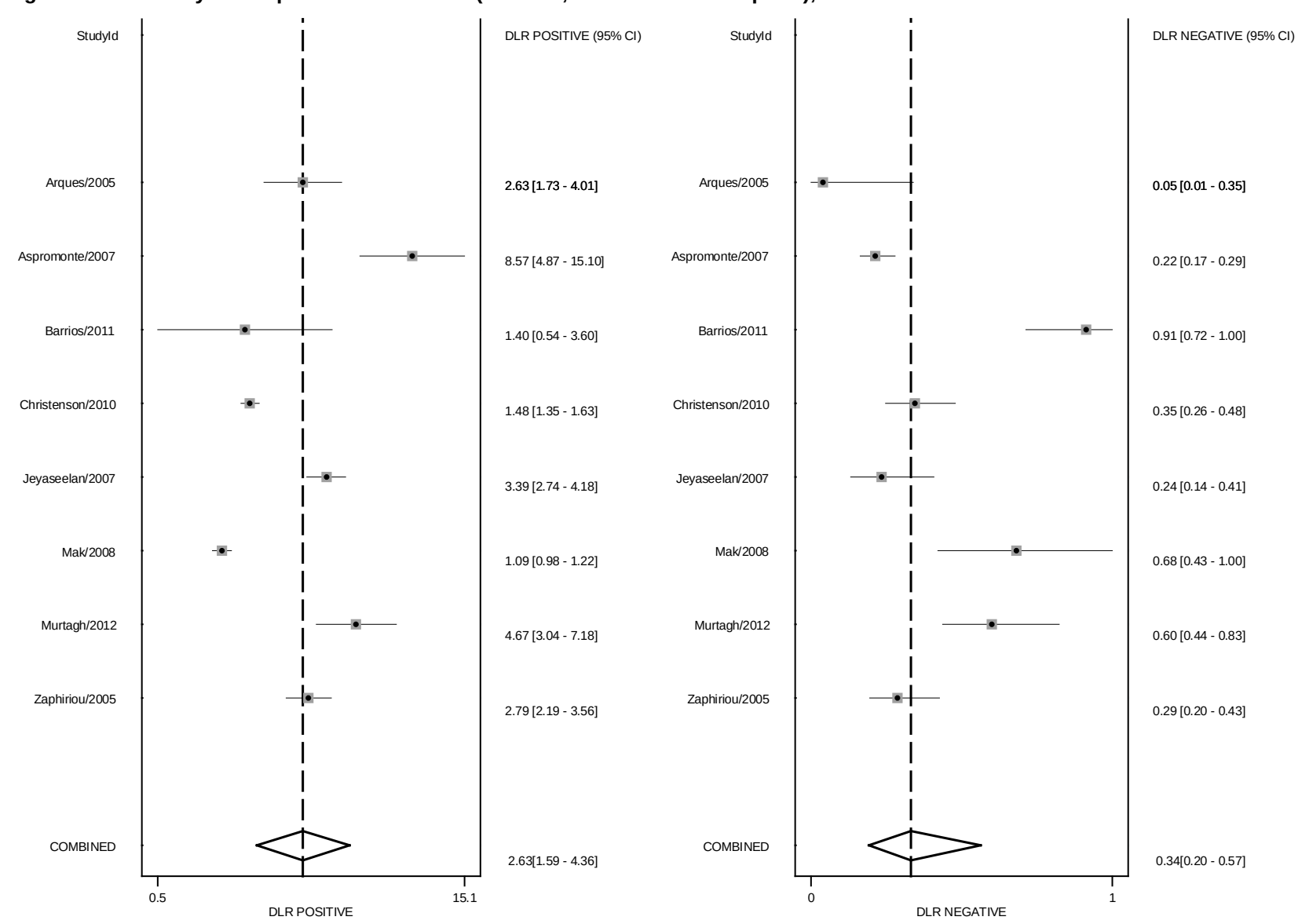


Figure I-5. Summary forest plot of LR+ and LR- (PC BNP, optimum cut-point), bivariate mixed effect model

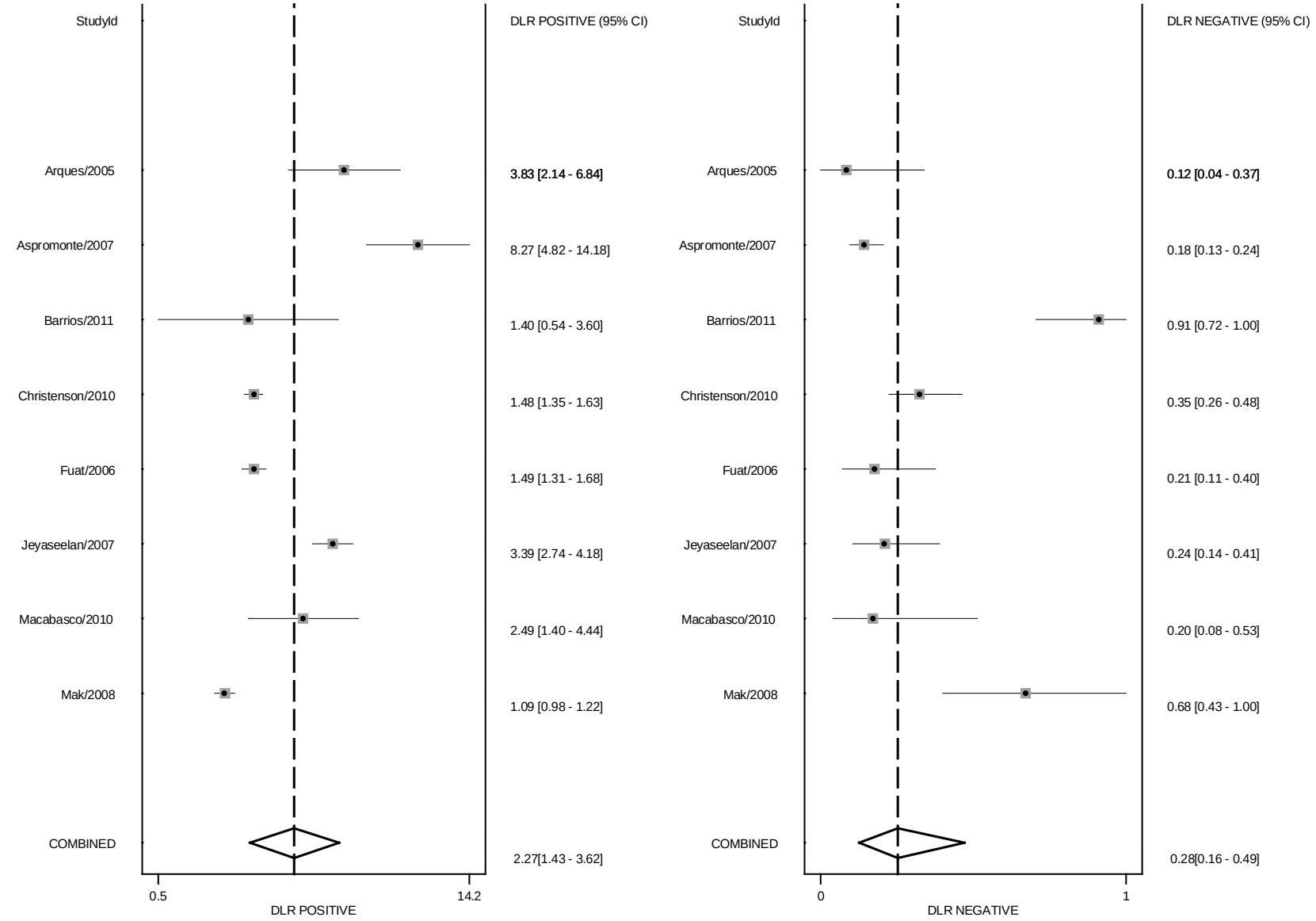


Figure I-6. Summary forest plot of LR+ and LR- (PC BNP, lowest cut-point), bivariate mixed effect model

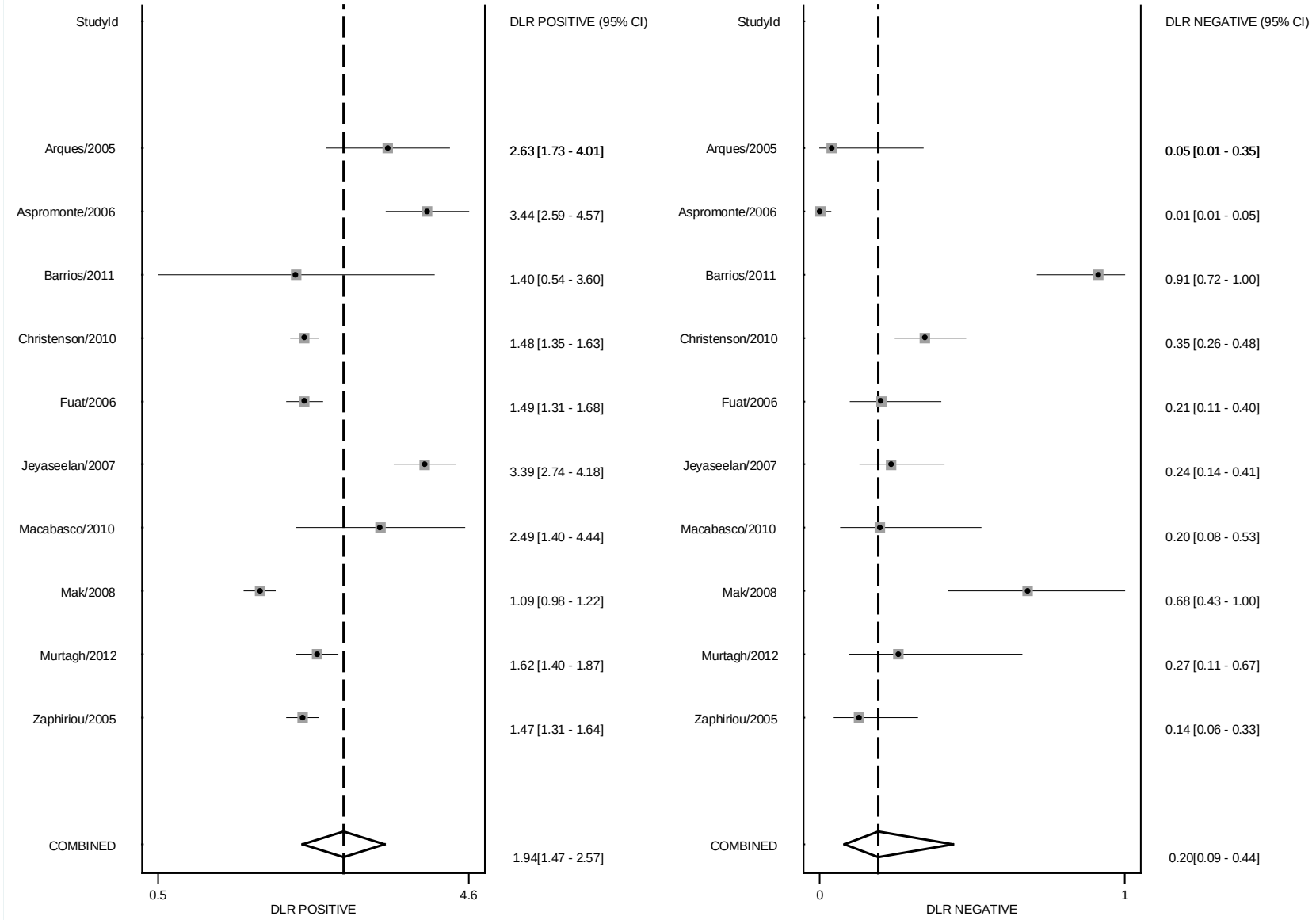


Figure I-7. Summary forest plot of LogDOR and DOR (PC BNP, manufacturer cut-point), bivariate mixed effect model

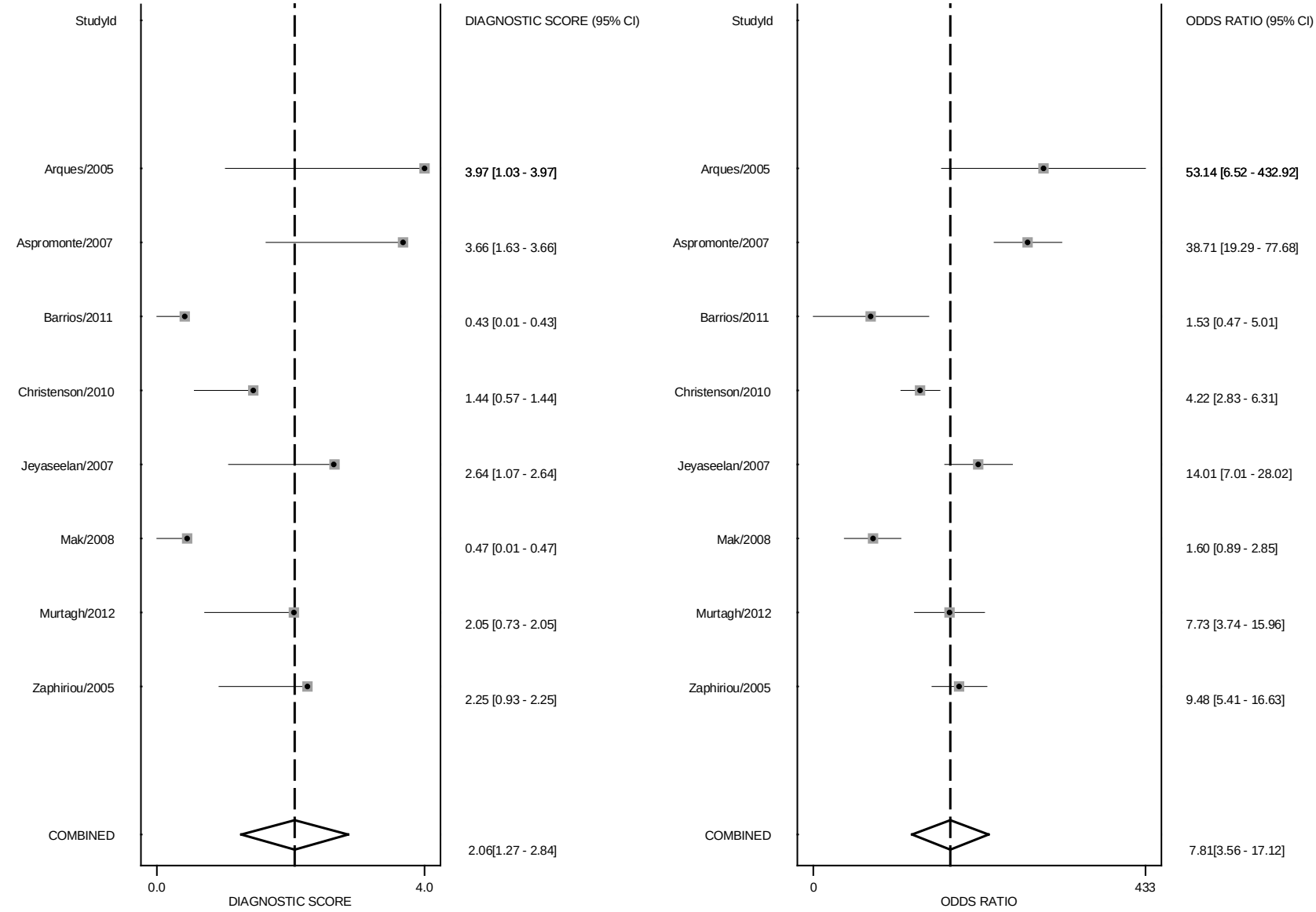


Figure I-8. Summary forest plot of LogDOR and DOR (PC BNP, optimum cut-point), bivariate mixed effect model

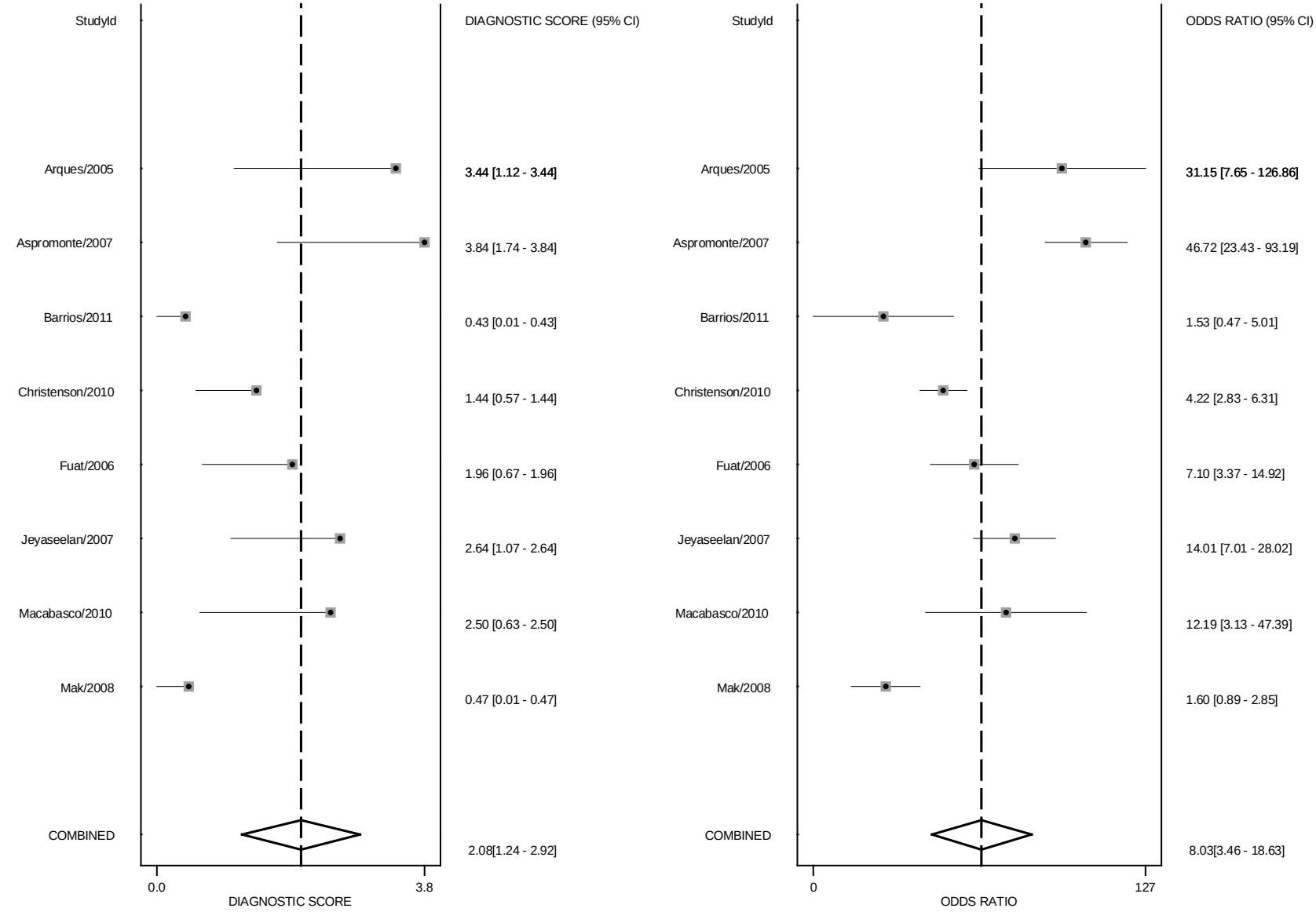


Figure I-9. Summary forest plot of LogDOR and DOR (PC BNP, lowest cut-point), bivariate mixed effect model

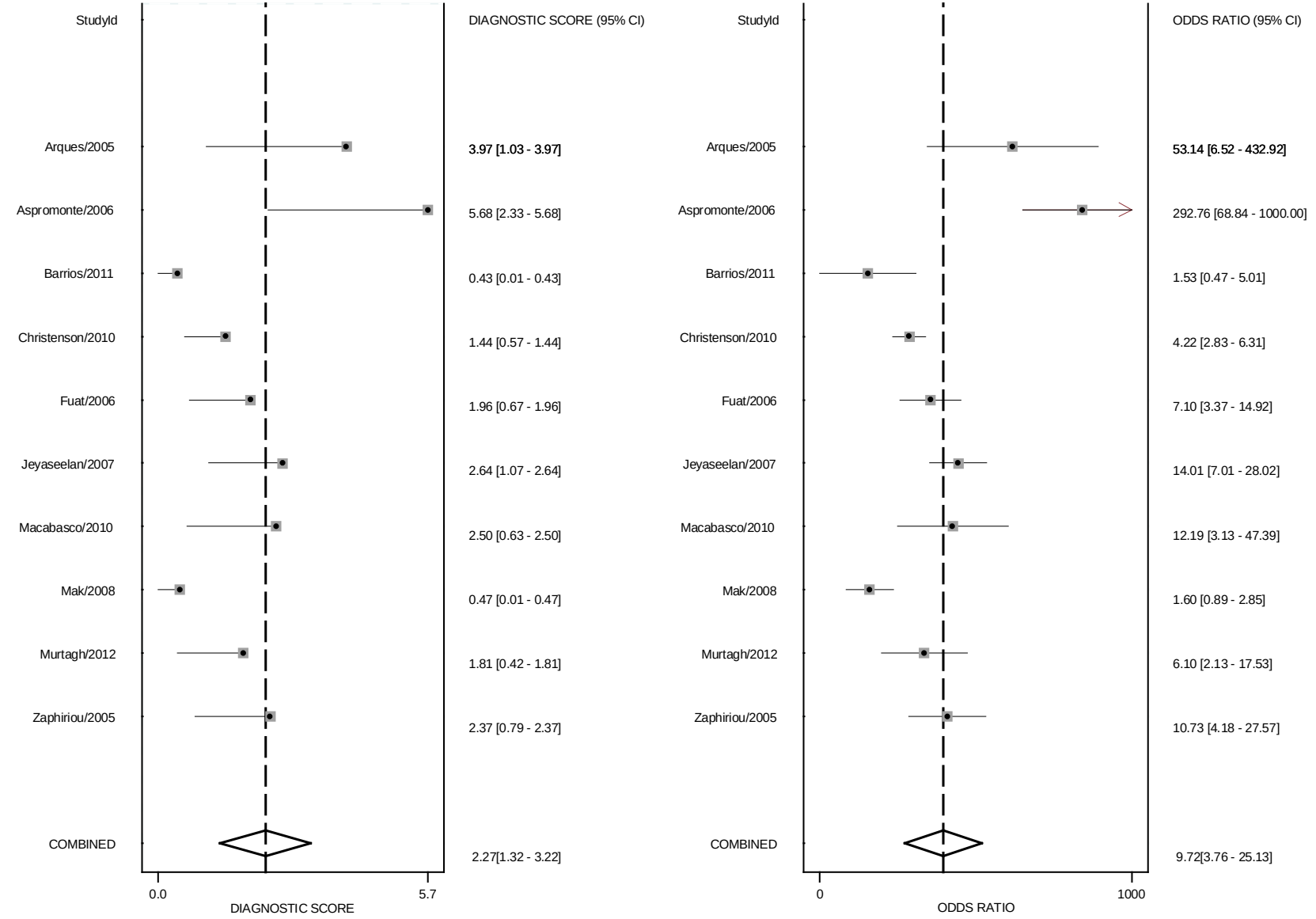


Figure I-10. Summary ROC-curve (PC BNP, manufacturer cut-point), bivariate mixed effect model

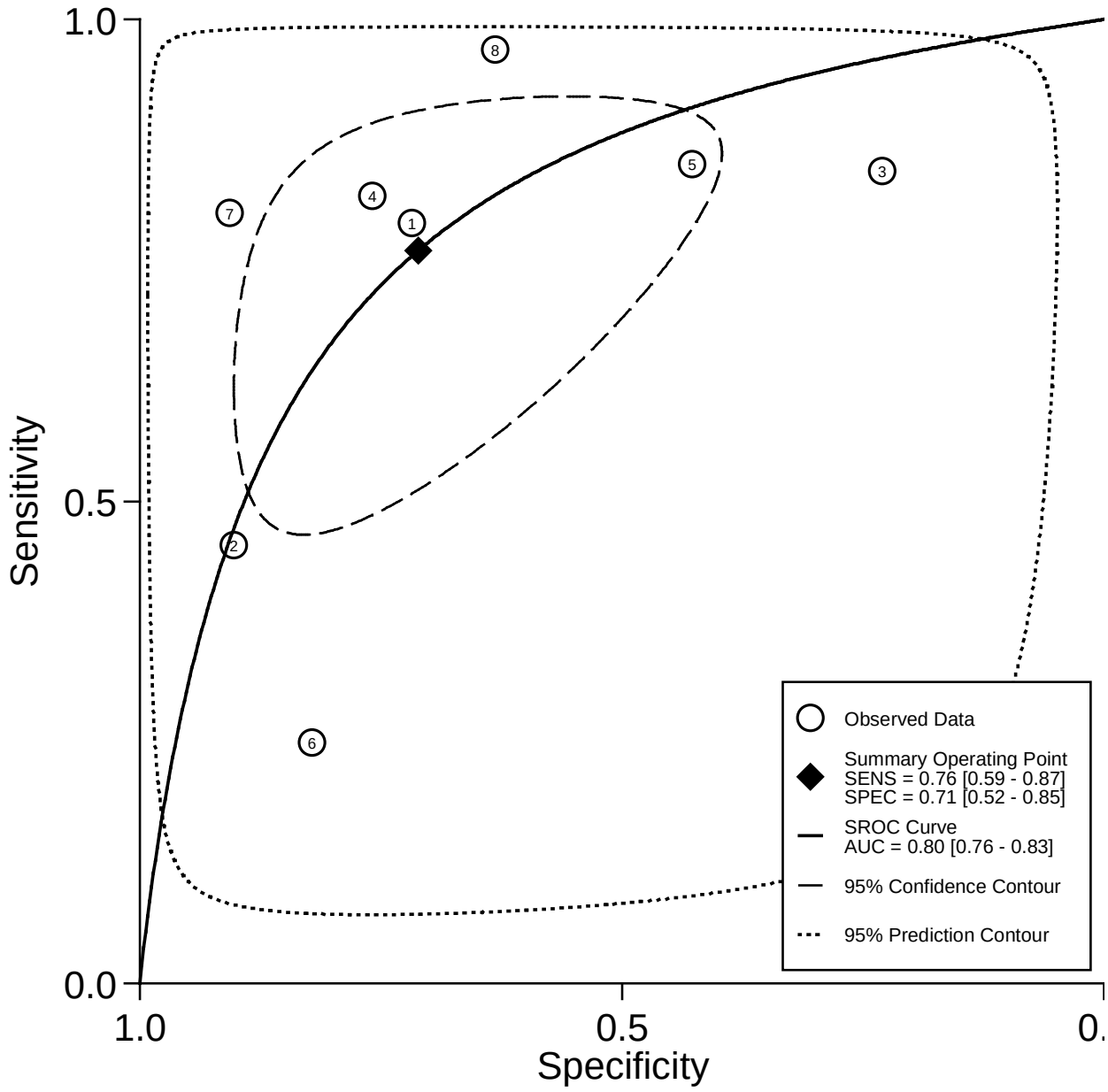


Figure I-11. Summary ROC-curve (PC BNP, optimum cut-point), bivariate mixed effect model

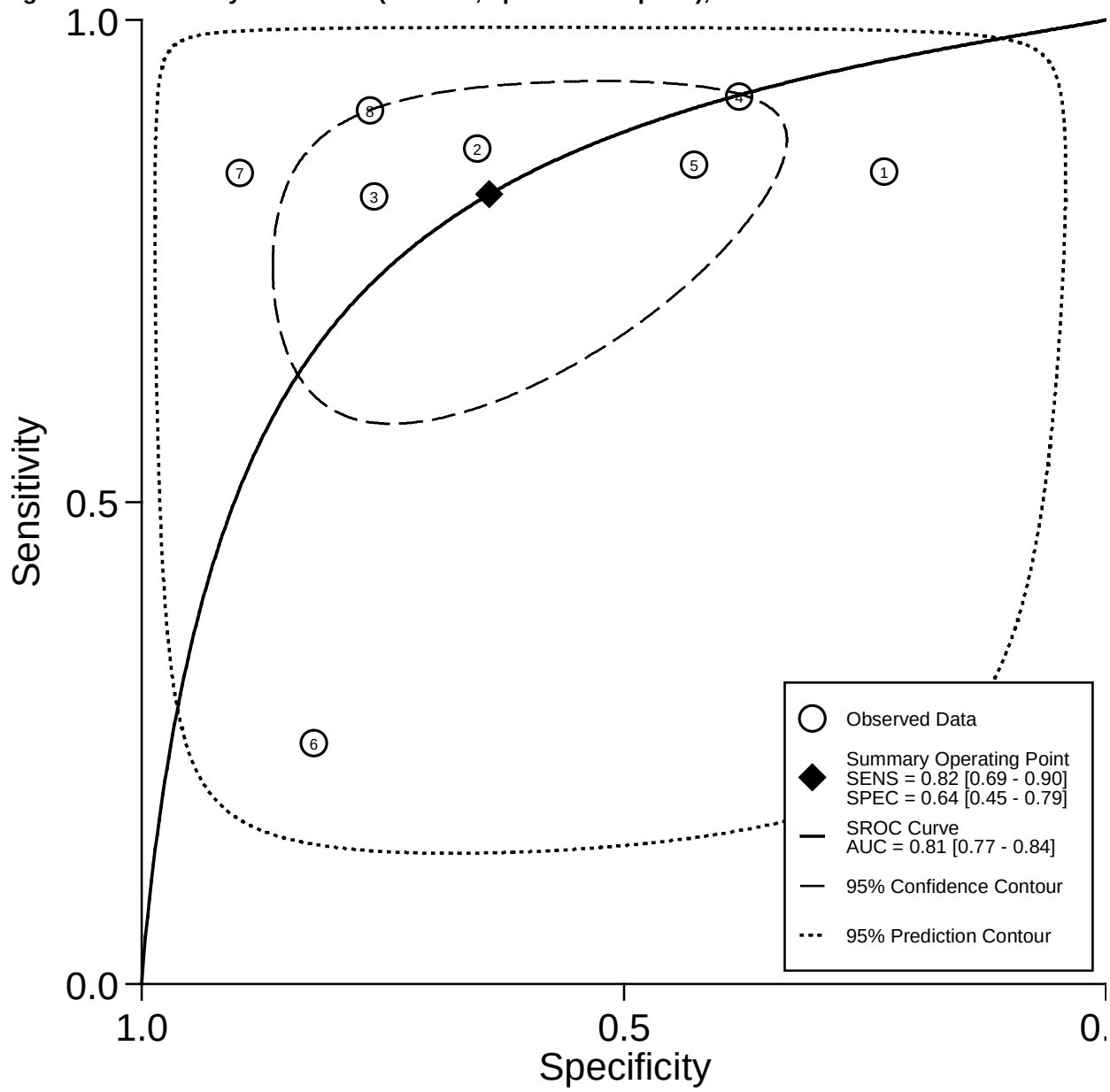


Figure I-12. Summary ROC-curve (PC BNP, lowest cut-point), bivariate mixed effect model

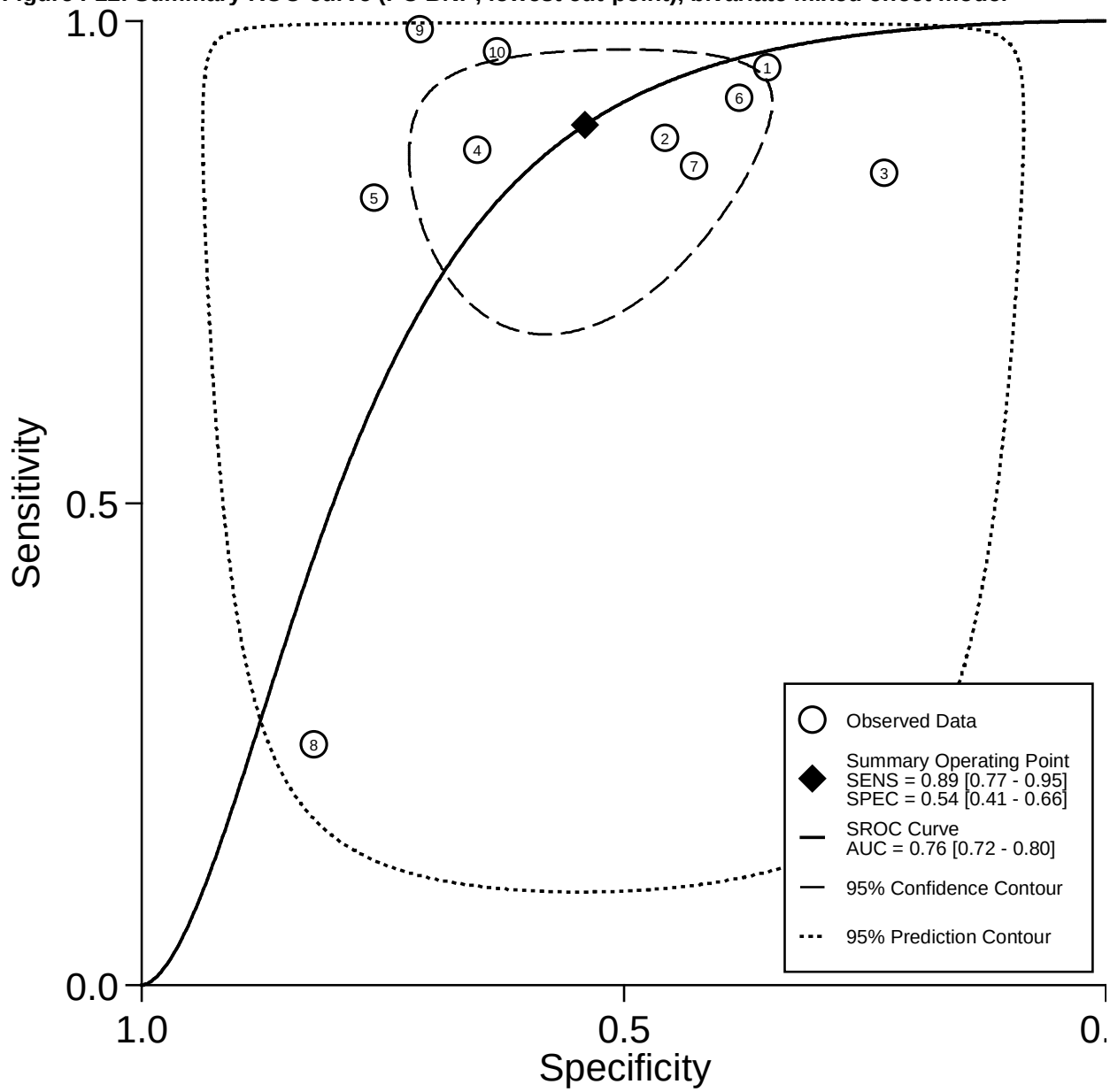


Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Christenson,[4] 2010 United States	Cross-Sectional (Independent Study) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF (n=147), Diabetes (n=245), Prior HF (n=236) Reference Standard: 1 Cardiologist	Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community-based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	NT-proBNP (ELECSYS - proBNP Immunoassay)	Dyspnea (decompensated HF, overall) n=675 mean age= NR %males= NR HF Prev=NR%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	NR	NR	NA	NA	0.72
				Dyspnea (decompensated HF, Normal Weight, BMI <25 kg/m n=211 mean age= 69.8y (15.5) %males=5 HF Prev=36%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	88	50	1.76	0.24	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Christenson,[4] 2010 United States (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: African-American (n=246) Comorbidities: HBP (n=209), CAD (n=227), AF (n=147), Diabetes (n=245), Prior HF (n=236) Reference Standard: 1 Cardiologist	(repeated data) Adjudicated acute HF, all-cause mortality (evaluated the accuracy of NTproBNP and BNP across a range of BMIs for diagnosis of decompensated HF in a community-based dyspneic patient population; also investigated whether the prognostic accuracies of NT-proBNP and BNP concentrations differed based on BMI for predicting 1-year all-cause mortality)	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea (decompensated HF, Over Weight, BMI 25-30 kg/m n=193 mean age= 66.6y (13.8) %males=58 HF Prev=37%; Age specific cutoffs, 450 pg/ml for age <50yrs, 900 pg/ml for 50-75yrs and 1800 pg/ml for >75yrs	Age specific	68	51	1.39	0.63	NR
				Dyspnea (decompensated HF, Obese, BMI >30 kg/m n=280 mean age= 62.5y (14.6) %males=38 HF Prev=32%; Age specific cut offs, 450pg/ml for age <50yrs, 900pg/ml for 50-75yrs and 1,800pg/ml for >75yrs	Age specific	69	64	1.92	0.48	NR
Fuat,[5] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=102), AF(n=56), COPD (n=69), Diabetes (n=27), Historical Mi (n=39), Ischemic (n=87) Reference Standard: Gps,15% Of Echo Verified By Cardiologists	To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT proBNP) in diagnosing HF due to left ventricular systolic dysfunction	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF referred by GPs n=297 mean age= (patients with LVSD) 73.5y; (patients with no LVSD) 74y, %males=37 HF Prev=38%	150	94	40	1.57	0.15	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[13] 2007 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=283), Diabetes (n=82),IHD (n=140), Ankle Oedema Or Worse (n=31), Previous MI (n=144), Angina (n=65), Reference Standard: 1 Cardiologist	LVSD (to assess the univariate and multivariable utility of NT-proBNP, QRS duration, symptoms and evidence of myocardial infarction (MI) to detect LVSD)	NT-proBNP (ELECSYS -proBNP Immunoassay)	HF (LVSD) n=427 mean age= 70y (8) %males=57 HF Prev=8%	150	84	45	1.52	0.35	NR
				Using upper 97.5th centile of normal population after Galasko et al; men <60yrs (100pg/ml);women <60yrs (164pg/ml); men ≥60yrs (172pg/ml); Women ≥60yrs (255pg/ml)	Age/Sex specific	84	53	1.79	0.29	NR
					NR	NR	NR	NA	NA	0.72
Goode,[14] 2008 United Kingdom	Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	HF (Overall) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=19%	NR	NR	NR	NA	NA	NR
				HF (Major LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=19%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<178	NR	47	NA	NA	0.88

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[14] 2008 United Kingdom (cont'd)	(repeated data) Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	(repeated data) To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	HF (Major LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=16%; Prevalence of HF and threshold for NT-proBNP changed due to revised Echo scoring	<464	NR	72	NA	NA	0.91
				HF (Any LVSD) n=94, mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=32%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<25	NR	3	NA	NA	0.82
				HF (Any LVSD) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=30%; Prevalence of HF and threshold for NT-proBNP changed due to revised Echo scoring	<76	NR	24	NA	NA	0.79

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Goode,[14] 2008 United Kingdom (cont'd)	(repeated data) Cohort (INDEPENDENT STUDY) Ethnicity: NR Comorbidities: HBP (n=52), AF(n=14), COPD (n=9), Diabetes (n=12), Historical MI (n=17), IHD (n=31), Angina (n=9), Anemia (n=17), GFR<30 Ml/Min/1.73 ^2 (n=3) Reference Standard: 1 Cardiologist	(repeated data) To assess the diagnostic utility of NT-proBNP and QRS width (independently and in combination) as the initial investigation for patients in whom the primary-care physician suspected HF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	HF (Major Structural heart disease) n=94 mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=36%; Prevalence of HF and threshold for NT-proBNP based on Original Echo Scoring	<93	NR	35	NA	NA	0.91
				HF (Major Structural heart disease) n=94, mean age= 77y* (70-81(IQR)) %males=46.8 HF Prev=35%; Prevalence of HF changed due to revised Echo scoring	<93	NR	35	NA	NA	0.91
Gustafsson,[15] 2003 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	Diagnosis of LVSD	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF (All) n=367, mean age= 68.8y* (39.0-84.0) %males=0 HF Prev=9%	NR	NR	NR	NA	NA	NR
				Suspected HF (LVEF > 40%) n=334 mean age= 68.0y* (38.0-84.5) %males=43 HF Prev=NR%	NR	NR	NR	NA	NA	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustafsson,[15] 2003 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	(repeated data) Diagnosis of LVSD	(repeated data) NT-proBNP (ELECSYS-proBNP Immunoassay)	Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%	125	97	46	1.80	0.07	NR
				Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%; Age specific cutoffs, 125 pg/ml for age <75yrs or 450 pg/ml for age ≥ 75yrs	Age specific	91	60	2.28	0.15	NR
				Suspected HF (LVEF ≤ 40%) n=33 mean age= 70.3y* (38.4-84.0) %males=76 HF Prev=NR%; Sex specific cut offs, 144pg/ml for Females and 93pg/ml for males	Sex specific	91	60	2.28	0.15	NR
				Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%	125	100	56	2.27	0.00	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustafsson,[15] 2003 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), AF(n=15), COPD (n=25), Diabetes (n=7), Ischemic (n=47) Reference Standard: NR	(repeated data) Diagnosis of LVSD	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%; Age specific cut offs, 125pg/ml for age <75yrs or 450pg/ml for age ≥ 75yrs	Age specific	100	58	2.38	0.00	NR
				Suspected HF (LVEF ≤ 30%) n=14 mean age= 67.0y* (51.0-84.0) %males=86 HF Prev=NR%; Sex specific cut offs, 144 pg/ml for Females and 93 pg/ml for males	Sex specific	100	44	1.79	0.00	NR
Gustafsson,[16] 2005 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), Obstructive Lung Disease (n=25), AF(n=15), Diabetes (n=7),IHD (n=47) Reference Standard: Blinded Investigator	Mortality and diagnosis	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected CHF (LVSD) n=367 mean age= 68.8y %males=46 HF Prev=9%	125	97	46	1.80	0.07	0.87
				LVSD (Age specific) n=367 mean age= 68.8y %males=46 HF Prev=9%; Age specific cut off values , 125pg/ml for Age <75yrs and 450pg/ml for Age ≥ 75yrs	Age specific	91	60	2.28	0.15	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Gustafsson,[16] 2005 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=68), Obstructive Lung Disease (n=25), AF(n=15), Diabetes (n=7),IHD (n=47) Reference Standard: Blinded Investigator	(repeated data) Mortality and diagnosis	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Severe LVSD (LVEF ≤ 30 %) n=367 mean age= 68.8y %males=46 HF Prev=4%	125	100	56	2.27	0.00	0.93
				Severe LVSD (Age specific) n=367 mean age= 68.8y %males=46 HF Prev=4%; Age specific cut off values , 125pg/ml for Age <75yrs and 45pg/ml for Age ≥ 75yrs	Age specific	100	58	2.38	0.00	NR
Hobbs,[17] 2004 United Kingdom	Cross-Sectional (Echoes) Ethnicity: Caucasian (n=573), Other (n=98) Comorbidities: HBP (n=232), Prior Ami/Angina (n=127), Diabetes (n=68), Historical Mi (n=87) Reference Standard: NR	no specified endpoint, diagnostic study	NT-proBNP (ELECSYS -proBNP Immunoassay)	All n=591 mean age= 65.8y (10.7) %males=54 HF Prev=6%. Prevalence for HF (LVSD, n=33) reported in overall population n=59 but not for individual groups	NR	NR	NR	NR	NR	NR
				General population over 45yrs n=307 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	80	73	2.96	0.27	0.76

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Hobbs,[17] 2004 United Kingdom (cont'd)	(repeated data) Cross-Sectional (Echoes) Ethnicity: Caucasian (n=573), Other (n=98) Comorbidities: HBP (n=232), Prior Ami/Angina (n=127), Diabetes (n=68), Historical Mi (n=87) Reference Standard: NR	(repeated data) no specified endpoint, diagnostic study	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Pts with previous HF diagnosis n=103 mean age= NR %males=NR HF Prev=NR%	40 pmol/L	100	18	1.22	0.00	0.7
				Pts on diuretics n=87 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	86	40	1.43	0.35	0.81
				Pts at high risk for HF n=133 mean age= NR %males= NR HF Prev=NR%	40 pmol/L	100	46	1.85	0.00	0.73
Kelder,[7] 2011 Netherlands	Cross-Sectional (Uhfo-Ia) Ethnicity: NR Comorbidities: HBP (n=88), AF(n=8), COPD (n=47), Diabetes (n=29), Stroke , TIA (n=15), MI, PCI, CABG (n=9) Reference Standard: Expert Panel (1 Cardiologist, 1 Pulmonologist, And 1 Gp	Data on the comparative performance of 3 popular automated assays in patients suspected of new slow-onset HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	HF n=172 mean age= 70.2y (11.3) %males=34 HF Prev=30%	NR	NR	NR	NA	NA	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Koschack,[18] 2008 Germany	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Dyslipidemia (n=282), HBP (n=468), Cad (n=166), Diabetes (n=170), Historical Mi (n=41), Family History Heart Disease (n=231) Reference Standard: 1 Cardiologist	Diagnostic power of the NT-proBNP assessment in ruling out left ventricular systolic dysfunction and compared it to a risk score derived from a logistic regression model of easily acquired clinical information	NT-proBNP (ELECSYS -proBNP Immunoassay)	HF (LVSD) n=542 mean age= (noLVSD) 63y (62-63); (LVSD) 69y (66-73) %males=57.55 HF Prev=4%	<98.5	91	46	1.69	0.20	0.83
Lim,[19] 2007 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=78), AF(n=19), Diabetes (n=24), History HID/MI (n=32) Reference Standard: Echo (Physician)	Determine cost effectiveness assessment of patients suspected HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF (overall) n=137 mean age= 71y (13) %males=50 HF Prev=24%	20 pmol/L	91	62	2.39	0.15	NR
				LVSD n=137, mean age= 71y (13) %males=50 HF Prev=14%	20 pmol/L	100	57	2.33	0.00	NR
				LVDD n=137, mean age= 71y (13) %males=50 HF Prev=9%	20 pmol/L	75	69	2.42	0.36	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Lim,[19] 2007 United Kingdom (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=78), AF(n=19), Diabetes (n=24), History HID/MI (n=32) Reference Standard: Echo (Physician)	(repeated data) Determine cost effectiveness assessment of patients suspected HF	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	LVSD + LVDD n=137 mean age= 71y (13) %males=50 HF Prev=23%	20 pmol/L	90	60	2.25	0.17	NR
				VHD or RVD n=137 mean age= 71y (13) %males=50 HF Prev=4%	20 pmol/L	100	51	2.04	0.00	NR
Mikklesen,[20] 2006 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=64), Diabetes (n=16),IHD (n=44) Reference Standard: History, Physical Exam, Chest Xray, Echo	Diagnosis of LVD	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected cardiac dyspnea (Left ventricular dysfunction (LVD) = LVSD + IDD) n=150 mean age= (LVSD) 70y* %males= (IDD) 68y* HF Prev=53%	≥87	95	76	3.96	0.07	0.95
				LVD (male) n=82 mean age= NR %males= NR HF Prev=NR%	≥85	95	71	3.28	0.07	NR
				LVD (female) n=68 mean age= NR %males= NR HF Prev=NR%	≥110	98	88	8.17	0.02	NR
				LVSD n=150 mean age= 70y* %males=54.6 HF Prev=15%	≥270	100	85	6.67	0.00	0.98

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Mikklesen,[20] 2006 Denmark (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=64), Diabetes (n=16),IHD (n=44) Reference Standard: History, Physical Exam, Chest Xray, Echo	(repeated data) Diagnosis of LVD	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	LVSD (male) n=82 mean age= NR %males= NR HF Prev=NR%	≥270	100	85	6.67	0.00	NR
				LVSD (female) n=68 mean age= NR %males= NR HF Prev=NR%	≥595	100	96	25.00	0.00	NR
Nielsen,[21] 2004 Denmark	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: COPD (n=166) Reference Standard: Combination Of History, Physical Exam, ECG Chest X-Ray Exam, Lung Spirometry, Echocardiography And Blood Tests (Blood-Haemoglobin, Thyroid Hormones, Creatinine, Sodium, Potassium And Glucose).	Diagnosis of HF	NT-proBNP (not stated)	Patients with dyspnoea, all n=345 mean age= 65y (18-89) %males=5 HF Prev=24%	NR	NR	NR	NR	NR	NR
				male patients ≥50 years n=146 mean age= NR %males= NR HF Prev=NR%	9 pmol/L	100	60	NR	NA	NR
					11 pmol/L	96	67	NA	NA	0.93
					18 pmol/L	89	79	NA	NA	NR
					8 pmol/L	100	27	NA	NA	NR
					17 pmol/L	94	69	NA	NA	0.9
					26 pmol/L	91	84	NA	NA	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Olofsson,[22] 2010 Sweden	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: HBP (n=43), AF(n=19), Historical MI (n=22), Valvular Heart Disease (n=18), Angina (n=37) Reference Standard: 1 Cardiologist	"Main outcome measures. NPV, PPV, sensitivity, specificity, and cut off levels. To explore the negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of natriuretic peptides, cut-off levels, and the impact of sex and age in elderly patients with systolic HF	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnoea (HF) n=109 mean age= (HF) 79y (6.4); (noHF) 76y (8.6), %males=32 HF Prev=44%	100 ng/L	96	18	1.17	0.22	NR
					200 ng/L	92	46	1.70	0.17	NR
					300 ng/L	81	69	2.61	0.28	NR
					400 ng/L	75	82	4.17	0.30	NR
					500 ng/L	73	87	5.62	0.31	NR
Park,[11] 2010 Korea	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	NT-proBNP (ELECSYS -proBNP Immunoassay)	Dyspnea or chest discomfort (Overall) n=1,032 mean age= 62.0y (13.0) %males=54 HF Prev=10%	NR	NR	NR	NA	NA	NR
				Men, LVSD n=555 mean age= NR %males=100 HF Prev=10%	510	81	81	4.22	0.23	0.867
				Men, advanced DD n=555 mean age= NR %males=100 HF Prev=7%	1,678	83	81	4.41	0.22	0.879
				Women, LVSD n=477 mean age= NR %males=100 HF Prev=10%	431	87	87	6.87	0.15	0.925

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	(repeated data) The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	Women, advanced DD n=477 mean age= NR %males=100 HF Prev=7%	860	85	85	5.51	0.18	0.878
				Age ≥ 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	1,446	82	81	4.32	0.22	0.875
				Age ≥ 65,advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	1,356	84	83	4.91	0.19	0.894
				Age < 65, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	379	84	84	5.26	0.19	0.912
				Age < 65, advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	276	83	82	4.73	0.20	0.893
				BMI ≥ 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	771	85	87	6.44	0.17	0.947
				BMI ≥ 25,advanced DD n=NR mean age= NR %males= NR HF Prev=NR%	309	80	80	4.02	0.25	0.893

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	(repeated data) The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	BMI < 25, LVSD n=NR mean age= NR %males= NR HF Prev=NR%	830	81	81	4.21	0.23	0.869
				BMI<25,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	682	81	81	4.29	0.23	0.885
				Hb ≥ 12, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	512	83	84	5.11	0.20	0.901
				Hb ≥ 12,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	389	83	84	5.03	0.20	0.906
				Hb < 12, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	2,464	83	82	4.63	0.21	0.856
				Hb < 12,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	1,912	77	77	3.27	0.30	0.82
				eGFR ≥ 60, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	418	84	84	5.41	0.18	0.915

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Park,[11] 2010 Korea (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Arrhythmia (n=90), Dyslipidemia (n=139), Diastolic Dysfunction (n=676), HBP (n=544), Diabetes (n=259), Ischemic (n=664), Valvular Heart Disease (n=22), Hypothyroidism (n=155), Hyperthyroidism (n=34), Cardiomyopathy (n=90) Reference Standard: 2 Cardiologists	(repeated data) The detection of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction (LVDD) in the symptomatic patients, To assess the direct correlation and its independent determinants between the BNP/NT BNP; to identify the factors that might influence the discrepancies between them	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	eGFR ≥ 60,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	276	83	82	4.65	0.20	0.889
				eGFR < 60, LVSD n=NR mean age=NR %males=NR HF Prev=NR%	1,981	78	78	3.55	0.28	0.832
				eGFR < 60,advanced DD n=NR mean age=NR %males=NR HF Prev=NR%	1,733	78	76	3.32	0.28	0.836

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Shelton,[23] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Cerebrovascular (n=91), HBP (n=585), Diabetes (n=276), IHD (n=707) Reference Standard: Echo, MSHD Classification(No Mention Of Clinicians)	Diagnostic Accuracy	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF / Dyspnea n=1321 mean age= (MSHD-AF) 74.5y; (No-MSHD with AF) 72.6y; (SR-MSHD) 69.7y; (SR-No MHSD) 69.1y, %males=58 HF Prev=60%	NR	NR	NR	NA	NA	NR
				MSHD with AF n=276 mean age=NR %males=6 HF Prev=40%	400	99	7	1.06	0.14	NR
					500	99	11	1.11	0.09	NR
					600	98	23	1.27	0.09	NR
					800	92	32	1.35	0.25	NR
					1,000	90	50	1.80	0.20	NR
					1,200	81	60	2.03	0.32	NR
					1,400	77	68	2.41	0.34	NR
					1,600	74	75	2.96	0.35	NR
					1,764	69	77	3.01	0.40	0.784
				MSHD with SR n=1,045 mean age=NR %males=57 HF Prev=57%	365	75	75	2.95	0.34	0.794
				MSHD with AF (Age > 75) n=140 mean age=NR %males=NR HF Prev=75%	757	100	3	1.03	0.00	NR
					1,764	69	61	1.75	0.51	NR
				MSHD with AF (Age ≤ 75) n=136, mean age=NR %males=NR HF Prev=72%	125	100	0	1.00	NR	NR
					1,758	70	90	7.12	0.33	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Shelton,[23] 2006 United Kingdom (cont'd)	(repeated data) Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Cerebrovascular (n=91), HBP (n=585), Diabetes (n=276), IHD (n=707) Reference Standard: Echo, MSHD Classification(No Mention Of Clinicians)	(repeated data) Diagnostic Accuracy	(repeated data) NT-proBNP (ELECSYS -proBNP Immunoassay)	MSHD with SR (Age ≤ 75) n=725 mean age=NR, %males=NR HF Prev=56%	125	89	43	1.56	0.26	NR
					357	73	79	3.43	0.34	NR
				MSHD with SR (Age>75) n=320 mean age=NR %males=NR HF Prev=58%	450	75	68	2.34	0.37	NR
					652	69	79	3.23	0.39	NR
Sivakumar,[24] 2006 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: BP (n=35), AF (n=35), Diabetes (n=10), IHD (n=38) Reference Standard: 1 Clinician	Diagnosis: systolic dysfunction, diastolic dysfunction, AF, and valve HD	NT-proBNP (ELECSYS -proBNP Immunoassay)	suspected HF/valvular disease (LVSD) n=100 mean age=82.4y %males=40 HF Prev=25%	424	96	45	1.75	0.09	0.71
					1,226	68	68	2.13	0.47	NR
					1,689	60	76	2.50	0.53	NR
					6,180	44	96	11.00	0.58	NR
				Valvular disease only n=75 mean age= NR %males= NR HF Prev=29%	227	91	43	1.60	0.21	NR
					334	91	53	1.94	0.17	NR
					424	82	55	1.82	0.33	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Stahrenberg,[25] 2010 Germany	Cohort (DIAST/CHF) Ethnicity: NR Comorbidities: HBP (n=210), CAD (n=94), AF(n=58), Diabetes (n=75), Hyperlipidemia (n=122, HF Patients Only) Reference Standard: Physicians, Framingham	Investigated the clinical relevance of GDF-15 plasma levels in HFnEF. ROC curves were constructed for discrimination between controls and subjects with HFnEFESC or HFnEFNew and sensitivity, specificity, and odds ratios HFnEF were calculated.	NT-proBNP (ELECSYS -proBNP Immunoassay)	Chronic HF (HFnEFESC) n=416 mean age= (HFnEFESC Grp) 73y (66-78); (HFrEF Grp) 71y (66-75); (Controls) 56y (52-63) %males=44.7; HF Prev=34%; Discrimination of HFnEFESC (HF normal Ejection Fraction) from healthy controls, Prevalence NR in paper but calculated using info on N's	>220 ng/L	65	97	20.34	0.36	NR
				Discrimination of HFnEFESC (HF normal Ejection Fraction) from healthy controls, Prevalence NR in paper but calculated using info on N's	NR	NR	NR	NA	NA	0.88
				Specificity Fixed, Prevalence NR in paper but calculated using info on N's	120 ng/L	74	80	3.70	0.33	NR
				Sensitivity Fixed, Prevalence NR in paper but calculated using info on N's	220 ng/L	55	97	18.33	0.46	NR
				Prevalence NR in paper but calculated using info on N's	NR	NR	NR	NA	NA	0.859

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Valle,[26] 2005 Italy	Cohort Ethnicity: NR Comorbidities: HBP (n=27), AF(n=8), COPD (n=3), Diabetes (n=10), Ischemic (n=7), Renal Disease (n=2), Valve Disease (n=6) Reference Standard: Framingham	Diagnosis HF, Deaths, hospitalization for chronic HF and cases of acute HF without hospitalization.	NT-proBNP(ELECSYS - proBNP Immunoassay)	suspected HF in elderly n=101, mean age= 84(9)y, %males=20); HF HF Prev=13%	NR	NR	NR	NA	NA	NR
				LVD (LVSD + DDF) n=101 mean age= 84y (9) %males=20 HF Prev=42%; 230 is optimal to distinguish between patients with or without some kind of ventricular dysfunction	150	93	41	1.58	0.17	NR
					200	83	53	1.77	0.32	NR
					230*	80	60	2.00	0.33	0.78
					250	76	60	1.90	0.40	NR
					300	73	66	2.15	0.41	NR
					350	70	70	2.33	0.43	NR
				LVSD + restrictive diastolic pattern n=101 mean age= 84y (9) %males=20 HF Prev=NR%; 530 is optimal threshold distinguish between patients with serious systolic and /or diastolic ventricular dysfunction	350	100	65	2.86	0.00	NR
					400	95	70	3.17	0.07	NR
					500*	95	82	5.28	0.06	0.93
					550	90	84	5.63	0.12	NR
					600	85	84	5.31	0.18	NR

Table I-3. Summary of diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of HF in the primary care settings (continued)

Author Year Country	Study Design (Companion Study) Ethnicity Comorbidities Reference Standard(S)	Objectives/end-points	BNP (Methods)	Sample Characteristics	Index Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC
Zaphiriou,[12] 2005 United Kingdom	Cross-Sectional (Independent Study) Ethnicity: NR Comorbidities: Dyslipidemia (n=67), HBP (n=168), Stroke (n=35), COPD (n=58), Diabetes (n=58), MI (n=42), PVD (n=20), Angina (n=80), CABG(n=18), PCI (n=7) Reference Standard: 1 Cardiologist	Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios for BNP, NTproBNP and the ECG for the diagnosis of HF. Area under the ROC curves for the two natriuretic peptides	NT-proBNP (ELECSYS -proBNP Immunoassay)	Suspected HF referred by GPs (all) n=306 mean age= 74y* (52-87) %males=4 HF Prev=34%	≥125	98	35	1.51	0.06	0.85
					≥166	96	43	1.68	0.09	NR

Abbreviations: AF = Atrial Fibrillation; AMI = Acute myocardial infarction; AUC = Area Under the Curve; BMI = Body Mass Index; BNP = B-Type Natriuretic Peptide; CAD = Coronary Artery Disease; CAGB = Coronary Artery Bypass Graft; CHF = Congestive Heart Failure; COPD = Chronic obstructive pulmonary disease; DD = Diastolic dysfunction; DDF = Diastolic dysfunction; DIAST-CHF = Diastolic congestive heart failure; ECG = Electrocardiogram; ECHO = Echocardiogram; ECHOES = Echocardiographic Heart of England Screening; eGFR = Estimated glomerular filtration rate; GDF-15 = Growth differentiation factor 15; GFR = Glomerular filtration rate; GP = General practitioner; Hb = Hemoglobin; HBP = High Blood Pressure/Hypertension; HF = Heart Failure; HFnEF = Heart failure with normal ejection fraction; HFnEFESC = Heart failure with normal ejection fraction recommended by European Society of Cardiology; HFnEFNew = Heart failure with normal ejection fraction recommended by American Society of ; HFrEF Grp Heart failure with reduced ejection fraction group; echocardiography; IDD = Isolated diastolic dysfunction ; IHD = Ischemic Heart Disease; IQR = Interquartile range; kg/m2 = Kilograms per metre squared; LR- = Negative Likelihood Ratio; LR+ = Positive Likelihood Ratio; LVD = Left ventricular dysfunction; LVDD = Left ventricular diastolic dysfunction; LVEF = Left Ventricular Ejection Fraction; LVSD = Left ventricular systolic dysfunction ; MI = Myocardial Infarction; mL/min/1.73m2 = Millilitre per minute per 1.73 metres squared; MSHD = Major structural heart disease; NA = Not applicable; ng/L = Nanogram per litre; NPV = Negative predictive value; NR = Not reported; NT-proBNP = N-Terminal proBNP; PCI = Percutaneous coronary intervention; pg/mL = Picograms per millilitre; pmol/L = Picomol per litre; PPV = Positive predictive value ; Pts = Patients; QRS = QRS complex on electrocardiogram; ROC = Receiver operating characteristic ; RVD = Right ventricular dysplasia; SOB = shortness of breath; SR = Sinus rhythm; TIA = Transient ischemic attack; UHFO-IA = Utrecht Heart Failure Organisation – Initial Assessment; VHD = Valvular heart disease; yrs = Years

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings

Author, Year Companion	Study Design	Population	n, Mean Age (SD), %Males	Prevalence of HF	Reference Standards	Index Test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Christenson,[4] 2010	Cross-sectional	Dyspnea (decompensated HF, overall)	675, NR, NR	NR	1 cardiologist	NT-proBNP	Age-specific	75	56	NA	NA	0.72
		Dyspnea (decompensated HF, normal weight, BMI <25kg/m^2)	211, 69.8 (15.5)y, 52	36	1 cardiologist	NT-proBNP	Age-Specific	88	50	1.76	0.24	NR
		Dyspnea (decompen-sated HF, over weight, BMI 25-30kg/m^2)	193, 66.6 (13.8)y, 58	37	1 cardiologist	NT-proBNP	Age-Specific	68	51	1.39	0.63	NR
		Dyspnea (decompensated HF, obese, BMI >30 kg/m^2)	280, 62.5 (14.6)y, 38	32	1 cardiologist	NT-proBNP	Age-Specific	69	64	1.92	0.48	NR
Fuat,[5] 2006	Cross-sectional	Suspected HF referred by GPs	297, (patients with LVSD) 73.5y; (patients with no LVSD) 74y, 37	38	GPs,15% of ECHO verified by cardiologists	NT-proBNP	150	94	40	1.57	0.15	R
Goode,[13] 2007	Cross-sectional	HF (LVSD)	427, 70 (8)y, 57.10	8	1 cardiologist	NT-proBNP	150	84	45	1.52	0.35	NR
						NT-proBNP	Age/Sex specific	84	53	1.79	0.29	NR
						NT-proBNP	NR	NR	NR	NA	NA	0.72
Goode[14] 2008	Cohort	HF (Overall)	94, 77*(70-81(IQR))y, 46.8	19	1 cardiologist	NT-proBNP	NR	NR	NR	NA	NA	NR
		HF (Major LVSD)	94, 77*(70-81(IQR))y, 46.8	19	1 cardiologist	NT-proBNP	<178	NR	47	NA	NA	0.88

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Goode[14] 2008 (cont'd)	Cohort	HF (Major LVSD)	94, 77*(70-81(IQR))y, 46.8	16	1 cardiologist	NT-proBNP	<464	NR	72	NA	NA	0.91
		HF (Any LVSD)	94, 77*(70-81(IQR))y, 46.8	32	1 cardiologist	NT-proBNP	<25	NR	3	NA	NA	0.82
		HF (Any LVSD)	94, 77*(70-81(IQR))y, 46.8	30	1 cardiologist	NT-proBNP	<76	NR	24	NA	NA	0.79
		HF (MSHD)	94, 77*(70-81(IQR))y, 46.8	36	1 cardiologist	NT-proBNP	<93	NR	35	NA	NA	0.91
		HF (MSHD)	94, 77*(70-81(IQR))y, 46.8	35	1 cardiologist	NT-proBNP	<93	NR	35	NA	NA	0.91
Gustafsson,[15] 2003	Cross-sectional	Suspected HF (All)	367, 68.8*(39.0-84.0)y, 0	9	NR	NT-proBNP	NR	NR	NR	NA	NA	NR
		Suspected HF (LVEF >40%)	334, 68.0*(38.0-84.5)y, 43	NR	NR	NT-proBNP	NR	NR	NR	NA	NA	NR
		Suspected HF (LVEF ≤ 40%)	33, 70.3*(38.4-84.0)y, 76	NR	NR	NT-proBNP	125	97	46	1.80	0.07	NR
		Suspected HF (LVEF ≤ 40%)	33, 70.3*(38.4-84.0)y, 76	NR	NR	NT-proBNP	Age-Specific	91	60	2.28	0.15	NR
		Suspected HF (LVEF ≤ 40%)	33, 70.3*(38.4-84.0)y, 76	NR	NR	NT-proBNP	Sex-Specific	91	60	2.28	0.15	NR
		Suspected HF (LVEF ≤ 30%)	14, 67.0*(51.0-84.0)y, 86	NR	NR	NT-proBNP	125	100	56	2.27	0.00	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Gustafsson[15] 2003 (cont'd)	Cross-sectional	Suspected HF (LVEF ≤ 30%)	14, 67.0*(51.0-84.0)y, 86	NR	NR	NT-proBNP	Age-Specific	100	58	2.38	0.00	NR
		Suspected HF (LVEF ≤ 30%)	14, 67.0*(51.0-84.0)y, 86	NR	NR	NT-proBNP	Sex-Specific	100	44	1.79	0.00	NR
Gustafsson[16] 2005	Cross-sectional	Suspected CHF (LVSD)	367, 68.8y, 46	9	Blinded investigator	NT-proBNP	125	97	46	1.80	0.07	0.87
		LVSD (Age-Specific)	367, 68.8y, 46	9	Blinded investigator	NT-proBNP	Age-Specific	91	60	2.28	0.15	NR
		Severe LVSD (LVEF ≤ 30 %)	367, 68.8y, 46	4	Blinded investigator	NT-proBNP	125	100	56	2.27	0.00	0.93
		Severe LVSD (Age-specific)	367, 68.8y, 46	4	Blinded investigator	NT-proBNP	Age-specific	100	58	2.38	0.00	NR
Hobbs[17] 2004 ECHOES Nielson[21] 2004	Cross-sectional	Pts at high risk for HF	n=133, NR, NR	NR	NR	NT-proBNP	40 pmol/L	100	46	1.85	0.00	0.73
		Patients with dyspnea, all	345, 65(18-89)y, 51	24	Combination of history, physical examination, ECG, chest X-ray examination, lung spirometry, ECHO, and blood tests (blood-Hb, thyroid hormones, creatinin, sodium, potassium, and glucose).	NR	NR	NR	NR	NR	NR	NR
Kelder,[7] 2011 UHFO-IA	Cross-sectional	HF	172, 70.2 (11.3)y, 34	30	Expert panel (1 cardiologist, 1 pulmonologist, and 1 GP)	NT-proBNP	NR	NR	NR	NA	NA	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Kelder,[27] 2011	Cross-sectional Design	Dyspnea, fatigue, sings of fluid retention	721 70.7±11.8y 5.4	28.7	Outcome panel using all available outcome	NT-proBNP	NR	NR	NR	NR	NR	0.86
Koschack,[18] 2008	Cross-sectional	HF (LVSD)	542, (noLVSD) 63(62-63)y; (LVSD) 69(66-73)y, 57.55	4	1 cardiologist	NT-proBNP	<98.5	91	46	1.69	0.20	0.83
Lim,[19] 2007	Cross-sectional	Suspected HF (overall)	137, 71(13)y, 50	24	ECHO (physician)	NT-proBNP	20 pmol/L	91	62	2.39	0.15	NR
		LVSD	137, 71(13)y, 50	14	ECHO (physician)	NT-proBNP	20 pmol/L	100	57	2.33	0.00	NR
		LVDD	137, 71(13)y, 50	9	ECHO (physician)	NT-proBNP	20 pmol/L	75	69	2.42	0.36	NR
		LVSD + LVDD	137, 71(13)y, 50	23	ECHO (physician)	NT-proBNP	20 pmol/L	90	60	2.25	0.17	NR
		VHD or RVD	137, 71(13)y, 50	4	ECHO (physician)	NT-proBNP	20 pmol/L	100	51	2.04	0.00	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Mikklesen,[20] 2006	Cross-sectional	Suspected cardiac dyspnea (LVD=LVSD + IDD)	150, (LVSD) 70y*, (IDD) 68y*, (NoLVD) 58y*, 54.6	53	History, physical exam, chest xray, ECHO	NT-proBNP	≥87	95	76	3.96	0.07	0.95
		LVD (male)	82, NR, NR	NR	History, physical exam, chest xray, ECHO	NT-proBNP	≥85	95	71	3.28	0.07	NR
		LVD (female)	68, NR, NR	NR	History, physical exam, chest xray, ECHO	NT-proBNP	≥110	98	88	8.17	0.02	NR
		LVSD	150, 70y*, 54.6	15	History, physical exam, chest xray, ECHO	NT-proBNP	≥270	100	85	6.67	0.00	0.98
		LVSD (male)	82, NR, NR	NR	History, physical exam, chest xray, ECHO	NT-proBNP	≥270	100	85	6.67	0.00	NR
		LVSD (female)	68, NR, NR	NR	History, physical exam, chest xray, ECHO	NT-proBNP	≥595	100	96	25.00	0.00	NR
Nielson,[21] 2004	Cross-sectional	Male patients ≥50 years	146, NR, NR	NR	Combination of history, physical examination, ECG, chest X-ray examination, lung spirometry, ECHO, and blood tests (blood-Hb, thyroid hormones, creatinin, sodium, potassium and glucose).	NT-proBNP	9 pmol/L	100	60	NR	NA	NR
						NT-proBNP	11 pmol/L	96	67	NA	NA	0.93
						NT-proBNP	18 pmol/L	89	79	NA	NA	NR
						NT-proBNP	8 pmol/L	100	27	NA	NA	NR
						NT-proBNP	17 pmol/L	94	69	NA	NA	0.9
						NT-proBNP	26 pmol/L	91	84	NA	NA	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Olofsson,[22] 2010	Cross-sectional	Dyspnea (HF)	109, (HF) 79(6.4)y; (noHF) 76(8.6)y, 32.1	44	1 cardiologist	NT-proBNP	100 ng/L	96	18	1.17	0.22	NR
						NT-proBNP	200 ng/L	92	46	1.70	0.17	NR
						NT-proBNP	300 ng/L	81	69	2.61	0.28	NR
						NT-proBNP	400 ng/L	75	82	4.17	0.30	NR
						NT-proBNP	500 ng/L	73	87	5.62	0.31	NR
Park,[11] 2010	Cross-sectional	Dyspnea or chest discomfort (Overall)	1032, 62.0 (13.0)y, 54	10	2 cardiologists	NT-proBNP	NR	NR	NR	NA	NA	NR
		Men, LVSD	555, NR, 100	10	2 cardiologists	NT-proBNP	510	81	81	4.22	0.23	0.867
		Men, advanced DD	555, NR, 100	7	2 cardiologists	NT-proBNP	1,678	83	81	4.41	0.22	0.879
		Women, LVSD	477, NR, 100	10	2 cardiologists	NT-proBNP	431	87	87	6.87	0.15	0.925

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 (cont'd)	Cross-sectional	Women, advanced DD	477, NR, 100	7	2 cardiologists	NT-proBNP	860	85	85	5.51	0.18	0.878
		Age ≥ 65y, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1,446	82	81	4.32	0.22	0.875
		Age ≥ 65,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1,356	84	83	4.91	0.19	0.894
		Age <65y, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	379	84	84	5.26	0.19	0.912
		Age <65y, advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	276	83	82	4.73	0.20	0.893
		BMI ≥ 25 kg/m^2, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	771	85	87	6.44	0.17	0.947
		BMI ≥ 25 kg/m^2,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	309	80	80	4.02	0.25	0.893
		BMI <25 kg/m^2, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	830	81	81	4.21	0.23	0.869
		BMI<25 kg/m^2,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	682	81	81	4.29	0.23	0.885
		Hb ≥ 12, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	512	83	84	5.11	0.20	0.901
		Hb ≥ 12,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	389	83	84	5.03	0.20	0.906
		Hb <12, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	2464	83	82	4.63	0.21	0.856
		Hb <12,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1912	77	77	3.27	0.30	0.82
		eGFR ≥ 60, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	418	84	84	5.41	0.18	0.915
		eGFR ≥ 60,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	276	83	82	4.65	0.20	0.889

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Park,[11] 2010 (cont'd)	Cross-sectional	eGFR <60, LVSD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1,981	78	78	3.55	0.28	0.832
		eGFR <60,advanced DD	NR, NR, NR	NR	2 cardiologists	NT-proBNP	1,733	78	76	3.32	0.28	0.836
Shelton,[23] 2006	Cross-sectional	Suspected HF/ Dyspnea	1321, (MSHD-AF) 74.5y; (No-MSHD with AF) 72.6y; (SR-MSHD) 69.7y; (SR-No MHSD) 69.1y, 58	60	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	NR	NR	NR	NA	NA	NR
		MSHD with AF	276, NR, 62	37	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	400	99	7	1.06	0.14	NR
						NT-proBNP	500	99	11	1.11	0.09	NR
						NT-proBNP	600	98	23	1.27	0.09	NR
						NT-proBNP	800	92	32	1.35	0.25	NR
						NT-proBNP	1,000	90	50	1.80	0.20	NR
						NT-proBNP	1,200	81	60	2.03	0.32	NR
						NT-proBNP	1,400	77	68	2.41	0.34	NR
						NT-proBNP	1,600	74	75	2.96	0.35	NR
						NT-proBNP	1,764	69	77	3.01	0.40	0.784
		MSHD with SR	1045, NR, 57	57	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	365	75	75	2.95	0.34	0.794
		MSHD with AF (Age >75)	140, NR, NR	75	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	757	100	3	1.03	0.00	NR
						NT-proBNP	1,764	69	61	1.75	0.51	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Shelton,[23] 2006 (cont'd)	Cross-sectional	MSHD with AF (Age ≤ 75y)	136, NR, NR	71	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	125	100	0	1.00	NR	NR
						NT-proBNP	1758	70	90	7.12	0.33	NR
		MSHD with SR (Age ≤ 75y)	725, NR, NR	56	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	125	89	43	1.56	0.26	NR
						NT-proBNP	357	73	79	3.43	0.34	NR
		MSHD with SR (Age>75y)	320, NR, NR	58	ECHO, MSHD classification (No mention of clinicians)	NT-proBNP	450	75	68	2.34	0.37	NR
						NT-proBNP	652	69	79	3.23	0.39	NR
Sivakumar,[24] 2006	Cross-sectional	Suspected HF/valvular disease (LVSD)	100, 82.4y, 40	25	1 Clinician	NT-proBNP	424	96	45	1.75	0.09	0.71
						NT-proBNP	1226	68	68	2.13	0.47	NR
						NT-proBNP	1689	60	76	2.50	0.53	NR
						NT-proBNP	6180	44	96	11.00	0.58	NR
		Valvular disease only	75, NR, NR	29	1 Clinician	NT-proBNP	227	91	43	1.60	0.21	NR
						NT-proBNP	334	91	53	1.94	0.17	NR
						NT-proBNP	424	82	55	1.82	0.33	NR
Stahrenberg,[25] 2010 DIAST/CHF	Cohort	Chronic HF ($HFnEF_{ESC}$)	416, (HFnEFESC Grp) 73 (66-78)y; (HFrEF Grp) 71 (66-75)y; (Controls) 56 (52-63)y, 44.71	34	Physicians, Framingham criteria	NT-proBNP	>220 ng/L	65	97	20.34	0.36	NR
						NT-proBNP	NR	NR	NR	NA	NA	0.88
						NT-proBNP	120 ng/L	74	80	3.70	0.33	NR
						NT-proBNP	220 ng/L	55	97	18.33	0.46	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Stahrenberg,[25] 2010 DIAST/CHF Hobbs,[17] 2004 ECHOES	Cohort Cross-sectional	Chronic HF ($HFnEF_{ESC}$) All general population over 45y Pts with previous HF diagnosis Pts on diuretics	416, (HFnEFESC Grp) 73 (66-78)y; (HFrEF Grp) 71 (66-75)y; (Controls) 56 (52-63)y, 44.71 591, 65.8 (10.7)y, 54 307, NR, NR 103 NR, NR 87, NR, NR	34 6 NR NR NR	Physicians, Framingham criteria NR NR NR NR	NT-proBNP	NR	NR	NR	NA	NA	0.859
						NT-proBNP	NR	NR	NR	NR	NR	NR
						NT-proBNP	40 pmol/L	80	73	2.96	0.27	0.76
						NT-proBNP	40 pmol/L	100	18	1.22	0.00	0.7
						NT-proBNP	40 pmol/L	86	40	1.43	0.35	0.81
Valle,[26] 2005	Cohort	Suspected HF in elderly	101, 84(9)y, 20	13	Framingham	NT-proBNP	NR	NR	NR	NA	NA	NR
		LVD (LVSD + DDF)	101, 84(9)y, 20	42	Framingham	NT-proBNP	150	93	41	1.58	0.17	NR
						NT-proBNP	200	83	53	1.77	0.32	NR
						NT-proBNP	230*	80	60	2.00	0.33	0.78
						NT-proBNP	250	76	60	1.90	0.40	NR
						NT-proBNP	300	73	66	2.15	0.41	NR
						NT-proBNP	350	70	70	2.33	0.43	NR
		LVSD + restrictive diastolic pattern	101, 84(9)y, 20	NR	Framingham	NT-proBNP	350	100	65	2.86	0.00	NR
						NT-proBNP	400	95	70	3.17	0.07	NR
						NT-proBNP	500*	95	82	5.28	0.06	0.93
						NT-proBNP	550	90	84	5.63	0.12	NR
						NT-proBNP	600	85	84	5.31	0.18	NR

Table I-4. Detailed diagnostic properties of studies that evaluated NT-proBNP in patients with symptoms suggestive of heart failure in the primary care settings (continued)

Author, Year Companion	Study Design	Population	n, mean age (SD), %males	Prevalence of HF	Reference standards	Index test	Index Cutpoint (pg/mL)	Sensitivity %	Specificity %	LR+	LR-	AUC
Zaphiriou,[12] 2005	Cross-sectional	Suspected HF referred by GPs (all)	306, 74*(52-87)y, 42	34	1 cardiologist	NT-proBNP	≥125	98	35	1.51	0.06	0.85
						NT-proBNP	≥166	96	43	1.68	0.09	NR

* median (range)

Abbreviations: AF = Atrial Fibrillation; AUC = area under the curve; BMI = body mass index; BNP=B-type natriuretic peptide; CHF = congestive heart failure; DD = diastolic dysfunction; DDF = diastolic dysfunction; ECG = electrocardiogram; ECHO = echocardiogram; ECHOES = Echocardiographic Heart of England Screening; eGFR = estimated glomerular filtration rate; GP = general practitioner; Hb = Hemoglobin; HF = heart failure; HFnEFESC = Heart failure with normal ejection fraction recommended by European Society of Cardiology; HFrEF Grp Heart failure with reduced ejection fraction group; IDD = isolated diastolic dysfunction ; IQR = interquartile range; kg/m2 = kilograms per meter squared; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; LVD = left ventricular dysfunction ; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction ; MSHD = major structural heart disease; MSHD-AF = major structural heart disease atrial fibrillation; MSHD-SR = major structural heart disease sinus rhythm; NA = not applicable ; ng/L = nanogram per liter; NR = not reported ; NT-proBNP=N-Terminal proBNP; pg/mL = picograms per milliliter; pmol/L = picomol per liter; SD = standard deviation; SR = sinus rhythm; UHFO-IA = Utrecht Heart Failure Organisation – Initial Assessment; y = years

Figure I-13. Summary forest plot of sensitivity and specificity (PC NTProBNP, optimum cut-point), bivariate mixed effect model

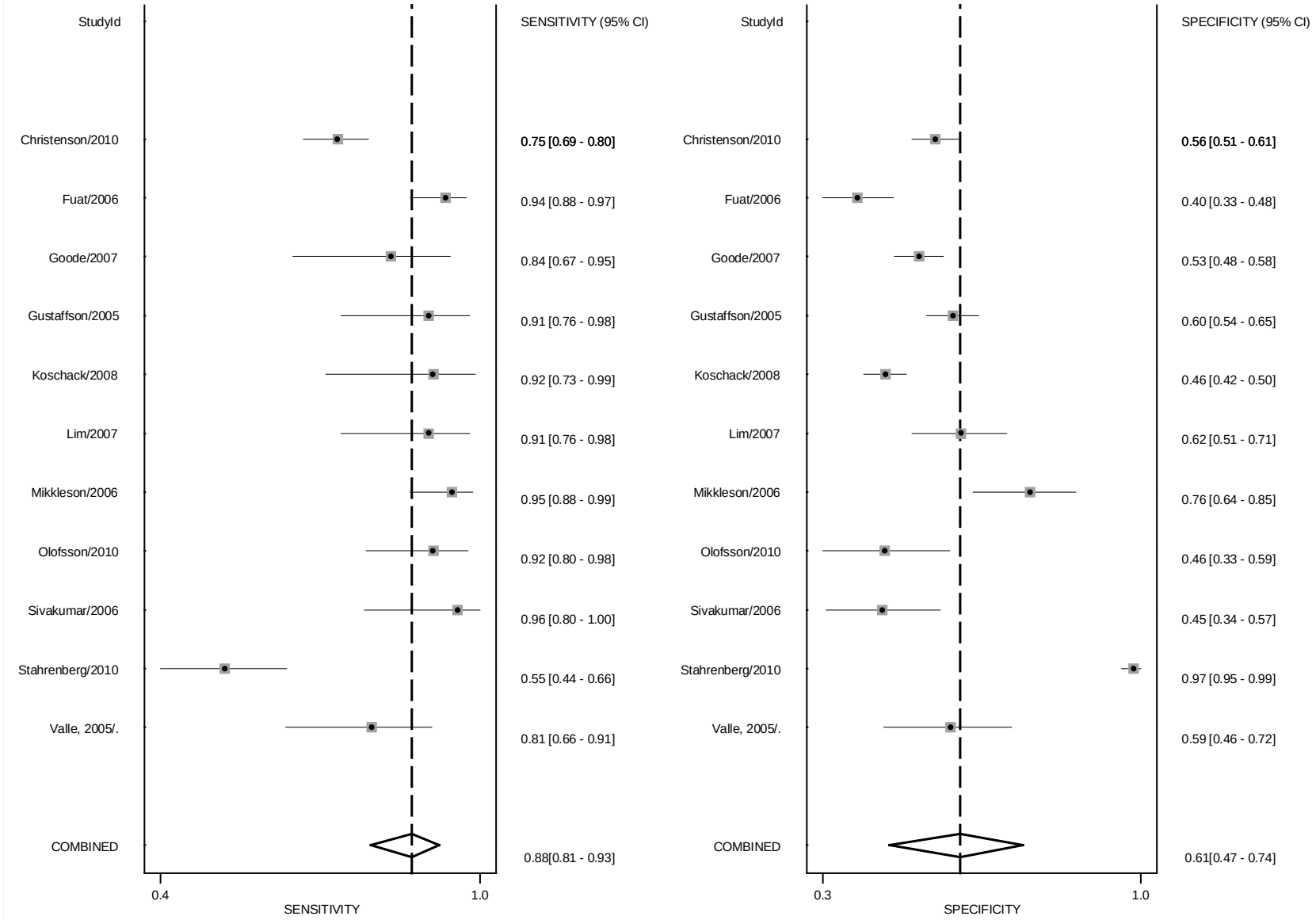


Figure I-14. Summary forest plot of sensitivity and specificity (PC NTProBNP, lowest cut-point), bivariate mixed effect model

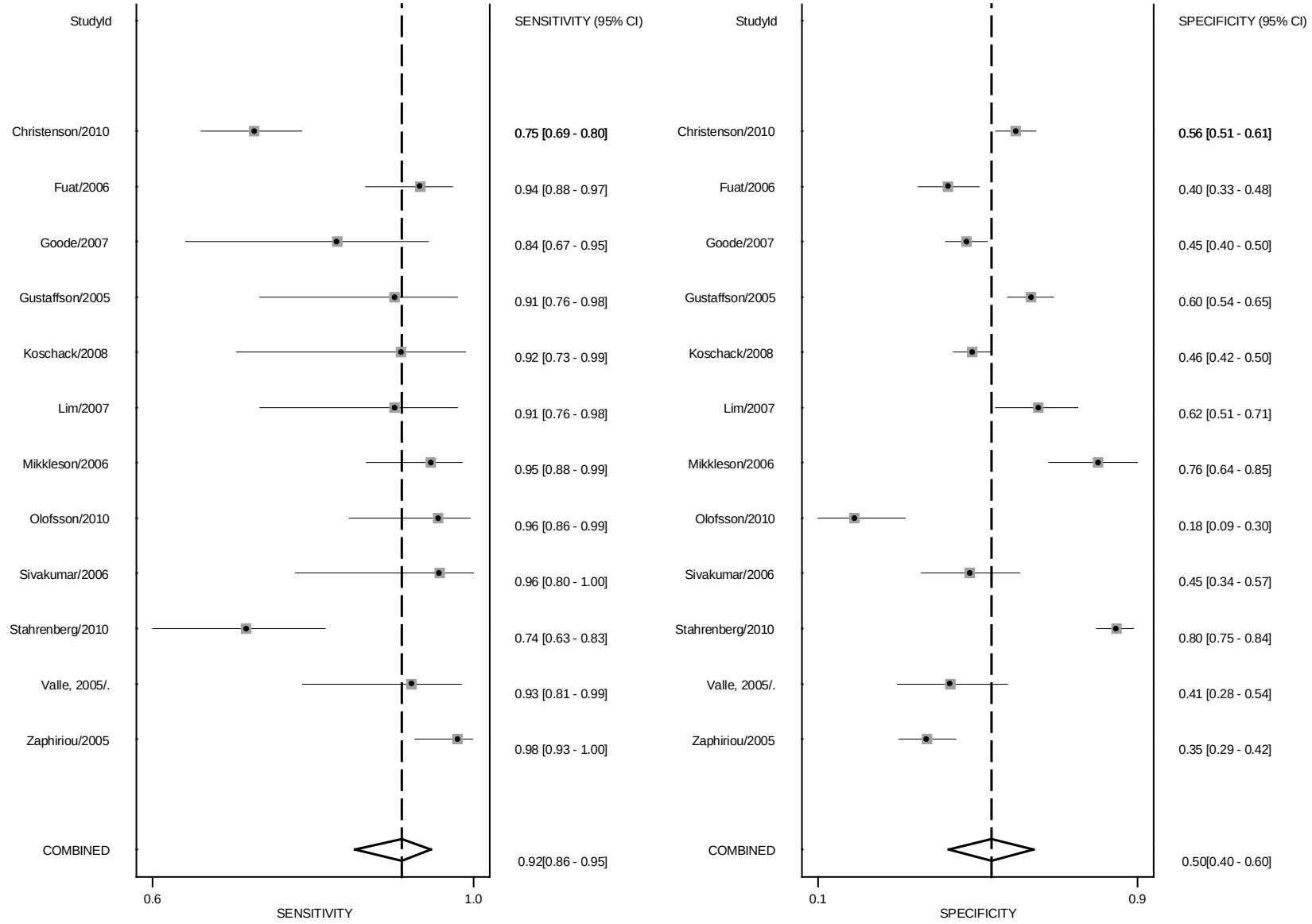


Figure I-15. Summary forest plot of LR+ and LR- (PC NTProBNP, optimum cut-point), bivariate mixed effect model

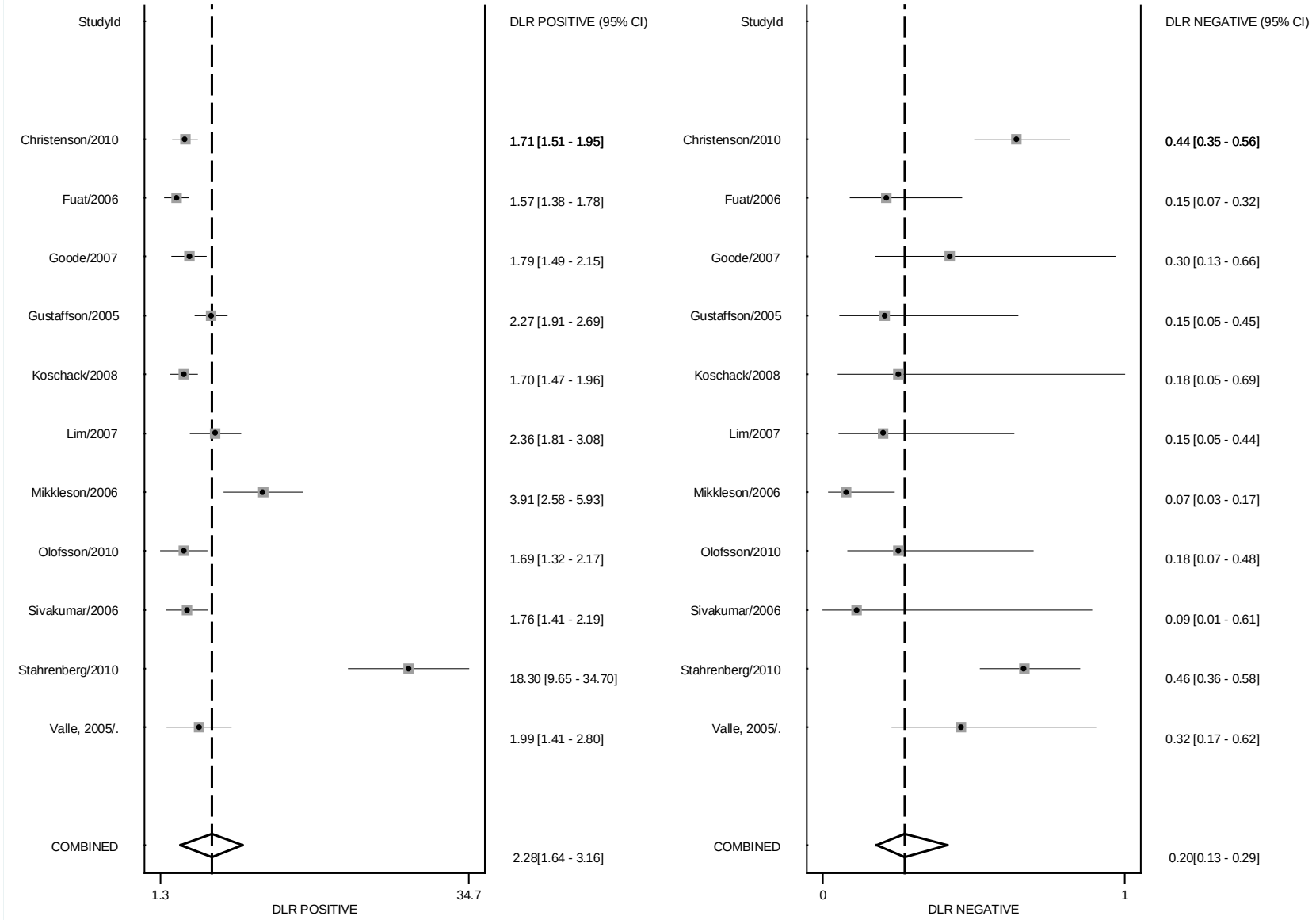


Figure I-16. Summary forest plot of LR+ and LR- (PC NTProBNP, lowest cut-point), bivariate mixed effect model

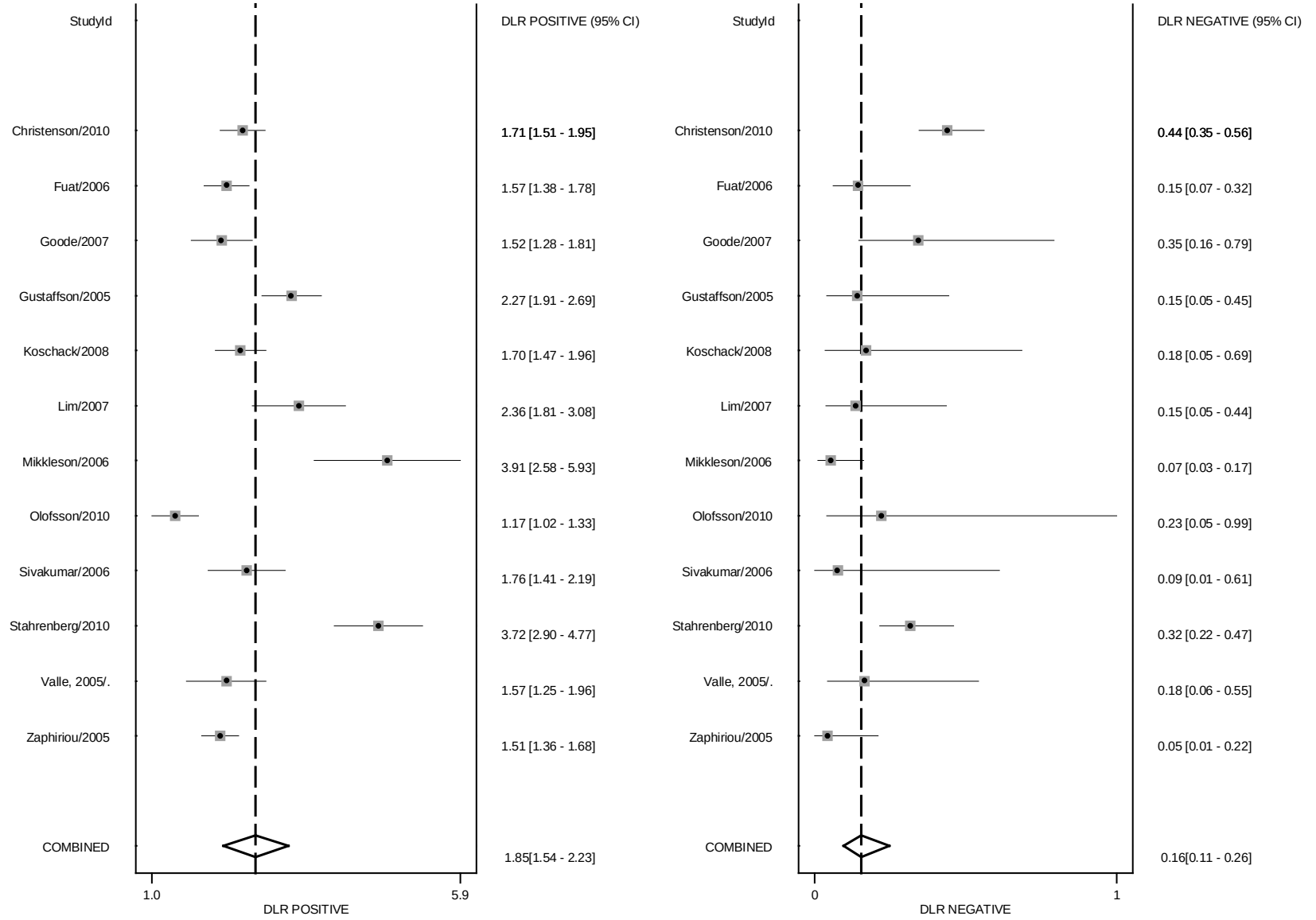


Figure I-17. Summary forest plot of LogDOR and DOR (PC NTProBNP, optimum cut-point), bivariate mixed effect model

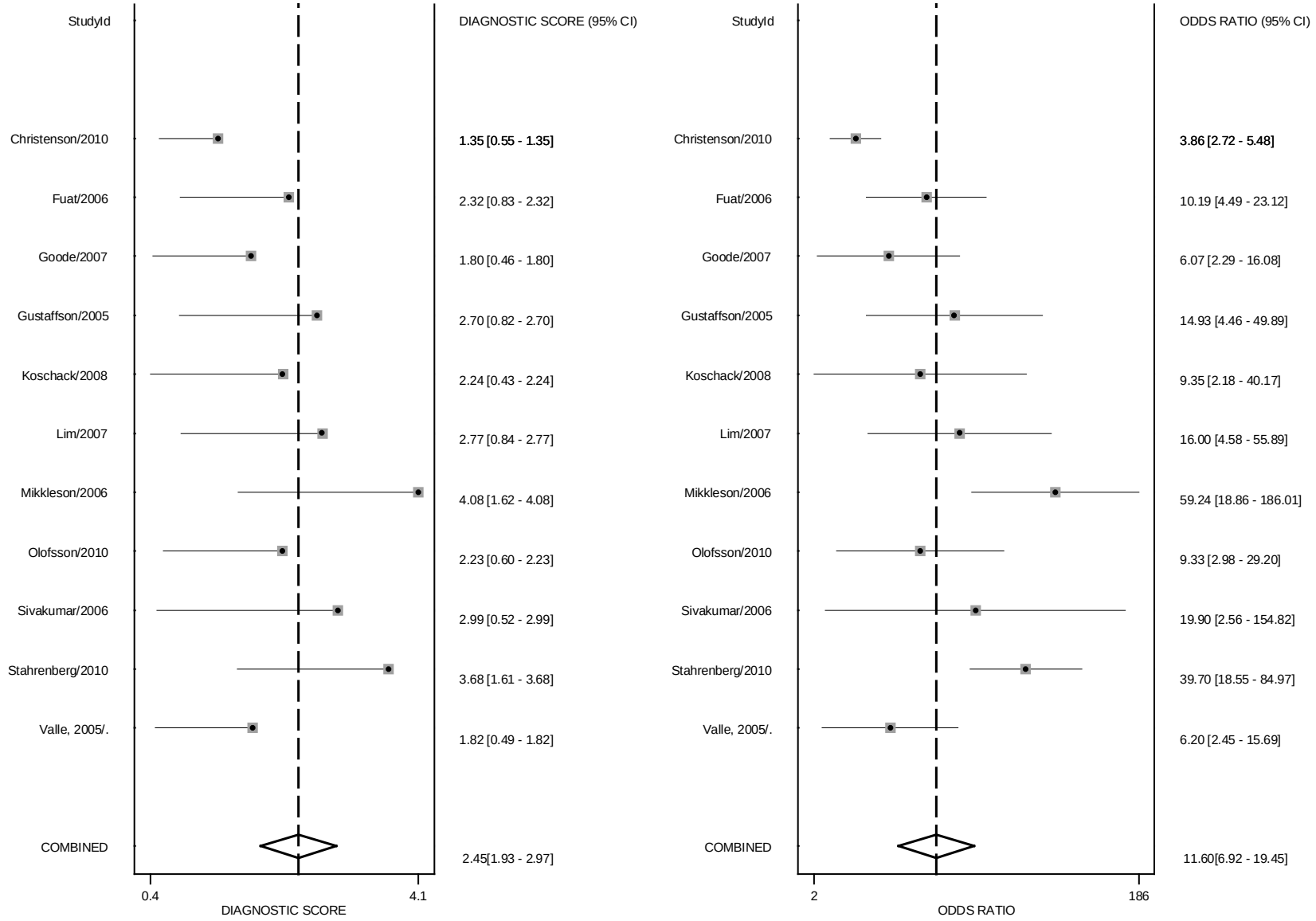


Figure I-18. Summary forest plot of LogDOR and DOR (PC NTProBNP, lowest cut-point), bivariate mixed effect model

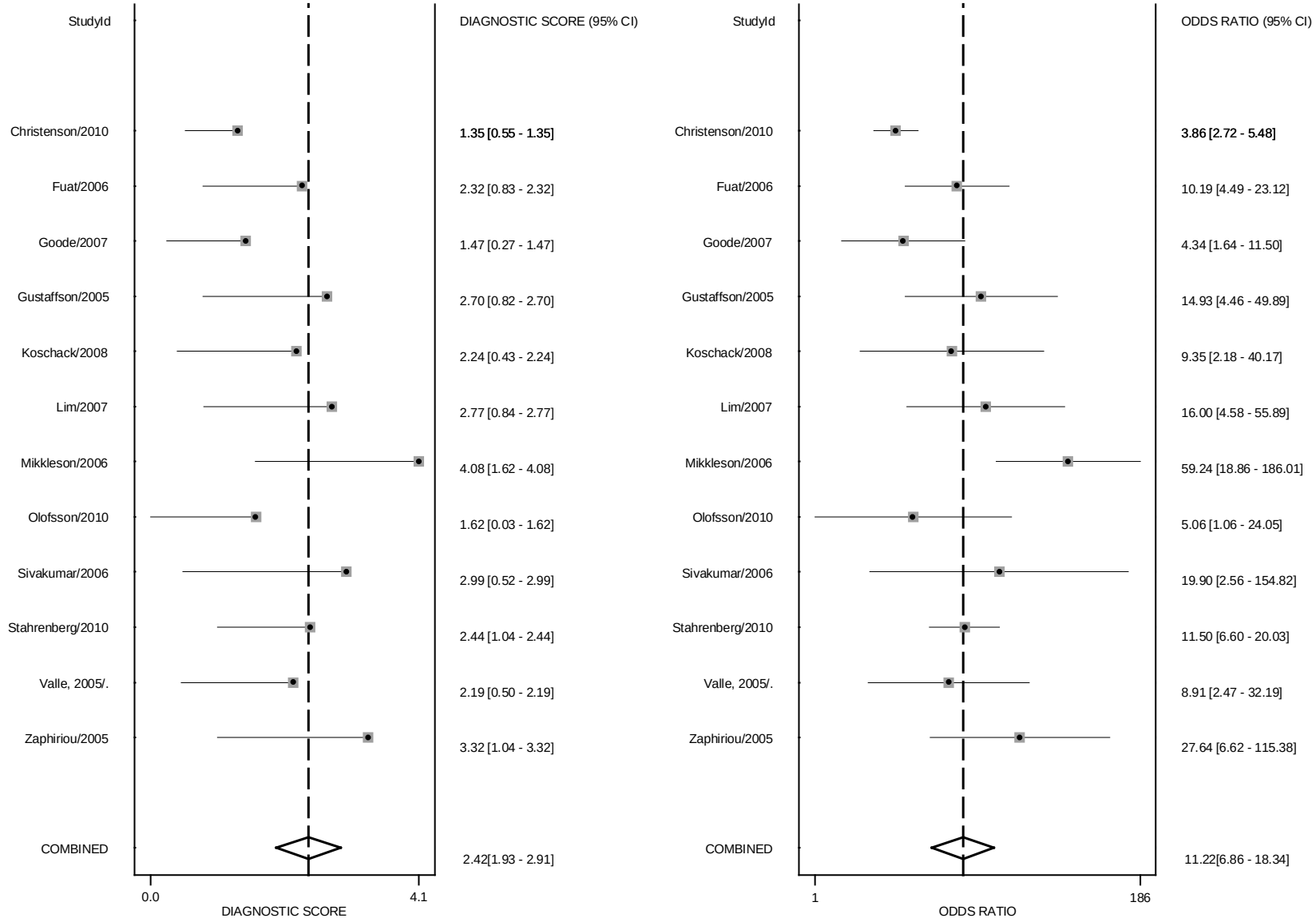


Figure I-19. Summary ROC-curve (PC NTProBNP, optimum cut-point), bivariate mixed effect model

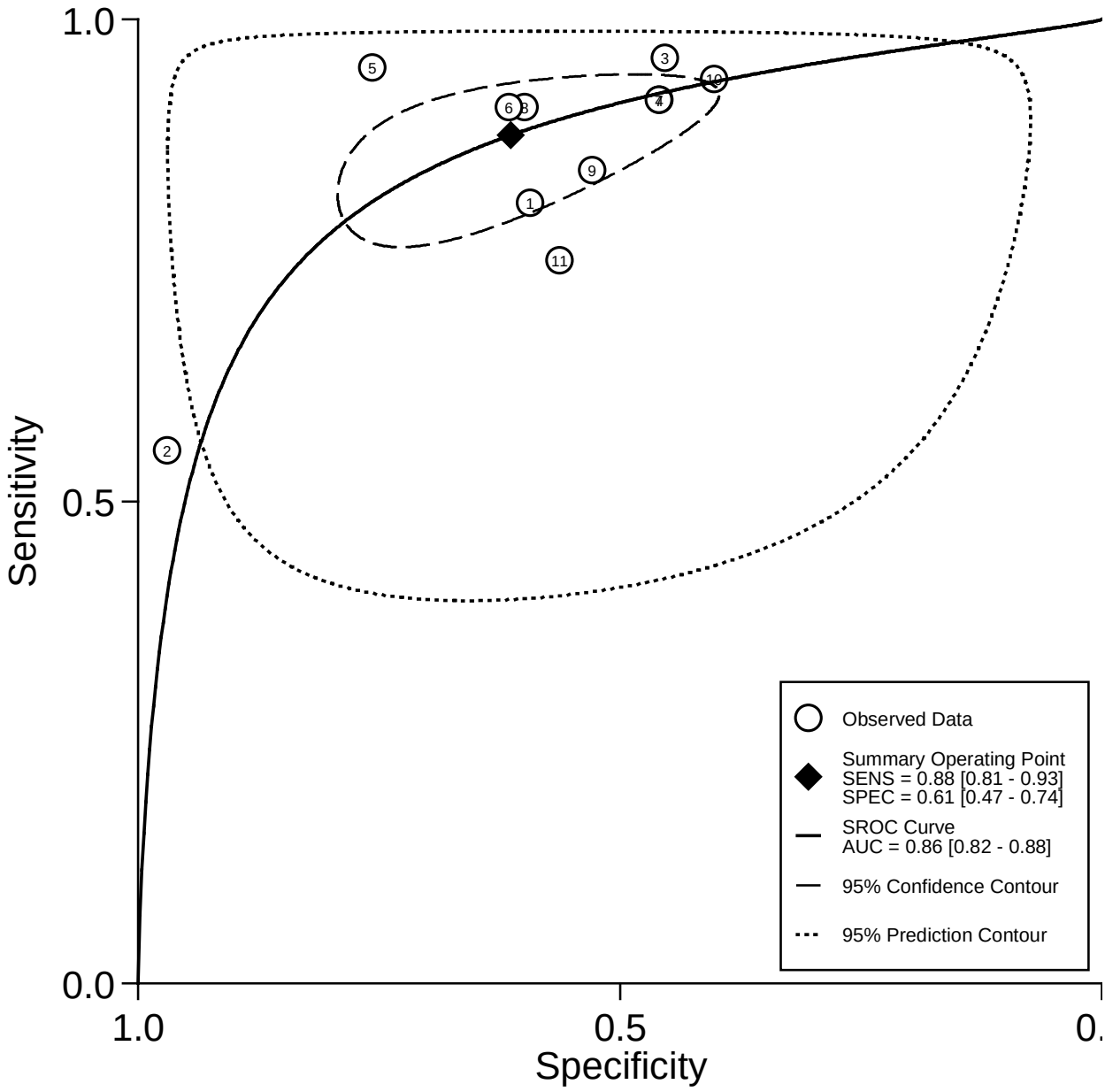


Figure I-20. Summary ROC-curve (PC NTProBNP, lowest cut-point), bivariate mixed effect model

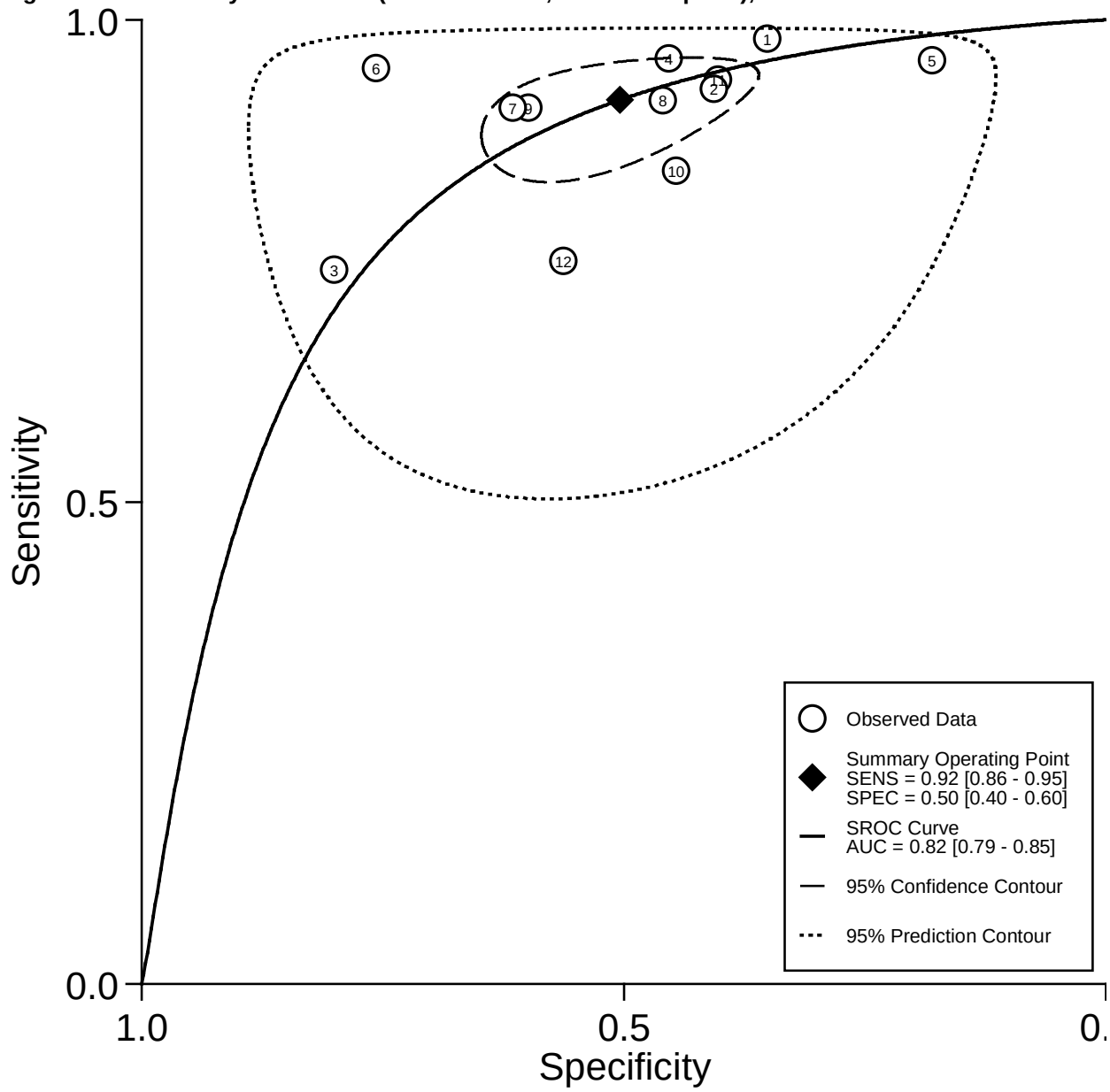


Table I-5. Risk of bias and applicability in all diagnosis studies using BNP in primary care

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Aspromonte,[2] 2006	?	?	?	✔	✘	✘	✘
Fuat,[5] 2006	?	✘	✔	✔	✘	✔	✔
Arques,[1] 2005	✔	✘	✔	✔	✘	✔	✔
Zaphiriou,[12] 2005	✔	?	✔	✔	✘	✘	✘
Jeyaseelan,[6] 2007	?	✔	✔	✔	✘	✔	✔
Park,[11] 2010	?	✘	?	✔	✘	✔	✔
Christenson,[4] 2010	✔	✔	✔	✔	✘	✔	✔
Murtagh,[10] 2012	?	?	?	?	?	?	?
Macabasco-O'Connell,[8] 2010	?	✘	✔	✔	✘	✔	✔
Mak,[9] 2008	?	?	✔	✔	✘	✔	✔
Barrios,[3] 2011	✔	?	✔	✔	✘	✘	✘
Kelder,[7] 2011	✔	✔	✘	✔	✔	✔	✔

✔ = Low Risk ✘ = High Risk ? = Unclear

Table I-6. Risk of bias and applicability in all diagnostic studies using NT-ProBNP in primary care

Author	Risk of Bias				Applicability Concerns		
	Patient selection	Index Test	Reference Standard	Flow & Timing	Patient selection	Index Test	Reference Standard
Hobbs,[17] 2004	✔	✘	✔	✔	✔	✔	✔
Nielsen,[21] 2004	✔	✘	✘	✔	✔	✔	✔
Gustafsson,[15] 2003	?	✔	✔	✔	?	✔	✔
Lim,[19] 2007	?	✘	✔	✔	?	✔	✘
Shelton,[23] 2006	✔	✘	✔	✔	✘	✘	✘
Mikkelsen,[20] 2006	✔	?	✔	✔	✘	✘	✘
Fuat,[5] 2006	?	✘	✔	✔	✘	✔	✔
Sivakumar,[24] 2006	✔	✘	✔	✔	✘	✔	✔
Gustafsson,[16] 2005	?	✔	✔	✔	✘	✘	✘
Valle,[26] 2005	?	?	?	?	✘	✘	✘
Kelder,[27] 2011	?	✔	✔	?	✔	✔	✔
Zaphiriou,[12] 2005	✔	?	✔	✔	✘	✘	✘
Park,[11] 2010	?	✘	?	✔	✘	✔	✔
Christenson,[4] 2010	✔	✔	✔	✔	✘	✔	✔
Olofsson,[22] 2010	✘	✔	✔	✔	✘	✔	✔
Goode,[14] 2008	?	✘	✔	✔	?	✔	✔
Koschack,[18] 2008	?	✘	?	✔	✘	✔	✔
Goode,[13] 2007	?	?	✔	✔	✘	✘	✘
Stahrenberg,[25] 2010	?	✔	?	✔	✘	✔	✔
Kelder,[7] 2011	✔	✔	✘	✔	✔	✔	✔

✔ = Low Risk ✘= High Risk ? = Unclear

Table I-7a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008	Sensitivity	Case-series (n=7), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=2,319	0.8 (0.71-0.89)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Mak,[9] 2008 Zaphiriou,[12] 2005	Specificity	Case-series (n=7), cohort (n=1)	Low	Direct – Specificity is a tool used and understood by clinicians	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=2,319	0.61 (0.43-0.80)	Moderate	Moderate

Table I-7b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=9), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3,439	0.84 (0.77-0.92)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Fuat,[5] 2006 Jeyaseelan,[6] 2007 Macabasco-O'Connell,[8] 2010 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Specificity	Case-series (n=9), cohort (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3,439	0.54 (0.42-0.66)	Moderate	Moderate

Table I-7c. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on manufacturer cutpoint for diagnostic studies utilizing BNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Jeyaseelan,[6] 2007 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=7), cohort (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3,089	0.73 (0.63-0.84)	High	High
Arques,[1] 2005 Aspromonte,[2] 2007 Barrios,[3] 2011 Christenson,[4] 2010 Jeyaseelan,[6] 2007 Mak,[9] 2008 Murtagh,[10] 2012 Zaphiriou,[12] 2005	Specificity	Case-series (n=7), cohort (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3,089	0.67 (0.50-0.85)	Moderate	Moderate

Table I-8a. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on optimal cutpoint for diagnostic studies utilizing NT-proBNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustafsson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikklesen,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005	Sensitivity	Case-series (n=9), cohort (n=1), unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	Consistent – range of estimates is small	n=3,321	0.86 (0.79-0.93)	High	High
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustafsson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikklesen,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005	Specificity	Case-series (n=9), cohort (n=1), unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but heterogeneity is large	No evidence to suggest	n=3,321	0.58 (0.42-0.75)	Moderate	Moderate

Table I-8b. Strength of evidence estimates of two primary outcomes, sensitivity and specificity, based on lowest cutpoint for diagnostic studies utilizing NT-proBNP in primary care settings

Included studies	Outcome	Study design	GRADE Risk of Bias*	GRADE Consistency	GRADE Directness	GRADE Precision	GRADE Publication bias	# of patients	Effect size	GRADE of evidence for outcome	Overall GRADE
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustafsson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikklesen,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005 Zaphiriou,[12] 2005	Sensitivity	Case-series (n=10), cohort (n=1), unknown (n=1)	Low	Consistent – range of estimates is small	Direct – Sensitivity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but hetero-geneity is large	Consistent – range of estimates is small	n=3,627	0.90 (0.85-0.95)	Moderate	Moderate
Christenson,[4] 2010 Fuat,[5] 2006 Goode,[13] 2007 Gustafsson,[16] 2005 Koschack,[18] 2008 Lim,[19] 2007 Mikklesen,[20] 2006 Olofsson,[22] 2010 Sivakumar,[24] 2006 Stahrenberg,[25] 2010 Valle,[26] 2005 Zaphiriou,[12] 2005	Specificity	Case-series (n=10), cohort (n=1), unknown (n=1)	Low	Inconsistent – range of estimates is large	Direct – Specificity is a tool used and understood by clinicians	Imprecise – confidence interval is small, but hetero-geneity is large	No evidence to suggest	n=3,321	0.5 (0.41-0.60)	Moderate	Moderate

*QUADAS2

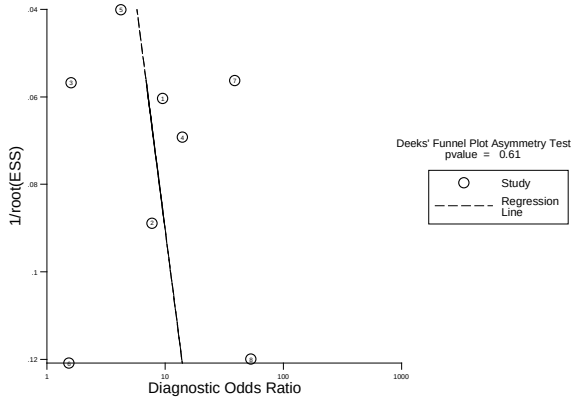
Table I-9. Summary test statistics of publication bias using log diagnostic odds ratios (logDOR), presented separately for different cut points.

Assay	Groups	n study	Deeks'	
			Coef.	P value
Primary care				
BNP	Manufacturer cut point	8	10.91	0.614
	Lowest cut point	10	6.33	0.800
	Optimum cut point	8	8.23	0.677
NT-proBNP	Manufacturer cut point	2	-	-
	Lowest cut point	12	13.77	0.202
	Optimum cut point	11	14.98	0.212

Background: The Deeks' method[28] assesses the publication bias by performing linear regression of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry in diagnostic meta-analyses and a non-zero slope coefficient is suggestive of significant small study bias (p-value <0.10). Based on the information provided in the attached table, publication bias was not significant for any of the cutpoints. The table also shows that there were insufficient studies to assess publication bias in NT-proBNP (primary care- Manufacturers cut-point).

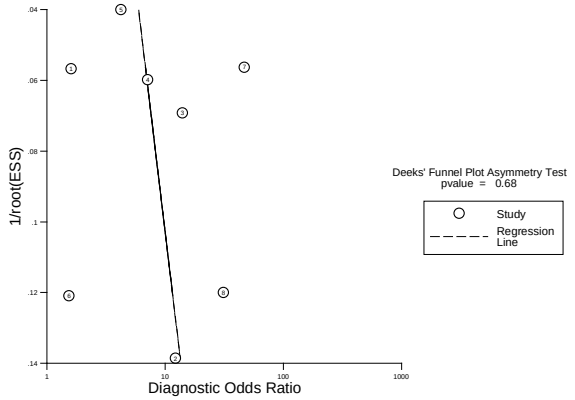
Figure I-21. Primary care publication bias: BNP and NT-proBNP

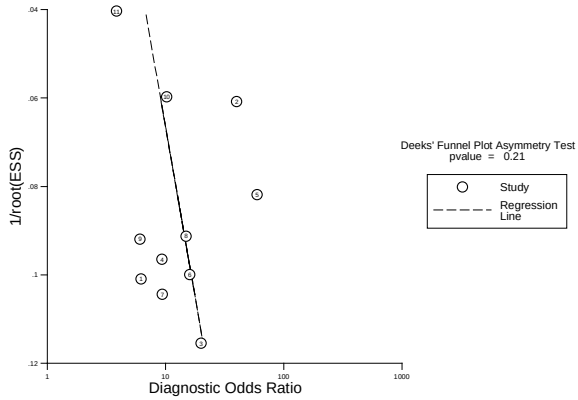
BNP



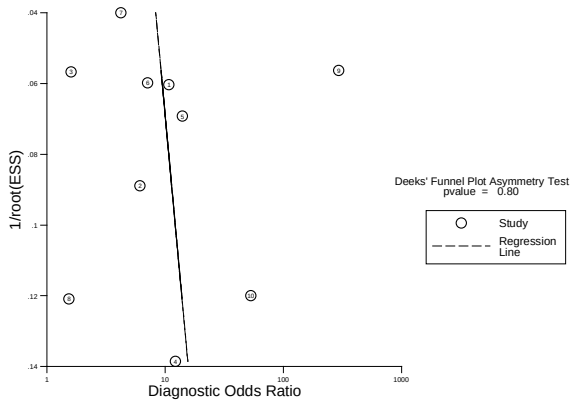
NT-ProBNP

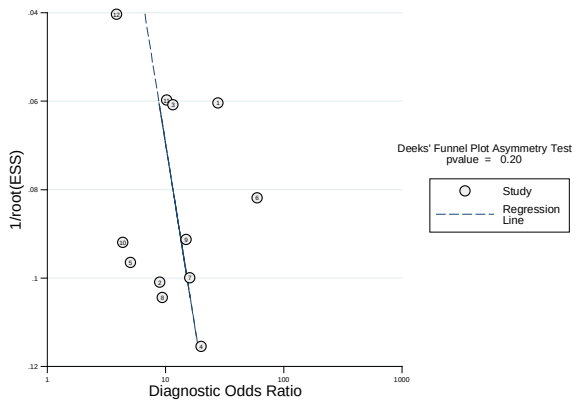
Manufacturer cut point





Optimum cut point





Lowest cut point

Appendix I Reference List

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Appendix J. Key Question 3 Evidence Set

Table J-1. Risk of bias for prognostic studies using the Hayden Criteria for decompensated population assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Maisel,[1] 2004	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Logeart,[2] 2004	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Aspromonte,[3] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Stoiser,[4] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Cournot,[5] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Sun,[6] 2007	√	√	√	√	√	√	√	√	√	√	?	X	√	X	X	√	√
Gegenhuber,[7] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Kellett,[8] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	?	?	√	√
Valle,[9] 2005	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dokainish,[10] 2005	√	√	√	X	?	√	√	√	√	√	√	X	X	X	X	√	√
DiSomma,[11] 2010	√	√	X	?	?	√	√	NA	√	NA	√	X	√	√	?	√	√
Zairis,[12] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Reichlin,[13] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Faggiano,[14] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	X	?	√	√
Farmakis,[15] 2010	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dunlay,[16] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Singer,[17] 2009	√	√	√	√	X	√	√	√	√	√	√	X	√	X	X	√	√
Parissis,[18] 2009	√	X	?	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Cohen-Solal,[19] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X
Dhaliwal,[20] 2009	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Nunez,[21] 2008	√	√	√	?	?	√	√	NA	?	NA	?	?	√	X	X	√	√
Feola,[22] 2008	√	√	√	√	√	√	√	NA	√	NA	√	?	X	X	X	√	√
Cournot,[23] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Valle,[24] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X

Table J-1. Risk of bias for prognostic studies using the Hayden Criteria for decompensated population assessing BNP (continued)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Parissis,[25] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	?	?	√	√
Valle,[26] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	X	X	X	√	√
Dieplinger,[27] 2009	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Nunez,[28] 2010	√	√	√	?	?	√	√	√	?	?	√	X	√	?	?	√	√
Pimenta,[29] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Noue,[30] 2011	√	√	√	?	?	√	√	√	?	?	√	X	X	X	X	√	√
Nahum,[31] 2010	√	√	√	√	√	?	√	√	√	√	√	X	X	X	√	√	√
Rychli,[32] 2011	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√	√	√
Arques,[33] 2011	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Allen,[34] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Coyne,[35] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Maisel,[36] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Arenja,[37] 2012	√	√	√	?	?	√	√	√	?	?	√		√	√	√	√	√
Neuhold,[38]2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Sakhuja,[39] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Maisel,[40] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Boisot,[41] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Noveanu,[42] 2011	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Rehman,[43] 2008	√	√	√	√	√	√	√	√	√	√	X	X	√	X	X	√	√
Peacock,[44] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest;
2. a) completeness of follow-up described, b) completeness of follow-up adequate;
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported;
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided;
5. a) confounders measured, b) confounders accounted for;
6. a) analysis described;
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✖ = High Risk ? = unclear

Table J-2. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (up to 31 days)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Peacock[44] 2011 BACH	Cohort Patients with acute HF	n=466 mean age: 70.8y (14) 58.6% male	ADM mean: 764 (402-1,415)** D/C mean: NA Cutpoint: NA	logBNP, logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	14d All-cause mortality (NR)	Cox proportional hazards	logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	logBNP: Chi-square=1 p=0.768 c index=0.513
Kellett[8] 2008	Unknown Patients with suspected HF	n=410 mean age: 76.2y (10.6) 59.5% male	ADM mean: survivors=549 (410) non-survivors=806 (437) D/C mean: NR Cutpoint: >700	BNP, 30d risk score, cancer, being unwell before HF, WCC>12.5 X 109/l, unable to stand unaided, serum Na	30d mortality (41, 410)	Multivariable logistic regression	30d risk score, cancer, being unwell before HF, WCC >12.5 X 109/l, unable to stand unaided, serum Na	OR=NR
Singer[17] 2009	RCT Patients presenting to ED with signs and symptoms of HF	n=472 mean age: 64y (NR) 51.0% male	ADM mean: Experimental = 1,189 Control=1,096 D/C mean: NR Cutpoint: NR	Serial BNP testing, age, gender, BUN, creatinine, systolic BP, heart rate	30d In-hospital mortality (NR)	Multivariable logistic regression	Age, gender, BUN, creatinine, systolic BP, heart rate	Knowledge of ADM and serial measurements vs. control: OR=0.6 (0.2-2.3), p=NS
				Serial BNP testing, age, gender, BUN, creatinine, systolic BP, heart rate	30d 30d mortality	Multivariable logistic regression	Age, gender, BUN, creatinine, systolic BP, heart rate	Knowledge of ADM and serial measurements vs. control: OR=0.6 (0.2-1.8), p=NS

Table J-2. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (up to 31 days) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y (73-85)** 60% male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 24h, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariate cox regression	Age, cTnT, eGFR, NYHA	24 hour: HR=NR per 100 pg/mL increase, p=significant
				BNP, NT-proBNP at 48h, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariate cox regression	age, cTnT, eGFR, NYHA	48h: HR=NR per 100 pg/mL increase, p=significant
				BNP, NT-proBNP D/C, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariate cox regression	age, cTnT, eGFR, NYHA	D/C: HR=NR per 100 pg/mL increase, p=significant

Table J-2. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (up to 31 days) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cohen-Solal[19] 2009 SURVIVE	Cohort Patients with severe acutely decompensated HF (received either levosimendan or dobutamine)	n=1,038 mean age: nonresponders = 66y(12) responders= 67y(12) 69.5% male	ADM mean: nonresponders = 1,462 (1,433) responders= 1,842 (1700) D/C mean: day 5, 768 Cutpoint: decrease of ≥30% by day 5	Change in BNP level by day 5, systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	31d Mortality (NR)	Multivariate cox regression	Systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	Change decrease >30% day 5: HR=0.33 (p<0.0001) (Reference group is non-responders (reduction in BNP level of <30%), so HR showing risk reduction in responders (reduction in BNP level of ≥30%)
				Day 5 BNP level, systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	31d Mortality (NR)	Multivariate cox regression	Systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	Change BNP <800 pg/mL day 5 HR=0.31 Reference group is non-responders (BNP level of >800 at day 5), so HR showing risk reduction in responders (BNP level of ≤800 at day 5)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; BACH = Biomarkers in Acute Heart Failure; BB = betablocker; BNP = B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; 95% CI, = confidence interval; cTnT = cardiac troponin T; d = day(s); D/C = discharge; ED = emergency department; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RCT = randomized controlled trial; SD = standard deviation; SURVIVE = Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; vs. = versus; WCC = white cell count; y = year(s)

Table J-3. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (2 to 3 months)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Maisel[1] 2004 REDHOT study	Cohort Patients presenting in ED with CHF	n=464 mean age: 64y(51-76)** 53.9% male	ADM Mean: 766 D/C Mean: 976 Cutpoint: 200	logBNP, NYHA, ED disposition (initial intent, actual disposition)	90d All-cause mortality (36, 452)	Multivariable logistic regression	NYHA, ED disposition (initial intent, actual disposition)	ADM: logOR=1.537 (SE = 0.42),
Peacock[44] 2011 BACH	Cohort Patients with acute HF	n=466 mean age: 70.8y(14) 58.7% male	ADM Mean: BNP 764 (402-1,415) D/C Mean: NA Cutpoint: NA	logBNP, logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	90d 90d mortality (NR)	Cox proportional hazards	logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	ADM: log BNP: Chi-square 12.5 p<0.001 c index 0.636
Maisel[40] 2010 BACH	Cohort Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y(13.8) 62.5% male	ADM Mean: NR D/C Mean: NR Cutpoint: NR	log BNP, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	age, gender, BMI, creatinine	ADM: HR=1.3 (0.9-1.9) per increase of 1 IQR
				log BNP, logMR-proADM, troponin	90d All-cause mortality (65, 568)	Multivariable cox regression	logMR-proADM, troponin, age, gender, BMI, creatinine	ADM: HR=0.9 (0.6 -1.4) (p=NS) per increase of 1 IQR
Boisot[41] 2008	Cohort Patients admitted to hospital with a diagnosis of acute decompensated HF	n=150 mean age: NR 99% male	ADM Mean: 635 (304, 1,501)** D/C Mean: 399 (174, 400)** Cutpoint: decrease of <10%	Decrease BNP<10%, age>65, BUN, ST2 decrease, EF, rales, wheezing murmurs, CAD, MI, AF	90d All-cause mortality (24, 150)	Multivariable logistic regression	Age>65, BUN, ST2 decrease, EF, rales, wheezing murmurs, CAD, MI, AF	Change decrease 10%: OR=1.15 (0.36-3.63), (p =0.817)

Abbreviations: ADM = admission; AF = atrial fibrillation; BACH = Biomarkers in Acute Heart Failure; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; CHF = congestive heart failure; 95% CI, = confidence interval; d = day(s); D/C = discharge; ED = emergency department; EF = ejection fraction; HF = heart failure; HR = hazard ratio; IQR = interquartile range; MI = myocardial infarction; MR-proADM = midregional pro-adrenomedullin; n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; REDHOT = Rapid Emergency Department Heart Failure Output Trial; SD = standard deviation; y = year(s)

Table J-4. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (6 to 11 months)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Núñez[28] 2010	Cohort Patients admitted with acute HF	n=1,111 mean age: 73y (11) 49.0% male	ADM mean: 237** (97-434) D/C mean: NR Cutpoint: 350	logBNP, logCA125, age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARBs, BB	6m All-cause mortality (181, 1,111)	Multivariable cox regression	Age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARBs, BB	ADM: HR=1.40 (1.08 to 1.79)
Núñez[21] 2008	Cohort Patients with acute HF	n=569 mean age: 73.8y (10.6) 47.6% male	311 (425) D/C mean: NR Cutpoint: NR	BNP, age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	9m ** All-cause mortality (156, 569)	Multivariable cox regression	Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	ADM: HR=1.05 (1.03 to 1.08), per unit Increase in BNP by increments of 100 pg/mL
	Cohort Q2=BNP level (85-123)	n=114 mean age: 73y (10y) 39.5% male	ADM mean: NR D/C mean: NR Cutpoint: 85-123	BNP quintiles,age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	9m ** All-cause mortality (23, 114)	Multivariable cox regression	Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	ADM: HR=2.75 (1.17 - 6.46)
	Cohort Q3=BNP level (123-250)	n=114 mean age: 74y (10) 48.2% male	ADM mean: NR D/C mean: NR Cutpoint: 123-250	BNP quintiles, age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	9m ** All-cause mortality (30, 114)	Multivariable cox regression	Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	ADM: HR=2.76 (1.20 - 6.33)
	Cohort Q4=BNP level (251-490)	n=113 mean age: 73y (12) 50.0% male	ADM mean: NR D/C mean: NR Cutpoint: 251-490	BNP quintiles,age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	9m ** All-cause mortality (34, 113)	Multivariable cox regression	Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	ADM: HR=3.38 (1.49 - 7.68)
	Cohort Q5=BNP level (495-3240)	n=113 mean age: 77y(9) 55.8% male	ADM mean: NR D/C mean: NR Cutpoint: 495-3,240	BNP quintiles, age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	9m ** All-cause mortality (62, 113)	Multivariable cox regression	Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, BB, systolic BP, serum creatinine, Hb	ADM: HR=5.82 (2.62 - 12.97)

Table J-4. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (6 to 11 months) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Allen[34] 2011 EVEREST Study	Case series Secondary analysis of RCT data Patients hospitalized with HF (BNP 500-999 vs. BNP <500)	n=1,047 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y*, diabetes*, history of stroke*, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ*	24w All-cause mortality (NR)	Multivariable cox regression	Age >70y*, diabetes*, history of stroke*, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ*	ADM: HR=1.84 (1.25, 2.71)
	Case series Patients hospitalized with HF (BNP 1,000 + vs. BNP <500)	n=1,112 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y*, diabetes*, history of stroke*, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ*	24w All-cause mortality (NR)	Multivariable cox regression	Age>70y*, diabetes*, history of stroke*, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ*	ADM: HR=3.22 (2.27, 4.55)
Cohen-Solal[19] 2009 SURVIVE	Cohort Patients with severe acutely decompensated HF (received either levosimendan or dobutamine)	n=1,038 mean age: nonresponders= 66y(12) responders= 67y(12) 69.5% male	ADM mean: nonresponders= 1,462 (1,433) responders= 1,842 (1,700) D/C mean: day 5, 768 Cutpoint: decrease of ≥30% by day 5	Change in BNP level, systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	180d 180d mortality (NR)	Multivariable cox regression	Systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	Change decrease >30% day 5: HR=0.54, (p =<0.0001)
			ADM mean: nonresponders= 1,462 (1,433) responders= 1,842 (1,700) D/C mean: 768 Cutpoint: 800	BNP level, systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	180d 180d mortality (NR)	Multivariable cox regression	Systolic BP, creatinine, history of HF, ACE inhibitor, BB, treatment allocation	Change BNP <800 pg/mL day 5: HR=0.59,(p=0.0009)

Table J-4. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (6 to 11 months) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cournot,[23] 2008	Cohort Elderly patients ≥70y hospitalized for decompensated HF (high risk group, BNP at D/C≥ 360 pg/mL or decrease of <50 %)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: 605 (median) Cutpoint: 360 pg/mL 50% change	logBNP BNP (grp 1 = D/C <360 pg/mL AND decrease >50%, grp 2=neither 1 or 3 and grp 3=D/C >360 pg/mL and decrease <50% or increase, HT*, diabetes*, history of CAD*, valvular HD, chronic kidney disease, COPD*, AF*, sodium*, anemia*, C reactive protein*, BB*, ACE inhibitor/ARB, antiplatelet*	7m** all-cause mortality (NR)	Multivariable cox regression	Age, sex, serum creatinine, NYHA class at D/C, LVEF, and length of hospitalization	Intermediate risk grp 2 vs. grp 1: HR=8.53 (1.71-42.43) (p=NR)
			ADM mean: NR D/C mean: 605 (median) Cutpoint: 360 pg/mL 50% change	logBNP BNP (grp 1 = D/C <360 pg/mL AND decrease >50%, grp 2=neither 1 or 3 and grp 3=D/C >360 pg/mL and decrease <50% or increase, HT*, diabetes*, history of CAD*, valvular HD, chronic kidney disease, COPD*, AF*, sodium*, anemia*, C reactive protein*, BB*, ACE inhibitor/ARB, antiplatelet*	7m** All-cause mortality (NR)	Multivariable cox regression	Age, sex, serum creatinine, NYHA class at D/C, LVEF and length of hospitalization	Change :D/C ≥ 360 pg/mL and decrease of <50% or increase (grp 3 vs. grp 1) High risk grp: HR=20.83 (4.46-97.21) (p=NR)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; ARB = angiotensin receptor blockers; BB = betablocker; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CA125 = carbohydrate antigen 125; CAD = coronary artery disease; 95% CI, = confidence interval; COPD = chronic obstructive pulmonary disease; d = day(s); D/C = discharge; EVEREST = Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan; grp = group; Hb = hemoglobin; HD = heart disease; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; m = month(s); n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; SD = standard deviation; SURVIVE = Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; w = week(s); y = year(s)

Table J-5. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (12 to 23 months)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Arenja[37] 2011 BASEL	Cohort Patients with acute HF	n=377 mean age: 79y (72 - 84)** 53% male	ADM mean: 848(471–639) D/C mean: NR Cutpoint: per 100 pg/mL	BNP, NYHA, BMI, age, cTnI, HT, DM, smoking, CAD, previous MI, creatinine	12m All-cause mortality (130, 377)	Multivariable cox regression	NYHA, BMI, age, cTnI, HT, DM, smoking, CAD, previous MI, creatinine	ADM: HR=1.01 (1.00, 1.05) per 100 pg/mL, p=0.02
Reichlin[13] 2010 BASEL	Cohort Patients presenting to the ED with acute dyspnea and acute HF	n=377 mean age: 79y (72-84)** 53% male	ADM mean: 847** D/C mean: NR Cutpoint: >847	BNP, MPO, age, sex, BMI, HT, DM, smoking, CAD, history of MI and HF, NYHA class	12m All-cause mortality (130, 377)	Multivariable cox regression	CV risk factors (age, sex, BMI, HT, DM, smoking, CAD, history of MI and HF), NYHA class	ADM: HR=1.65 (1.15-2.37)
Dieplinger,[27] 2009 Mueller et al, 2005; Gegenhuber et al, 2006	Cohort Patients consulting the ED with acute HF	n=137 mean age: survivors= 75y (65,80)** deceased= 79y (72-83)** 93% male	ADM mean: NR D/C mean: NR Cutpoint: >1,250	BNP, adiponectin, CRP, renal dysfunction	12m All-cause mortality (41, 137)	Multivariable cox regression	Adiponectin, age, systolic BP, renal dysfunction, systolic dysfunction, NYHA class III/IV, arterial hypertension, CAD, smoking, BMI, CRP	ADM: RR=2.45 (1.29-4.65)
Gegenhuber[7] 2007 Mueller et al, 2005; Gegenhuber et al, 2006	Cohort Patients consulting the ED with acute HF	n=137 mean age: alive= 75y (65,80)** dead= 79y (72-83)** 93% male	ADM mean: alive=668** dead=1,461** D/C mean: NR Cutpoint: >1,250	BNP, advanced age, low systolic BP, renal dysfunction, systolic dysfunction, NYHA III/IV	12m All-cause mortality (41, 137)	Multivariable cox regression	Advanced age, low systolic BP, renal dysfunction, systolic dysfunction, NYHA III/IV	ADM: HR=3.34 (1.61 - 6.97)
Rehman[43] 2008 PRIDE	Cohort 346 patients with acute HF	n=346 mean age: 73y (13) 68% male	ADM Mean: 494 (203, 1,180)** D/C Mean: NR Cutpoint: >494	BNP, ST2, CRP, BNP, age, prior CHF, BB, ACE inhibitor, NYHA, systolic BP, creatinine	12m Mortality (97, 346)	Multivariable cox regression	ST2, CRP, NT-proBNP, age, prior HF, BB, ACE inhibitor, NYHA, BP, BMI, S3 gallop, rates on lung exam, creatinine, BUN, WCC, Hb, pleural effusion	ADM: HR=2.12 (1.37-3.27),

Table J-5. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (12 to 23 months) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Sakhuja[39] 2007 PRIDE	Cohort Patients with acute HF presenting to urban academic center	n=209 mean age: increased cTnT= 74.3y (11.6) no increased cTnT= 71.4y (14.9) 52% male	ADM mean: increase cTnT = 544** no-increase CTnT= 221** D/C mean: NR Cutpoint: 352	BNP, cTnT, age, GFR, NYHA class	12m All-cause mortality (NR)	Multivariable cox regression	cTnT, age, GFR, NYHA class	ADM: HR=2.53 (1.53-6.21)
Dunlay[16] 2009	Cohort HF patients	n=593 mean age: 76.4y (NR) 48% male	ADM mean: 350 (174-647)** D/C mean: NR Cutpoint: 350	BNP>350, age, BMI, creatinine clearance, NYHA III/IV, serum Na, systolic BP, CRP, cTnT	12m All-cause mortality (122,593)	Multivariable logistic regression	Age, BMI, creatinine clearance, NYHA, serum Na<135mmol/L, systolic BP	ADM: HR=1.29 (1.03-1.62)
Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y (73-85)** 60% male	ADM mean: 1,315 (759, 2,349)** D/C mean: NR Cutpoint: NR	BNP at 24h, age, cTn, eGFR, NYHA	12m All-cause mortality (60, 171)	Multivariable cox regression	age, cTn, eGFR, NYHA	24 hours: HR=1.02 (1.01-1.04) per 100 pg/mL increase, p = 0.013
				BNP at 48h, age, cTn, eGFR, NYHA	12m All-cause mortality (60, 171)	Multivariable cox regression	age, cTn, eGFR, NYHA	48 hours HR=1.03 (1.01-1.06) per 100 pg/mL increase, p=0.002
				BNP D/C, age, cTn, eGFR, NYHA	12m All-cause mortality (60, 171)	Multivariable cox regression	age, cTn, eGFR, NYHA	D/C: HR=1.02 (1.01-1.03) per 100 pg/mL increase, p<0.001

Table J-5. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (12 to 23 months) (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Coyne[35] 2011 COACH Study	Case series Secondary analysis of RCT Patients in hospital for symptomatic HF	n=706 mean age: 70.7y (11.5) 61.8% male	ADM mean: 674 (720) D/C mean: NR Cutpoint: NR	BNP at D/C, CES-D, type D	18m All-cause mortality (192, 706)	Multivariable cox proportional hazard regression	CES-D, type D	D/C: HR=1.588 (1.391-1.812)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; BASEL = B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation; BB = betablocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression; 95% CI, = confidence interval; COACH = Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure; CRP = C-reactive protein; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = cardiovascular; d = day(s); D/C = discharge; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; h = hour(s); Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; m = month(s); mmol/L = millimoles per liter; MI = myocardial infarction; MPO = myeloperoxidase; n=number; Na = sodium; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; PRIDE = Pro-BNP Investigation of Dyspnea in the Emergency Department; RR = relative risk; SD = standard deviation; w = week(s); WCC = white cell count; y = year(s)

Table J-6. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality (24 months and greater)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Rychli[32] 2011 Niessner, 2009	Cohort Patients with advanced HF (symptoms of cardiac decompensation, NYHA class III or IV at time of ADM), LVEF <40%	n=351 mean age: 75y (63-82)** 66% male	ADM mean: 441 (231 - 842)** D/C mean: NR Cutpoint: >441	BNP, hepatocyte GF, PEDF, M-CSF, G-CSF, MCP-1, sFAS, sTWEAK	24m All-cause mortality (93, 351)	Multivariable cox regression	Hepatocyte GF, PEDF, M-CSF, G-CSF, MCP-1, sFAS, sTWEAK	ADM: HR=NR, p=0.003
Neuhold[38] 2010	Cohort Patients with chronic systolic HF	n=181 mean age: 70y (12) 65% male	ADM mean: 658.14 D/C mean: 460.54 Cutpoint: NR	BNP followup, copeptin, MR-proADM, MR-proANP, CT-proET-1	24m All-cause mortality (36, 181)	Multivariable cox regression	Age, gender, GFR, diabetes, ischemic etiology of HF	ADM: HR=1.57 (1.07, 2.30), per concentration unit increase
			ADM mean: 658.14 D/C mean: 460.54 Cutpoint: NR	BNP at D/C, copeptin, MR-proADM, MR-proANP, CT-proET-1	24m All-cause mortality (36, 181)	Multivariable cox regression	Age, gender, GFR, diabetes, ischemic etiology of HF	D/C: HR=1.46 (1.04, 2.05), per concentration unit increase
Stoiser[4] 2006	Cohort Patients diagnosed with chronic HF admitted to hospital	n=268 mean age: 71y (13) 67% male	ADM mean: 699 (811) D/C mean: NR Cutpoint: 448	D/C BNP, copeptin, age, history of diabetes, HT, CAD, kidney dysfunction, gender	24m Mortality (83, 268)	Multivariable cox regression	Copeptin, age, history of diabetes, HT, CAD, kidney dysfunction*, gender	D/C HR=NR, p=NS

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; 95% CI, = confidence interval; CT-proET-1 = C-terminal pro-endothelian-1 precursor fragment; D/C = discharge; G-CSF = granulocyte colony-stimulating factor; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; HT = hypertension; LVEF = left ventricular ejection fraction; m = month(s); MCP-1 = monocyte chemoattractant protein 1; M-CSF = macrophage colony-stimulating factor; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PEDF = pigment epithelium-derived factor; pg/mL = picograms per milliliter; PRIDE = Pro-BNP Investigation of Dyspnea in the Emergency Department; SD = standard deviation; sFAS = soluble apoptosis-stimulating fragment; sTWEAK = soluble tumor necrosis factor-like weak inducer of apoptosis; y = year(s)

Table J-7. Studies evaluating independent predictive value of BNP for the outcome cardiovascular mortality

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Zairis,[12] 2010	Cohort Patients hospitalized with acutely decompensated severe low-output chronic HF (NYHA class III/IV)	n=577 mean age: 74.2y(8.2) 68.3% male	ADM mean: 1,110.1 (410.7) D/C mean: NR Cutpoint: ≥ 952	BNP, age≥75y, acute pulmonary edema, LVEF<25%, GFR<30 ml/min, history of MI, chronic HF of ischemic etiology, AF or flutter, Hb (g/dl), serum cTnI, serum hs-CRP	31d Cardiac mortality (102, 577)	Multivariable cox regression	Age≥75y, acute pulmonary edema, LVEF<25%, GFR<30 ml/min, history of MI, CHF of ischemic etiology, AF or flutter, Hb (g/dl), serum cTnI, serum hs-CRP	ADM: HR=2.2 (1.5-3.7), p=0.002
Arques,[33] 2011	Cohort Aged >70y with severe, acute HF, all	n=207 mean age: 86y(NR) 32% male	ADM mean: survivors= 919 Non-survivors = 1,194 D/C mean: NR Cutpoint: >840	Serum albumin, serum TC*, logBNP, systolic BP*, serum creatinine*, creatinine clearance*, BUN, serum troponin I*, CRP*,serum albumin*	31d In hospital CV mortality (40, 207)	Multivariable stepwise logistic regression	Age, sex, heart rate, systolic BP, LVEF, serum Na	ADM: OR=5.1 (1.2-21.7), p=0.02
Nunez,[28] 2010	Cohort Patients admitted with acute HF	n=1111 mean age: 73y(11) 49% male	ADM mean: 237** (97-434) D/C mean: NR Cutpoint: 350	logBNP, logCA125, age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARB, BB	6m CV mortality (154, 1111)	Multivariable cox regression	Age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARB, BB	ADM: HR=1.48 (1.24-1.77), p<0.001
	Cohort Patients admitted with acute HF	n=1111 mean age: 73y(11) 49% male	ADM mean: 237** (97-434) D/C mean=NR Cutpoint: 350	logBNP, logCA125, age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARB, BB	6m HF mortality (99, 1111)	Multivariable cox regression	Age, gender, prior ADM for acute HF, acute HF category, systolic BP, ARB, BB	ADM: HR=1.47 (1.19-1.81), p<0.001
Sun,[6] 2007	Cohort Patients with acute HF (NYHA functional classes III & IV)	n=50 mean age: survivors= 67y(6) non-survivors= 66y(5) 62% male	ADM mean: 520 D/C mean: NR Cutpoint: <520	BNP, age, sex, duration of HF, LVEF and serum creatinine levels	12m HF mortality (12, 50)	Multivariable stepwise logistic regression	Age, sex, duration of HF, LVEF and serum creatinine levels	ADM: OR=1.21 (1.06-2.32), p<0.01

Table J-7. Studies evaluating independent predictive value of BNP for the outcome cardiovascular mortality (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Rychli,[32] 2011 Niessner, 2009	Cohort Patients with advanced HF (symptoms of cardiac decompensation, NYHA class III or IV at time of ADM), LVEF <40%	n=351 mean age: 75y(63-82)** 66% male	ADM mean: 441 (231-842)** D/C mean: NR Cutpoint: >441	BNP, HGF, PEDF, M-CSF,G-CSF, MCP-1, sFAS, sTWEAK	24m CV mortality (66, 351)	Multivariable cox regression	HGF, PEDF,M-CSF,G-CSF, MCP-1, sFAS, sTWEAK	ADM: HR=NR, p=0.015

Abbreviations: ADM = admission; AF = atrial fibrillation; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CA125 = carbohydrate antigen 125; 95% CI, = confidence interval; cTnI = cardiac troponin I; CV = cardiovascular; d = day(s); D/C = discharge; G-CSF = granulocyte colony-stimulating factor; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; hs-CRP = high-sensitivity c-reactive protein; LVEF = left ventricular ejection fraction; m = month(s); MCP-1 = monocyte chemoattractant protein 1; M-CSF = macrophage colony-stimulating factor; MI = myocardial infarction; n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; PEDF = pigment epithelium-derived factor; pg/mL = picograms per milliliter; SD = standard deviation; sFAS = soluble apoptosis-stimulating fragment; sTWEAK = soluble tumor necrosis factor-like weak inducer of apoptosis; vs. = versus; y = year(s)

Table J-8. Studies evaluating independent predictive value of BNP for the outcome of morbidity

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Singer[17] 2009	RCT Patients presenting to ED with signs and symptoms of HF	n=472 mean age: 64y (NR) 51% male	ADM Mean: Experimental= 1,189 Control=1,096 D/C mean: NR Cutpoint: NR	Serial BNP testing, age, gender, BUN, creatinine, systolic BP, heart rate	30d ICU ADM (NR)	Multivariable logistic regression	Age, gender, BUN, creatinine, systolic BP, HR	Knowledge of ADM and serial testing vs. control: ADM: OR=0.7 (0.2-2.1)
				Serial BNP testing, age, gender, BUN, creatinine, systolic BP, heart rate	30d HF reADM (NR)	Multivariable logistic regression	age, gender, BUN, creatinine, systolic BP, HR	Knowledge of ADM and serial testing vs. control: OR=0.8 (0.5-1.3)
Allen[34] 2011 EVEREST Study	Case series Secondary analysis of RCT data Patients hospitalized with HF (BNP 500-999 vs. BNP <500)	n=1,047 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Unfavorable QoL (NR)	Modified poisson regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	D/C: RR=1.15 (0.81, 1.62)
	Case series Patients hospitalized with HF (BNP 1,000+ vs. BNP <500)	n=1,112 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Unfavorable QoL (NR)	Modified poisson regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	D/C: RR=1.22 (0.85, 1.75)
Allen 2011 EVEREST Study (cont'd)	Case series Patients hospitalized with HF (BNP 500-999 vs. BNP <500)	n=1,047 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Rehospitalization (NR)	Multivariable cox regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	D/C: HR=1.51 (1.18, 1.93)
	Case series Patients hospitalized with HF (BNP 1,000+ vs. BNP <500)	n=1,112 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Rehospitalization (NR)	Multivariable cox regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	D/C: HR=1.70 (1.34, 2.15)

Table J-8. Studies evaluating independent predictive value of BNP for the outcome of morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Neuhold[38] 2010	Cohort Patients with chronic systolic HF	n=181 mean age: 70y (12) 65% male	ADM mean: 658.14 D/C mean: 460.54 Cutpoint: NR	BNP D/C, copeptin, MR-proADM, MR-proANP, CT-proET-1	24m Rehospitalization for worsening HF (72, 181)	Multivariable cox regression	Age, gender, GFR, diabetes, ischemic etiology of HF	D/C: HR=NR, p=NS
Stoiser[4] 2006	Cohort Patients diagnosed with chronic HF admitted to hospital	n=268 mean age: 71y (13) 67% male	ADM mean: 699 (811) D/C mean: NR Cutpoint: 448	BNP at D/C, copeptin, age, history of diabetes, HT, CAD, kidney dysfunction, gender	24m Chronic HF reADM (122, 268)	Multivariate cox regression	Age, history of diabetes, HT, CAD, kidney dysfunction*, gender	D/C: chi-square 18, p=0.0001

Abbreviations: ADM = admission; BB = betablocker; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; 95% CI, = confidence interval; CT-proET-1 = C-terminal pro-endothelian-1 precursor fragment; CV = cardiovascular; d = day(s); D/C = discharge; ED = emergency department; EVEREST = Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan; HF = heart failure; HR = hazard ratio; hs-CRP = high-sensitivity c-reactive protein; HT = hypertension; ICU = intensive care unit; KCCQ = Kansas City Cardiomyopathy Questionnaire; m = month(s); MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; QoL = quality of life; RR = relative risk; SD = standard deviation; vs. = versus; w = week(s); y = year(s)

Table J-9. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and morbidity

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
DiSomma[11] 2010	Cohort Patients presenting to ED with acute decompensated HF	n=247 mean age: 76y (12) 47.8% male	ADM mean: 822(412-1,390)** D/C mean: 325(160-725)** Cutpoint: D/C BNP >300 pg/mL	BNP level at D/C, decrease in BNP level at D/C	180d Composite (all-cause mortality or rehospitalization) (78, 247)	Multivariable logistic regression	Decrease in BNP level at D/C, interaction between BNP level at D/C and decrease in BNP level at D/C, others (NR)	D/C greater than or equal to 300 pg/mL: OR=1.93 (1.03 - 3.59)
	Cohort Patients presenting to ED with acute decompensated HF	n=247 mean age: 76y (12) 47.8% male	ADM mean: 822(412-1,390)** D/C mean: 325(160-725)** Cutpoint: decrease of 46 %	Decrease in BNP level at D/C, BNP level at D/C	180d Composite (all-cause mortality or rehospitalization) (78, 247)	Multivariable logistic regression	BNP level at D/C, Interaction between BNP level at D/C and decrease in BNP level at D/C, others (NR)	Change decrease less than 46%: OR=5.06 (2.78 - 9.22)
	Cohort BNP <300 & decrease of <46% vs. BNP <300 & decrease of >46%	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: less than 300 pg/mL at D/C and decrease greater than 46%	BNP level at D/C, decrease in BNP level at D/C	180d Composite (all-cause mortality or rehospitalization) (NR)	Multivariable logistic regression	Decrease in BNP level at D/C	Change greater than 46% and D/C BNP less than 300 pg/mL: OR=4.75 (1.76 - 12.83), p<0.002
	Cohort BNP >300 & decrease of <46% vs. BNP <300 & decrease of >46%	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: greater than 300 pg/mL at D/C and decrease of less than 46%	BNP level at D/C, decrease in BNP level at D/C	180d Composite (all-cause mortality or rehospitalization) (NR)	Multivariable logistic regression	Decrease in BNP level at D/C	Change less than 46% and BNP greater than 300 pg/mL at D/C: OR=9.61 (4.51 - 20.47), p<0.001

Table J-9. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and morbidity (continued)

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Allen[34] 2011 EVEREST Study	Case series Secondary analysis of RCT data Patients hospitalized with HF	n=1,458 mean age: 66.5y (11.7) 75.0% male	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Composite (all-cause mortality or unfavorable QoL) (NR)	Multivariable cox regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ	RR=NR
	Case series Patients hospitalized with HF (BNP 500-999 vs. BNP <500)	n=1,047 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Composite (all-cause mortality or unfavorable QoL) (171, 1047)	Multivariable cox regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ	D/C: RR=1.37 (1.11, 1.69)
	Case series Patients hospitalized with HF (BNP 1000+ vs. BNP <500)	n=1,112 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP, age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia, KCCQ	24w Composite (all-cause mortality or unfavorable QoL) (261, 1112)	Multivariable cox regression	Age >70y, diabetes, history of stroke, arrhythmia, BB, BUN, hyponatremia, hypernatremia*, KCCQ	D/C: RR=1.61 (1.32, 1.96)

Abbreviations: ADM = admission; BB = betablocker; BNP = B-type natriuretic peptide; BUN=blood urea nitrogen; 95% CI, = confidence interval; d = day(s); D/C = discharge; ED = emergency department; EVEREST = Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; m = month(s); n=number; NR = not reported; OR = odds ratio; pg/mL = picograms per milliliter; QoL = quality of life; RR = relative risk; SD = standard deviation; vs. = versus; w = week(s); y = year(s)

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Maisel[36] 2011	Cohort Acute HF patients admitted for decompensation	n=186, mean age: 67y (13.2) 98.6 % male	ADM mean: with events= 837 (500–1,465)** no events= 672 (359–1,350)** D/C mean: with events= 585 (375–1,380)** no events= 84 (172–818)** Cutpoint: per log unit	logBNP, NGAL, eGFR	1m (30d) composite (all-cause mortality and HF hospitalization) (29, 186)	Multivariable cox regression	NGAL, eGFR	ADM: HR=2.47 (0.99, 6.14), p=0.052
			ADM mean: with events= 837 (500–1,465)** no events= 672 (359–1,350)** D/C mean: with events= 585 (375–1,380)** no events= 84 (172–818)** Cutpoint: per log unit	logBNP, NGAL, creatinine	1m (30d) composite (all-cause mortality and HF hospitalization) (29, 186)	Multivariable cox regression	NGAL, creatinine	ADM: HR=2.327 (0.934, 5.795), p=0.07
Pimenta[29] 2010	Cohort Patients admitted for acute HF	n=163, mean age: 73y (61-80)** 70.0% male	ADM mean: 1,129.90 (681.35 - 2,094.50)** D/C mean: 659.30 (253 – 1,474)** Cutpoint: per 10 pg/mL	BNP (D/C), albumin, serum Na, renal failure, stroke index, thoracic fluid content, age, NYHA class, LVEF, hemoglobin	2m Composite (all-cause mortality and HF hospitalization) (45, 163)	Multivariable cox regression	Albumin, serum Na, renal failure, stroke index, thoracic fluid content, age, NYHA class, LVEF, Hb	D/C: HR=1.002 (1.001, 1.004) per 10 pg/mL
Maisel[1] 2004 REDHOT study	Cohort Patients presenting in ED with CHF	n=464 mean age: 64y (51-76)** 53.9% male	ADM mean: 766 D/C mean: 976 Cutpoint: 200	logBNP, NYHA, ED disposition (initial intent, actual disposition)	90 days Composite (mortality or cardiac-related reADM or ED visit) (129, 452)	Multivariable logistic regression	NYHA, ED disposition (initial intent, actual disposition)	logOR=0.708 (SE=0.254), OR=2.030

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Xue[30] 2011	Cohort Acute HF patients admitted for decompensation	n=144 mean age: 67y (13.2) 98.6 % male	ADM mean: NR D/C mean: NR Cutpoint: >360	BNP (D/C), cTnI, BUN, history of MI, cardiac murmurs, chronic renal insufficiency, pleural effusions on X-ray, cardiomegaly on X-ray	3m (90d) composite (all-cause mortality and HF hospitalization) (38, 144)	Multivariable cox regression	cTnI, BUN, history of MI, cardiac murmurs, chronic renal insufficiency, pleural effusions on X-ray, cardiomegaly on X-ray	D/C: HR=1.8 (p=0.12)
			ADM mean: NR D/C mean: NR Cutpoint: per unit increase	BNP (D/C), troponin I, TnI, Blood urea nitrogen, History of MI, cardiac murmurs, Chronic renal insufficiency, Pleural effusions on X-ray, Cardiomegaly on X-ray	3m (90 days) Composite (all-cause mortality and HF hospitalization) (38, 144)	Multivariable cox regression	troponin I, TnI, Blood urea nitrogen, History of MI, cardiac murmurs, Chronic renal insufficiency, Pleural effusions on X-ray, Cardiomegaly on X-ray	D/C: HR=2.066 (p=0.051)
Aspromonte[3] 2007	Cohort Ambulatory patients with CHF and diabetes	n=145 mean age: 72y (9) 60.0% male	ADM mean: NR D/C mean: 186** (75-348) Cutpoint: NR	D/C BNP, LVEF, NYHA, creatinine, restrictive pattern, age, AF, ischemic etiology	6m Composite (all-cause mortality or HF reADM) (41, 145)	Multivariable cox regression	LVEF, NYHA, creatinine, restrictive pattern, age, AF, ischemic etiology	D/C: HR=NR
	BNP, 201-499 vs. BNP ≤200	n=118, mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: 201-499	D/C BNP, LVEF, NYHA, creatinine, restrictive pattern*	6m Composite (all-cause mortality or HF reADM) (NR)	Multivariable cox regression	LVEF, NYHA, creatinine, restrictive pattern, age, AF, ischemic etiology	D/C: HR=3.82 (1.1379-12.8339)
	BNP ≥500 vs. BNP ≤200	n=102 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: ≥ 500	D/C BNP, LVEF, NYHA, creatinine, restrictive pattern	6m Composite (all-cause mortality or HF reADM) (NR)	Multivariable cox regression	LVEF, NYHA, creatinine, restrictive pattern	D/C: HR=7.7 (2.2192-26.7696)

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Faggiano[14] 2010	Cohort Patients with acute worsening of chronic HF	n=150 mean age: 69y (12) 100% male	ADM mean: 1,000 (684) D/C mean: NR Cutpoint: ≥250	BNP at D/C, age, sex, LVEF, NYHA class, creatinine, restrictive pattern	6m Composite (all-cause mortality and HF hospitalization) (59, 150)	Multivariable cox regression	Age, sex, LVEF, NYHA class, creatinine, restrictive pattern	D/C: HR=4.5 (2.0, 10.3)
Feola[22] 2008	Cohort CHF patients enrolled at hospital D/C after an acute decompensation	n=250 mean age: 73y (12) 66.0% male	ADM mean: NR D/C mean: 643 (566) Cutpoint: per unit increase	BNP (D/C), age, serum creatinine, NYHA class, LVEF, DT, AF, ischemic etiology	6m Composite (all-cause mortality and HF hospitalization) (141, 250)	Multivariable cox regression	Age, serum creatinine, NYHA class, LVEF, DT, AF, ischemic etiology	D/C: HR=1.0006 (1.0004, 1.0009) per unit increase, p<0.00001
Valle[24] 2008	Cohort Patients admitted for HF	n=166 mean age: 77y (9) 48.0% male	ADM mean: 764 D/C mean: 456 Cutpoint: 250	D/C BNP, LVEF, age*, NYHA*, restrictive mitral pattern*, creatinine	6m Mortality and HF reADM (60, 166)	Multivariable cox regression	Age, NYHA, restrictive mitral pattern*, creatinine	D/C: HR=0.2717 (0.1412, 0.5227) P=0.0001
Valle[26] 2008	Cohort Patients admitted for acute HF	n=186, mean age: 77y (10) 50.0% male	ADM mean: 716 (567) D/C mean: 404 (607) Cutpoint: >250	BNP (D/C), restrictive mitral pattern, age, serum creatinine, NYHA class, LVEF, serum creatinine	6m Composite (all-cause mortality and HF hospitalization) (65, 186)	Multivariable cox regression	Restrictive mitral pattern, age, serum creatinine, NYHA class, LVEF, serum creatinine	D/C HR=3.2 (1.6, 5.8), p=0.004
Farmakis[15] 2010	Non-randomized Patients with acutely decompensated chronic HF	n=98 mean age: 64y (10) 90.8% male	ADM mean: Levosimendan grp=1,043 (644) standard therapy grp=919 (605) D/C mean: NR Cutpoint: NR	BNP, systolic BP, serum Na, NYHA class, LVEF, age	6m Composite (all-cause mortality and HF re-hospitalization) (88, 98)	Multivariable cox regression	Systolic BP, serum Na, NYHA class, LVEF, age	ADM: OR=NS

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Farmakis[15] 2010 (cont'd)	Non-randomized Patients with acutely decompensated chronic HF treated with Levosimendan	n=69 mean age: 65y (9) 93.0% male	ADM mean: 1,043 (644) D/C mean: NR Cutpoint: <58% change	Change in BNP, systolic BP, serum Na, NYHA class, LVEF, age	6m Composite (all-cause mortality and HF re-hospitalization) (62, 69)	Multivariable cox regression	Systolic BP, serum Na, NYHA class, LVEF, age	Change <58%: OR=0.970 (0.954, 0.986), p<0.001
Logeart[2] 2004	Cohort Decompensated patients with chronic HF	n=114 mean age: 69.4y (14.4) 44.0% male	ADM mean: 1,015 (604) D/C mean: 457 (451) Cutpoint: per unit increase	BNP (preD/C), % change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	6m All-cause mortality or chronic HF rehospitalization (51, 114)	Multivariable cox regression	% change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	D/C: HR=1.14 (1.02, 1.28) per unit increase
				BNP (preD/C), % change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	6m 1m mortality or chronic HF rehospitalization (15, 114)	Multivariable cox regression	% change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	D/C: HR=1.17 (1.06 to 1.28), per unit increase
				BNP (preD/C), % change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	6m All-cause mortality or chronic HF rehospitalization (39, 114)	Multivariable cox regression	% change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	D/C: HR=1.25 (1.16 to 1.34) per unit increase

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Logeart[2] 2004 (cont'd)	Cohort Decompensated patients with chronic HF	n=223, mean age: derivation Cohort= 69.4y (14.4) validation Cohort= 70.9y (13.3) 43.5% male	ADM mean: derivation cohort= 1,015 (604) validation cohort= 941 (526) D/C mean: derivation cohort= 457 (451) validation cohort= 441 (501) Cutpoint: >350 (subgroup)	BNP (preD/C), % change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	6m All-cause mortality or chronic HF rehospitalization (86, 223)	Multivariable cox regression	% change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	D/C: HR=5.1 (2.8, 9.1)
				BNP (preD/C), % change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	6m All-cause mortality or chronic HF rehospitalization (86, 223)	Multivariable cox regression	% change in BNP level, age, gender, LVEF, ischemic etiology, use of inotropes	D/C: HR=15.2 (8.5 to 27)
Parissis[18] 2009	Cohort Patients hospitalized due to chronic HF	n=300 mean age: 65y (12) 83.0% male	ADM mean: depression=735 (737) no depression=455 (334) D/C mean: NR Cutpoint: 290	BNP, age, sex, NYHA class, 6MWT, LVEF, sIAM-1, IL-6, IL-10, TN factor-α	12m Composite (All-cause mortality and HF hospitalization) (NR, 300)	Multivariable logistic regression	Age, sex, NYHA class, 6MWT, LVEF, sIAM-1, IL-6, IL-10, TN factor-α	OR=NR

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Dhaliwal[20] 2009	Cohort Patients with decompensated HF	n=203 mean age: 67.2y (10.7) 99.0% male	ADM mean: 1,107.3 (868.4) D/C mean: 646.6 (674.3) Cutpoint: Tertiles	BNP (F/U=last available measurement in hospital or 30d from D/C), age, race, BB, LVEF, prior HF hospitalization, NYHA class, presence of renal insufficiency, ACE inhibitor or ARB,	392d** Composite (all-cause mortality and HF hospitalization) (126, 203)	Multivariable cox regression	Age, race, LVEF, history of prior HF hospitalization, presence of renal insufficiency, BB, ACE inhibitor or ARB, and NYHA class	Post ADM up to 30d post D/C: HR=1.4 (1.1, 1.8), p=0.003
			ADM mean: 1,107.3 (868.4) D/C mean: 646.6 (674.3) Cutpoint: % reduction in BNP	BNP (% reduction), age, race, LVEF, BB, prior HF hospitalization, NYHA class, presence of renal insufficiency, ACE inhibitor or ARB,	392d** Composite (all-cause mortality and HF hospitalization) (126, 203)	Multivariable cox regression	Age, race, LVEF, history of prior HF hospitalization, presence of renal insufficiency, BB, ACE inhibitor or ARB, and NYHA class	Change % reduction: HR=0.7 (0.6, 0.9), p= 0.006
			ADM mean: 1,107.3 (868.4) D/C mean: 646.6 (674.3) Cutpoint: % reduction in BNP	BNP (% reduction), age, race, LVEF, BB, prior HF hospitalization, presence of renal insufficiency, ACE inhibitor or ARB, NYHA class	392d** Composite (all-cause mortality and HF hospitalization) (126, 203)	Multivariable cox regression	Age, race, LVEF, history of prior HF hospitalization, presence of renal insufficiency, BB, ACE inhibitor or ARB, and NYHA class	Change % reduction: HR=0.7 (0.6, 0.9), p= 0.006

Table J-10. Studies evaluating independent predictive value of BNP for the composite outcome of all-cause mortality and cardiovascular morbidity (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Stoiser[4] 2006	Cohort Patients diagnosed with chronic HF admitted to hospital	n=268 mean age: 71y (13) 67.0% male	ADM mean: 699 (811) D/C mean: NR Cutpoint: 448	D/C BNP, copeptin, age, history of diabetes, HT, CAD, kidney dysfunction*, gender	24m Composite (mortality or chronic HF reADM) (145, 268)	Multivariable cox regression	Age, history of diabetes, HT, CAD, kidney dysfunction*, gender	D/C: Chi-square 4.9, p=0.0002

Abbreviations: 6MWT = 6 minute walk test; ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; ARB = angiotensin receptor blockers; BNP = B-type natriuretic peptide; BUN=blood urea nitrogen; CAD = coronary artery disease; CHF = congestive heart failure; 95% CI, = confidence interval; cTnI = cardiac troponin I;d = day(s); D/C = discharge; DT=deceleration time; ED = emergency department; eGFR = estimated glomerular filtration rate; grp = group; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; IL-6=interleukin-6; IL-10=interleukin-10; LVEF = left ventricular ejection fraction; m = month(s); MI = myocardial infarction; n=number; Na = sodium; NGAL-neutral gelatinase-associated lipocalin; NR = not reported; NS = non-significant; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; sIAM-1=soluble intercellular adhesion molecule-1; TN factor-α = tumor necrosis factor-alpha; vs. = versus; w = week(s); y = year(s)

Table J-11. Studies evaluating independent predictive value of BNP for the composite outcome of cardiovascular mortality and morbidity

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Parissis[25] 2007	cohort patients hospitalized due to chronic heart failure	n=155 mean age: 65y (12) 83.0% male	ADM mean: depression=735 (737) no depression=455 (334) D/C mean: NR Cutpoint: >290	BNP, age, sex, NYHA class, 6MWT, BDI, KCCQ, DASI, Zung SDS	6m Composite (cardiac mortality and HF hospitalization) (61, 155)	Multivariable logistic regression	Age, sex, NYHA class, 6MWT, BDI, KCCQ, DASI, Zung SDS	ADM: OR=1.003 (1.001, 1.005), p=0.002
Valle[9] 2005	Cohort Outpatients with acute HF and preserved systolic function	n=233 mean age: 76y (11) 42.0% male	ADM mean: 221 (289) D/C mean: NR Cutpoint: >200	BNP, creatinine clearance, restrictive mitral pattern, age, NYHA class, recent hospitalization	6m Composite (CV mortality or HF reADM) (48, 233)	Multivariable cox regression	Creatinine clearance, restrictive mitral pattern, age, NYHA class, recent hospitalization	ADM: HR=2.215 (1.023, 4.797)
			ADM mean: 221 (289) D/C mean: NR Cutpoint: ≥500	BNP, Creatinine clearance, Restrictive mitral pattern, age, NYHA class, recent hospitalization	6m Composite (CV mortality or HF reADM) (48, 233)	Multivariable cox regression	Creatinine clearance, Restrictive mitral pattern, age, NYHA class, recent hospitalization	ADM: HR=5.824 (1.058, 14.589)
Cournot[5] 2006	Cohort Elderly patients admitted for decompensated HF	n=61 mean age: 82.7y (5.8) 52.5% male	ADM mean: 1133 (582-1829)** D/C mean: 711 (409-1197)** Cutpoint: per pg/mL	BNP at ADM, age, gender, length of hospitalization, LVEF, CHD, renal failure	7m Composite (cardiac mortality or HF reADM) (29, 61)	Multivariable cox regression	Age, gender, length of hospitalization, LVEF, CHD, renal failure	ADM: HR=1.20 (0.71, 2.00) per pg/mL, p=NS
			ADM mean: 1133 (582–1829)** D/C mean: 711 (409–1197)** Cutpoint: decrease in BNP level of less than 40%	BNP decrease <40%, age, gender, length of hospitalization, LVEF, CHD, renal failure	7m Composite (cardiac mortality or HF reADM) (29, 61)	Multivariable cox regression	Age, gender, length of hospitalization, LVEF, CHD, renal failure	Change Decrease <40% HR=4.03 (1.50, 10.84), p<0.001

Table J-11. Studies evaluating independent predictive value of BNP for the composite outcome of cardiovascular mortality and morbidity (continued)

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cournot[23] 2008	Cohort Patients ≥70y hospitalized for decompensated HF	n=157 mean age: 83y (6) 51.0% male	ADM mean: 1057** (639; 1764) D/C mean: 605** (302; 1165) Cutpoint: 360	BNP, age, gender, HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, LVEF, Na, anemia, CRP, creatinine, length of hospitalization, NYHA D/C, BB, ACE inhibitor/ARB, antiplatelet	7m** Composite (cardiac mortality or cardiac reADM) (75, 157)	Multivariable cox regression	Age, gender, HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, LVEF, Na, anemia, CRP, creatinine, length of hospitalization, NYHA D/C, BB, ACE inhibitor/ARB, antiplatelet	ADM: HR=NR
	Cohort Elderly patients ≥70y hospitalized for decompensated HF (high risk grp 3, BNP at D/C ≥360 pg/mL and decrease of <50% or increase)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: 360	BNP, age, gender, HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, LVEF, Na, anemia, CRP, creatinine, length of hospitalization, NYHA D/C, BB, ACE inhibitor/ARB, antiplatelet	7m ** Composite (cardiac mortality or cardiac reADM) (NR)	Multivariable cox regression	Age, gender, HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, LVEF, Na, anemia, CRP, creatinine, length of hospitalization, NYHA D/C, BB, ACE inhibitor/ARB, antiplatelet	Change: D/C ≥360 pg/mL and decrease of <50% or increase (Group 3 vs. 2): HR=5.97 (2.98-11.94), p<0.001
	Cohort Elderly patients ≥70y hospitalized for decompensated HF (intermediate risk grp 2, BNP at D/C <360 pg/mL and decrease of ≥50%)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: 360	BNP, HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, Na, anemia, CRP, BB, ACE inhibitor/ARB, antiplatelet	7m** Composite (cardiac mortality or cardiac reADM) (NR)	Multivariable cox regression	HT, diabetes, history of CAD, valvular HD, chronic kidney disease, COPD, AF, LVEF, Na, anemia, CRP, creatinine, length of hospitalization, NYHA D/C, BB, ACE inhibitor/ARB, antiplatelet	Change: D/C <360 pg/mL and decrease of ≥50%) HR=3.13 (1.44-6.77) (grp 1 vs. 2), p=0.004

Table J-11. Studies evaluating independent predictive value of BNP for the composite outcome of cardiovascular mortality and morbidity (continued)

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Nahum[31] 2010	Cohort Patients with HF	n=125 mean age: 63y (16) 77.0% male	ADM mean: 1031 (1182) D/C mean: NR Cutpoint: NR	lnBNP, global- E, age, sex, LVEF, NYHA class, TAPSE, systolic BP, heart rate	283d Composite (CV mortality and HF hospitalization and cardiac transplantation) (47, 125)	Multivariable cox regression	Global- E, age, sex, LVEF, NYHA class, TAPSE, systolic BP, heart rate,	ADM: HR=NR, p=NS
Dokainish[10] 2005	Cohort Outpatients with acute HF and preserved systolic function	n=110 mean age: no event= 56.1y (11.8) with events= 58.6y (13.0) 53.0% male	ADM mean: no event = 293.3 (362.2) with events= 506.2 (352.7) D/C mean: NR Cutpoint: ≥250	BNP D/C, age, gender, LVEF, Mitral E/Ea, LAVi, mitral deceleration time	527d Composite (cardiac mortality and HF re-hospitalization) (54, 110)	Multivariable cox regression	Age, gender, LVEF, Mitral E/Ea, LAVi, mitral deceleration time	D/C: chi-square=17.0, p=0.001

Abbreviations: 6MWT = 6 minute walk test; ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; ARB = angiotensin receptor blockers; BB = betablocker; BDI = Beck Depression Inventory; BNP = B-type natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CHD = chronic heart disease; 95% CI, = confidence interval; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CV = cardiovascular; d = day(s); DASI = Duke Activity Status Index; D/C = discharge; E/Ea = transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity; global-E = global systolic longitudinal strain; grp = group; HD = heart disease; HF = heart failure; HR = hazard ratio; HT = hypertension; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVi = left atrial volume index; ln=natural log; LVEF = left ventricular ejection fraction; m = month(s); n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; SD = standard deviation; SDS = Self-rating Depression Scale; TAPSE = tricuspid annular plane systolic excursion; vs. = versus; y = year(s)

Table J-12. Risk of bias for prognostic studies using the Hayden Criteria for decompensated population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Bettencourt,[45] 2004	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√
Baggish,[46] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bettencourt,[47] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Perna,[48] 2006	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Sakhuja,[39] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
van Kimmenade,[49] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
van Kimmenade,[50] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Marcucci,[51] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Januzzi,[52] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Bayes-Genis,[53] 2005	√	√	√	X	√	√	√	NA	√	NA	√	?	√	X	?	√	√
Bayes-Genis,[54] 2007	√	√	√	√	√	√	√	NA	X	NA	√	?	X	?	?	√	√
Ferreira,[55] 2007	√	√	√	√	√	√	√	NA	?	NA	√	X	X	X	X	√	√
Martins,[56] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Siswanto,[57] 2006	√	√	√	?	?	√	√	√	√	√	X	X	X	√	√	√	√
Park,[58] 2010	√	√	√	√	√	√	√	√	√	√	√	?	X	√	X	√	√
Davutoglu,[59] 2010	√	√	√	√	√	X	√	√	√	√	√	X	√	X	X	√	X
Dini,[60] 2010	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Mohammed,[61] 2010	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Baggish,[62] 2010	√	?	?	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Maisel,[40] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Lourenco,[63] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Manzano-Fernández,[64] 2009	√	√	√	?	?	√	√	√	?	?	√	X	X	√	√	√	√

Table J-12. Risk of bias for prognostic studies using the Hayden Criteria for decompensated population assessing NT-proBNP (continued)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Kubler,[65] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	X	X	√	√
Paul,[66] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Boisot,[41] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Verdiani,[67] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	X	X	√	√
Andersson,[68] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
Petretta,[69] 2007	√	√	√	√	√	√	√	√	√	√	?	X	√	√	√	√	√
Metra,[70] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Lassus,[71] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	?	?	√	√
Luers,[72] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Carrasco-Sanchez,[73] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Noveanu,[42] 2011	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Rehman,[43] 2008	√	√	√	√	√	√	√	√	√	√	X	X	√	X	X	√	√
Pascual-Figal,[74] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Ho,[75] 2011	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Michtalik,[76] 2011	√	√	√	√	√	√	√	√	?	?	√	?	X	X	X	√	√
Korewicki,[77] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√		√	√
Krackhardt,[78] 2011	√	√	√	?	?	√	√	NA	?	NA	√	√	√	X	X	√	√
Peacock,[44] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√
Harutyunyan,[79] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NTBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for;
6. a) analysis described;
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✖ = High Risk ? = unclear

Table J-13. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (up to 31 days) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	AdJ-usted/Non-adJ-usted Covariates	Measure(s) of Risk (95% CI,)
Peacock[44] 2011 BACH	Cohort Patients with acute HF	n=466 mean age: 70.8y (14) 58.7% male	ADM mean: 5,165 (2,332-10,096) D/C mean: NA Cutpoint: NA	logNT-proBNP (ADM), logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	14d 14d mortality (NR)	Cox proportional hazards	logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	HR=NR, Chi-square=1.8, p=0.179, c-index=0.586
Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y (73, 85)** 60.0% male	ADM mean: 6,964 (3,068-14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 24h, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	24h: HR=NR per 1,000pg/mL increase, p=NS
				BNP, NT-proBNP at 48h, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariable cox regression	Age, cTnT, eGFR, NYHA	48h: HR=NR per 1,000pg/mL increase, p=NS
				BNP, NT-proBNP D/C, age, cTnT, eGFR, NYHA	30d All-cause mortality (60, 171)	Multivariable cox regression	Age, cTnT, eGFR, NYHA	D/C: HR=NR per 1,000pg/mL increase, p=0.05

Abbreviations: ADM = admission; BACH = Biomarkers in Acute Heart Failure; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; 95% CI, = confidence interval; cTnT = cardiac troponin T; d = day(s); D/C = discharge; ED = emergency department; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; m = month(s); MR-proADM = midregional pro-adrenomedullin; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; y = year(s)

Table J-14. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 2 to 3 months) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
van Kimmenade[49] 2006 ICON	Cohort Acute HF	n=690 mean age: alive=74.4y (11.7) deceased = 78.5y (10.6) 52% male	ADM mean: 4,647** D/C mean: NR Cutpoint: 4,647	NT-proBNP>4647 pg/mL, age, prior HF, prior MI, NYHA, Hb, troponin T, GFR <60ml/min/1.73m2,	60d mortality (89,720)	Multivariable forward stepwise logistic regression	Age, prior HF, prior MI, NYHA, Hb, troponin T, GFR <60ml/min/1.73m2,	ADM: OR=2.67 (1.58-4.51), p<0.001
Baggish[46] 2007 ICON	Cohort Patients with AHF	n=690 mean age: alive=74.4y (11.7) deceased = 78.5y (10.6) 52% male	ADM mean: alive= 4,077 (1,740-9,989)**, dead= 9,448 (3,805-22,179)** D/C mean: NR Cutpoint: ≥ 5,180	NT-proBNP, Anemia, Creatinine clearance, Fever, Age	2m All-cause mortality (84, 690)	Multivariable logistic regression	Anemia, creatinine clearance, fever, age	ADM: OR=2.32 (1.36–3.94), p=0.002
van Kimmenade[50] 2006 PRIDE	Cohort Patients admitted with acute HF	n=209 mean age: 72.8y (13.6) 51% male	ADM mean: dead= 9,332 (3,864-15,717)** alive= 3,511 (1,610-9,541)** D/C mean: NR Cutpoint: NR	logNT-proBNP*, log galectin-3, GFR, NYHA functional classification, age	2 months All-cause mortality (17, 209)	Multivariable logistic regression	log galectin-3, GFR, NYHA functional classification, age	ADM: OR=2.11 (0.63–7.1), p=0.22
Januzzi[52] 2006 ICON/PRIDE/and others	Cohort Patients with acute destabilized HF	n=720 mean age: NR % male: NR	ADM mean: 4,639** D/C mean: NR Cutpoint: >5,180	NT-proBNP, troponin T, Hb, NYHA class, age	78d All-cause mortality (89, 720)	Bootstrapped multivariable logistic regression	troponin T, Hb, NYHA class, age	ADM: OR=5.2 (2.2 – 8.1), p<0.001
Peacock,[44] 2011 BACH	Cohort Patients with acute HF	n=466 mean age: 70.8y (14) 58.7% male	ADM mean: 5,165 (2,332-10,096) D/C mean: NA Cutpoint: NA	logNT-proBNP, logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	90d 90 day mortality (NR)	Cox proportional hazards	logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	ADM: log NT-proBNP: Chi-square= 25.6, p<0.001, c-index= 0.693

Table J-14. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 2 to 3 months) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Maisel,[40] 2010 BACH	Cohort Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y (13.8) 62.5% male	ADM mean: NR D/C mean: NR Cutpoint: NR	logNT-proBNP, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	Age, gender, BMI, creatinine	ADM: HR=1.5 (1.0 - 2.3) per increase of 1 IQR, p=0.041
			ADM mean: NR D/C mean: NR Cutpoint: NR	log NT-proBNP, logMR-proADM, troponin, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	logMR-proADM, troponin, age, gender, BMI, creatinine	ADM: logNT-proBNP HR=0.8 (0.5 -1.4) per increase of 1 IQR, p=0.46
Boisot,[41] 2008	Cohort Patients admitted with a diagnosis of acute decompensated HF	n=150 mean age: NR 99% male	ADM mean: 5,878 (2,297, 11,918)** D/C mean: 3,580 (1,379, 10,102)** Cutpoint: decrease of <3%	decrease in NT-proBNP <3%, BUN, ST2 decrease	90d All-cause mortality (24, 150)	Multivariate logistic regression	Age >65, BUN, ST2 decrease, EF*, rales, wheezing murmurs, CAD, MI, AF	OR=0.19 (0.06-0.61), p=0.005

Abbreviations: ADM = admission; AF = atrial fibrillation; BACH = Biomarkers in Acute Heart Failure; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; 95% CI, = confidence interval; d = day(s); D/C = discharge; ED = emergency department; EF = ejection fraction; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; ICON=International Collaboration of NT-proBNP; IQR = interquartile range; m = month(s); mL/min/m2 = milliliters per minute per meter squared; MI = myocardial infarction; MR-proADM = midregional pro-adrenomedullin; n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; PRIDE = Pro-BNP Investigation of Dyspnea in the Emergency Department; SD = standard deviation; y = year(s);

Table J-15. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 6 to 11 months) in patients with decompensated HF

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bettencourt[45] 2004	Cohort Decompensated HF, NT-proBNP change<30%	n=49 mean age: 73.4y (NR) 49.0% males	ADM mean: NR D/C mean: NR Cutpoint: NA	NT-proBNP change <30%, NT-proBNP increase ≥30%, volume overload at D/C	6m Death (NR)	Multivariable cox regression	NYHA, age, volume overload at D/C	Change <30%: HR=2.59 (0.98-6.87)
	Cohort Decompensated HF, NT-proBNP Increase >=30%	n=25 mean age: 74.4y (NR) 44.0% males	ADM mean: NR D/C mean: NR Cutpoint: NA	NT-proBNP change <30%, NT-proBNP increase ≥30%, volume overload at D/C	6m Death (NR)	Multivariable cox regression	NYHA, age, volume overload at D/C	Increase=>30%: HR=3.67 (1.36-9.87)
Lourenco[63] 2009	Cohort Decompensated HF patients, NYHA III/IV, with depressed LVEF	n=133 mean age: 71.2y (NR) 52.6% male	ADM mean: 7,685** D/C mean: NA Cutpoint: 11,378	NT-proBNP extreme tertiles, gender, age, ischemic etiology, arterial HT, DM, chronic AF, renal dysfunction, severe LVSD, systolic BP, diastolic BP, heart rate, Hb, creatinine, Na, ACE use, BB use, spironolactone	6m All-cause mortality (33,133)	Multivariable regression	Gender, age, ischemic etiology, arterial HT, DM, chronic AF, renal dysfunction, severe LVSD, systolic BP, diastolic BP, heart rate, Hb, creatinine, Na, ACE use, BB use, spironolactone	Between extreme tertiles: HR=5.34 (1.76-16.24), p=0.003
Metra[70] 2007	Cohort Patients with acute HF admitted to hospital	n=107 mean age: survivors= 66y (13) dead= 68y (10) 92.0% male	ADM mean: 4,421 (1,621-8,536)** D/C mean: 2,779 (967-6,392)** Cutpoint: ≥3,000	NT-proBNP at D/C, age, gender, BMI, systolic BP, heart rate, LVEF, Na, cTnT, NYHA class	184d** All-cause mortality (21, 107)	Multivariable cox regression	Age, gender, BMI, systolic BP, heart rate, LVEF, Na, cTnT, NYHA class	D/C >3000pg/mL: HR=13.63 (12.15-15.10)

Table J-15. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 6 to 11 months) in patients with decompensated HF (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Siswanto[57] 2006	Cohort Patients hospitalized through the ED with HF	n=97 mean age: 55.2y (10.3) 53.0% males	ADM mean: 10.283.76 (10210.61) D/C mean: 6.681.44 (7.64137) Cutpoint: >17.860pg/mL, >8.499pg/mL	NT-proBNP>17.860 pg/mL, NT-proBNP >8.499, decrease in NT-proBNP >35% during hospitalization, BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb <12 g/dL, Na <130mmol/L	6m All-cause mortality (NR)	Cox proportional hazards	BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb <12 g/dL, Na <130mmol/L	ADM >17.860 pg/mL : HR=7.15 (2.08-24.56) p=.002, ADM >8.499 pg/mL: HR=9.55 (1.06-85.77) p=0.044,
			ADM mean: 10,283.76 (10,210.61) D/C mean: 6,681.44 (7.64137) Cutpoint: decrease in NT-proBNP >35% during hospitalization	NT-proBNP>17.860 pg/mL, NT-proBNP >8.499, decrease in NT-proBNP >35% during hospitalization, BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb <12 g/dL, Na <130mmol/L	6m All-cause mortality (NR)	Cox proportional hazards	BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb <12 g/dL, Na <130mmol/L	Decrease >35%: HR=0.13 (0.02-1.19) p=0.071
Paul[66] 2008	Cohort Patients with decompensated HF	n=133 mean age: Impaired EF=73y (12) preserved EF=77y (11) 52.6% male	ADM mean: 5,043 (2,693-10,784)** impaired EF= 6,363 (3,648-13,250)** preserved EF=3,569 (1,707-6,340)** D/C mean: NR, impaired EF= 3,876 (2,129-11,085)** preserved EF=2,285 (1,242-5,621)** Cutpoint: NR	logNT-proBNP at ADM, age, serum urea, serum creatinine, EF	6m All-cause mortality (19, 133)	Multivariable logistic regression	Age, serum urea, serum creatinine, EF	ADM: OR=3.25 (0.90-11.65) D/C: OR=7.05 (1.91 - 26.02)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; BB = betablocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; 95% CI, = confidence interval; cTnT = cardiac troponin T; d = day(s); D/C = discharge; DM = diabetes mellitus; ED = emergency department; EF = ejection fraction; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; m = month(s); mmol/L = millimoles per liter; n=number; Na = sodium; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; SD = standard deviation; y = year(s)

Table J-16. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 12 to 23 months) in patients with decompensated heart failure

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Sakhuja[39] 2007 PRIDE	Cohort Patients with acute HF presenting to urban academic center ED	n=209 mean age: increased cTnT= 74.3y (11.6) no increased cTnT= 71.4y (14.9) 51.0% male	ADM mean: Increase cTnT = 7703** no-increase cTnT= 2287** D/C mean: NR Cutpoint: 3,174	NT-proBNP, cTnT, age, GFR, NYHA class	12m All-cause mortality (NR)	Multivariable cox regression	cTnT, age, GFR, NYHA class	ADM: HR=2.76 (1.62-5.36), p=0.004
Rehman[43] 2008 PRIDE and Other	Cohort Patients with acute HF	n=346 mean age: 73y (13) 68.0% male	ADM mean: 3578 (1574, 9446)** D/C mean: NR Cutpoint: >3,578	NT-proBNP, ST2, CRP, BNP, age, prior chronic HF, BB, ACE inhibitor, NYHA, systolic BP, creatinine	1y Mortality (97, 346)	Multivariable cox regression	ST2, CRP, BNP, age, prior chronic HF, BB, ACE inhibitor, NYHA, BP, BMI, S3 gallop, rates on lung exam, creatinine, BUN, WCC, Hb, pleural effusion	ADM: HR=1.87 (1.20-2.91), p=0.006
Mohammed[61] 2010 ICON/PRIDE/ and others	Cohort Acute decompensated HF	n=628 mean age: no hyponatremia= 75y (11) hyponatremia= 75y (13) 50.0% males	ADM mean: no hyponatremia= 3,907 hyponatremia= 7,214 D/C mean: NR Cutpoint: 4,690	NT-proBNP, hyponatremia, age, troponin T, GFR	12m All-cause mortality (NR)	Multivariable stepwise cox regression	Hyponatremia, age, troponin T, GFR	ADM: HR=1.49 (1.1-2), p=0.009
Baggish[62] 2010 ICON/PRIDE/ and others	Cohort Patients with acute decompensated HF	n=720 mean age: NYHA-II= 72.1y (13.7) NYHA-III= 75.1y (11.8) NYHA-IV= 75.1y (11.1) 52.0% male	ADM mean: NYHA-II=3,512 (1,395–8,588)**, NYHA-III=5,610 (2,260–11,001)** NYHA-IV=6,196 (2,757–13,295)** D/C mean: NR Cutpoint: ≥ 5,180	NT-proBNP, age, serum creatinine, tobacco use, history of HT, NYHA class	12m All-cause mortality (225, 720)	Multivariable cox regression	Age, serum creatinine, tobacco use, history of HT, NYHA class	ADM: HR=2.14 (1.65-2.81), p<0.001

Table J-16. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 12 to 23 months) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Baggish[62] 2010 ICON/PRIDE/ and others (contd)	Cohort Patients with acute decompensated HF with LVSD	n=362 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: ≥ 5,180	NT-proBNP, age, serum creatinine, tobacco use, history of HT, NYHA class	12m All-cause mortality (116, 362)	Multivariable cox regression	Age, serum creatinine, tobacco use, history of HT, NYHA class	ADM: HR=2.43 (1.49-3.97)
	Cohort Patients with acute decompensated HF with preserved LVSF	n=293 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: ≥ 5,180	NT-proBNP, age, serum creatinine, tobacco use, history of HT, NYHA class	12m All-cause mortality (88, 293)	Multivariable cox regression	Age, serum creatinine, tobacco use, history of HT, NYHA class	ADM: HR=2.19 (1.32-3.64)
Lassus[71] 2007 FINN-AKVA	Cohort Patients with acute HF	n=480 mean age: 74.8y (10.4) 50.0% male	ADM mean: 7,863 (10,876) D/C mean: NR Cutpoint: >3,916	NT-proBNP, cystatin C, creatinine clearance, creatinine, age, gender, systolic BP, history of (HF, chronic renal failure, CVD, CAD), diastolic BP, hyponatremia, anemia	12m All-cause mortality (122, 480)	Multivariable cox proportional hazard regression	Cystatin C, creatinine clearance, creatinine, age, gender, systolic BP, history of (HF, chronic renal failure, CVD, CAD), diastolic BP, hyponatremia, anemia	ADM: HR=1.5 (1.0-2.3), p=0.06
Carrasco-Sanchez[73] 2011	Cohort Patients admitted with HF and preserved EF (LVEF >45%)	n=218 mean age: 75.6y (8.7) 39.9% male	ADM mean: 3,606 (1,824-7,123)** D/C mean: NR Cutpoint: >3,606	NT-proBNP, cystatin C, age, creatinine, BUN, eGFR, Hb, Hyponatremia, NYHA class	12m All-cause mortality (70, 218)	Multivariable cox regression	Cystatin C, age, creatinine, BUN, eGFR, Hb, hyponatremia, NYHA class	ADM: HR=NR, p=NS

Table J-16. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 12 to 23 months) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Kubler[65] 2008	Cohort Patients with acute HF admitted to cardiology department (LVEF <45%)	n=103 mean age: 64y (13) 84.0% male	ADM mean: 6,116 (3,575-10,958)** D/C mean: NR Cutpoint: NR	change in NT-proBNP, SBP, Creatinine, sodium	1y All-cause mortality (29, 103)	Multivariable Cox regression	Systolic BP, creatinine, Na	HR=1.04 (1.01-1.06) per 5% change in NT-proBNP, p=0.002
			ADM mean: 6,116 (3,575-10,958)** D/C mean: NR Cutpoint: NR	NT-proBNP after stabilization, SBP, Creatinine, sodium	1y All-cause mortality (29, 103)	Multivariable Cox regression	Systolic BP, creatinine, Na	After clinical stabilization HR=1.02 (1.00-1.03) per 500 pg/mL increase, p=0.04
Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y (73, 85)** 60.0% male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	NT-proBNP at 24h, age, cTnT, eGFR, NYHA	1y All-cause mortality (60, 171)	Multivariable cox regression	age, cTnT, eGFR, NYHA	24h: HR=1.01 (0.99-1.04) per 1,000 pg/mL increase, p=0.230
			ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	NT-proBNP at 48h, age, cTnT, eGFR, NYHA	1y All-cause mortality (60, 171)	Multivariable cox regression	age, cTnT, eGFR, NYHA	48h: HR=1.03 (0.99-1.07) per 1,000 pg/mL increase, p=0.063
			ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	D/C NT-proBNP D/C, age, cTnT, eGFR, NYHA	1y All-cause mortality (60, 171)	Multivariable cox regression	age, cTnT, eGFR, NYHA	D/C: HR=1.07 (1.01-1.13) per 1,000 pg/mL increase, p=0.016

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; 95% CI, = confidence interval; CRP = C-reactive protein; cTnT = cardiac troponin T; CVD = cerebrovascular disease; d = day(s); D/C = discharge; ED = emergency department; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; h = hour(s); Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; ICON=International Collaboration of NT-proBNP; LVEF = left ventricular ejection fraction; LVSF = left ventricular systolic function; LVSD = left ventricular systolic dysfunction; m = month(s); n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; PRIDE = Pro-BNP Investigation of Dyspnea in the Emergency Department; RR = relative risk; SD = standard deviation; WCC = white cell count; y = year(s);

Table J-17. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 24 months to 7 years) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Andersson[68] 2008	Cohort Elderly patients (age >65y) admitted to ED with HF	n=365 mean age: alive=80y (73-85)** dead=83y (78-88)** 51.0% male	ADM mean: alive=5,734 (3,696-10,966)** dead=1,668 (6,337-28,605)** D/C mean: NR Cutpoint: NR	log2NT-proBNP, age, systolic BP, furosemide, ACE inhibitors/ARBs	24m All-cause mortality (127, 365)	Multivariable cox regression	Age, systolic BP, furosemide, ACE inhibitors/ARBs	ADM: HR=1.6 (1.4-1.9) per doubling the NT-proBNP levels, p<0.001
	Cohort Patients in Q2 (NT-proBNP, 3,001-5,000) vs. Q1 (NT-proBNP <3,000)	n=131 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: 3,001-5,000	NT-proBNP (quartiles), LVEF, NYHA class, chest radiology	24m All-cause mortality (NR)	Multivariable cox regression	LVEF, NYHA class, chest radiology	ADM: HR=3.4 (0.79-15.0), p=0.10
	Cohort Patients in Q3 (NT-proBNP, 5,001-10,000) vs. Q1 (NT-proBNP <3,000)	n=129 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: 5,001-10,000	NT-proBNP (quartiles), LVEF, NYHA class, chest radiology	24m All-cause mortality (NR)	Multivariable cox regression	LVEF, NYHA class, chest radiology	ADM: HR=4.5 (1.1-19.0), p=0.04
	Cohort Patients in Q4 (NT-proBNP >10,000) vs. Q1 (NT-proBNP <3,000)	n=165 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >10,000	NT-proBNP (quartiles), LVEF, NYHA class, chest radiology	24m All-cause mortality (NR)	Multivariable cox regression	LVEF, NYHA class, chest radiology	ADM: HR=7.4 (1.8-30.0), p=0.006
Pascual-Figal[74] 2011	Cohort Patients admitted with acute decompensated HF	n=107 mean age: 72y (13) 56.0% male:	ADM mean: 3,724 (1,954-7,666)** D/C mean: NR Cutpoint: NR	NT-proBNP, sST2, hs-cTnT, age, sex, BMI, Hb, NYHA class, BUN, prior MI, creatinine, LVEF	739** d All-cause mortality (29, 107)	Bootstrapped multivariable cox regression	sST2, hs-cTnT, age, sex, BMI, Hb, NYHA class, BUN, prior MI, creatinine	HR=1.005 (1.000-1.01) per 100pg/mL increase

Table J-17. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality - admission and discharge (from 24m to 7 years) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Harutyunyan [79] 2012 ECHO	Cohort Patients with HF and severe LVSD	n=717 mean age: 70y (NR) 73.0% male	ADM mean: NR D/C mean: NR Cutpoint: NR	log2NT-proBNP, age, gender, and LVEF, Hb, history of HF, ischemic HD, COPD, stroke/TIA, and DM, log2hs-CRP, eGFR	6.8y All-cause mortality (458, 717)	Multivariable cox regression	Age, gender, and LVEF, Hb, history of HF, ischemic HD, COPD, stroke/TIA, and DM, log2hs-CRP, eGFR	ADM HR=1.28 (1.15, 1.44), p<0.0001

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; ARB = angiotensin receptor blockers; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; 95% CI, = confidence interval; COPD = chronic obstructive pulmonary disease; d = day(s); D/C = discharge; DM = diabetes mellitus; ECHO = EchoCardiography and Heart Outcome Study; ED = emergency department; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HD = heart disease; HF = heart failure; HR = hazard ratio; hs-CRP = high-sensitivity c-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; m = month(s); MI = myocardial infarction; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; sST2 = soluble ST2; TIA = transient ischemic attack; vs. = versus; y = year(s)

Table J-18. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality – admission and discharge (up to 31 days) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Luers[72] 2010	Cohort Patients admitted to ICU with decompensated HF	n=116 mean age: 70y (12) 61% male	ADM mean: 3,861 (740, 8,717)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (12h after ADM), LVEF<50%*, age >65 years, HT*, DM*	30d CV mortality (38, 116)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT, DM*	12h: OR=NS
	Cohort Patients admitted to ICU with decompensated HF	n=116 mean age: 70y (12) 61% male	ADM mean: 3,861 (740, 8,717)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (ADM-1h after ADM, LVEF<50%, age >65 years, HT, DM	30d CV mortality (38, 116)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT, DM*	Change at 12h: OR=1.000 (1.000-1.000), p=0.004
	Cohort Patients with chronic ischemic CMP	n=38 mean age: 74y (11) 53% male	ADM mean: 4,161 (850, 8,405)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (12h after ADM), LVEF<50%, age >65 years, HT, DM	30d CV mortality (10, 38)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT, DM	12h: OR=1.000 (1.000-1.000), p=0.5929
	Cohort Patients with ischemic CMP	n=38 mean age: 74y (11) 53% male	ADM mean: 4,161 (850, 8,405)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (ADM-12h after ADM, LVEF<50%, age >65 years, HT, DM	30d CV mortality (10, 38)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT, DM	Change at 12h: OR=1.000 (0.999-1.000), p=0.0664
	Cohort Patients with decompensated non-ischemic CMP	n=29 mean age: 71y (10) 52% male	ADM mean: 5,690 (2,960, 12,641)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (12h after ADM), LVEF<50%, age >65 years, HT, DM	30d CV mortality (7, 29)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT, DM	12h: OR=1.000 (1.000-1.000), p=0.0401
	Cohort Patients with non-ischemic CMP	n=29 mean age: 71y (10) 52% male	ADM mean: 5,690 (2,960, 12,641)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (ADM-12h after ADM, LVEF<50%, age >65 years, HT, DM	30d CV mortality (7, 29)	Multi-variable logistic regression	LVEF<50%*, age >65 years*, HT, DM*	Change at 12h: OR=1.000 (0.999-1.000), p=0.0147
	Cohort Patients with acute ischemia	n=49 mean age: 66y (13) 74% male	ADM mean: 2,026 (320, 8,235)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (12h after ADM), LVEF<50%, age >65 years, HT, DM	30d CV mortality (21, 49)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT*, DM	12h: OR=1.000 (1.000-1.000), p=0.0531

Table J-18. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality - admission and discharge (up to 31 days) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Luers[72] 2010 (cont'd)	Cohort Patients with acute ischemia	n=49 mean age: 66y (13) 74% male	ADM mean: 2,026 (320, 8,235)** D/C mean: NR Cutpoint: NR	lnNT-proBNP (ADM-12h after ADM, LVEF<50%, age >65 years, HT, DM	30d CV mortality (21, 49)	Multi-variable logistic regression	LVEF<50%, age >65 years, HT*, DM*	Change at 12h: OR=1.000 (1.000-1.000), p=0.2350

Abbreviations: ADM = admission; BNP = B-type natriuretic peptide; BP = blood pressure; 95% CI, = confidence interval; CMP = cardiomyopathy; CV = cardiovascular; d = day(s); D/C = discharge; DM = diabetes mellitus; ED = emergency department; HF = heart failure; HR = hazard ratio; HT = hypertension; ICU = intensive care unit; ln=natural log; LVEF = left ventricular ejection fraction; m = month(s); MI = myocardial infarction; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; y = year(s)

Table J-19. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality - admission and discharge (all time periods) in patients with decompensated heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Davutoglu[59] 2010	Cohort Acute decompensated HF	n=100 mean age: 65y (10) % male: 41	ADM mean: no pleural effusion=6,640.8 (13,368.6) g/dl pleural effusion)= 6,737.1 (161,108.2) g/dl D/C mean: NR Cutpoint: elevated NT-proBNP (1,000 pg/dl)	NT-proBNP, pleural effusion, CA125	6m Cardiac mortality (27, 100)	Multivariable cox regression	Pleural effusion, CA125	ADM: RR=1.049 (0.988-1.113), p=0.119
Marcucci[51] 2006	Cohort HF patients	n=214, mean age: 71.9y (9.8) % male: 79	ADM mean: NR D/C mean: NR Cutpoint: NR	NT-proBNP, DD, TAT, IL-6, CRP	8.5m** CV mortality (13, 214)	Multivariable stepwise cox	Age, gender, NYHA, EF, renal failure, HT, hypercholesterolemia, smoking, DM, Hb, Na	ADM: HR=NR, p=NS
Bayes-Genis[53] 2005 Bayes-Genis, 2004	Cohort Acute HF with ventricular dysfunction	n=69 mean age: deceased =73.7y (7.5) survivors = 71.4y (10.4) % male: 61	ADM mean: NR D/C mean: NR Cutpoint: 30% decrease	NT-proBNP reduction >30% during hospitalization, 7d NT-proBNP concentration, age, gender, patient history	12m CV mortality (12, 69)	Multivariable stepwise logistic regression	Age, gender, patient history	Reduction by 30%: OR=4.4 (1.12-17.4), p=0.03
Petretta[69] 2007	Cohort Patients with chronic HF admitted to hospital	n=153, mean age: 64y (19-87)** % male: 72	ADM mean: survivors =1,167 (1,694) dead = 3,333 (2,791) D/C mean: NR Cutpoint: NR	NT-proBNP, GFR, age, DM, NYHA class, iron, hematocrit	456d** CV mortality (32, 153)	Multivariable cox regression	GFR, age, DM, NYHA class, iron, hematocrit	ADM: HR=1.002 (1.001-1.003), p=0.001
				log NT-proBNP (tertiles), GFR, age, DM, NYHA class, iron, hematocrit	456d** CV mortality (32, 153)	Multivariable cox regression	GFR, age, DM, NYHA class, iron, hematocrit	ADM: HR=2.27 (1.61-3.19), p=0.001

Abbreviations: ADM = admission; BNP = B-type natriuretic peptide; CA125 = carbohydrate antigen 125; 95% CI, = confidence interval; CMP = cardiomyopathy; CRP = C-reactive protein; CV = cardiovascular; d = day(s); DD = D-dimer; D/C = discharge; DM = diabetes mellitus; ED = emergency department; EF = ejection fraction; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; ICU = intensive care unit; IL-6=interleukin-6; ln=natural log; m = month(s); MI = myocardial infarction; n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; TAT = thrombin antithrombin III complex; y = year(s)

Table J-20. Studies evaluating independent predictive value of NT-proBNP for the outcome of morbidity - admission, discharge, and change levels (all time periods) in patients with decompensated heart failure

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/ml)	Prognostic Markers	Follow Up Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Michtalik,[76] 2011	Cohort Patients With HF	n=217 mean age: 63.3yrs (14.4) 50% male	ADM Mean: 5,913 (1,831-10,989)** D/C Mean: NR Cutpoint: > 50 % change	NT-proBNP, age, gender, race, admission creatinine level, LVEF, LOS	30 days Hospital re-admission (86, 217)	Multivariable cox regression	age, gender, race, and admission creatinine level, LVEF, LOS	Change Decrease < 50%: HR= 1.42 (0.64 to 3.12), p=0.39
Paul,[66] 2008	Cohort Patients with decompensated HF	n=133 mean age: Impaired EF: 73yrs (12) preserved EF: 77yrs (11) 52.6% male	ADM Mean: 5,043 (2,693 – 10,784)** Impaired EF= 6,363 (3,648 – 13,250)** preserved EF= 3,569 (1,707 -6,340)** D/C Mean: NR, Impaired EF= 3,876 (2,129 -11,085)** preserved EF= 2,285 (1,242 – 5,621)** Cutpoint: NR	log NT-proBNP at admission, age, serum urea, serum creatinine, EF	6 months all-cause re-hospitalization (57, 133)	Multivariable logistic regression	age*, serum urea*, serum creatinine*, EF	Admission: OR = 2.42 (1.03 - 5.69)
			ADM Mean: 5,043 (2,693 – 10,784)** Impaired EF= 6,363 (3,648 – 13,250)** preserved EF= 3,569 (1,707 -6,340)** D/C Mean: NR, Impaired EF= 3,876 (2,129 -11,085)** preserved EF= 2,285 (1,242 – 5,621)** Cutpoint: NR	log NT-proBNP at D/C, age, serum urea, serum creatinine, EF	6 months all-cause re-hospitalization (57, 133)	Multivariable logistic regression	age*, serum urea*, serum creatinine*, EF*	D/C OR = 3.13 (1.43 - 6.83)

Table J-20. Studies evaluating independent predictive value of NT-proBNP for the outcome of morbidity - admission, discharge, and change levels (all-time periods) in patients with decompensated heart failure

Author Year	Study Design Population	n mean age (SD) % male	BNP Levels (pg/ml)	Prognostic Markers	Follow Up Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Siswanto,[57] 2006	Cohort patients hospitalized via ER with HF	n=97 mean age: 55.2yrs (10.3) 53% males	ADM Mean: 10,283.76 (10,210.61) D/C Mean: 6,681.44 (7.64137) Cutpoint: decrease in NT-proBNP >35% during hospitalization	decrease in NT-proBNP >35% during hospitalization, BMI, acute lung edema, NYHA class IV, LV wall thickness, not using beta blockers, Hemoglobin <12 g/dL, Na <130mmol/L	6 months re-hospitalization (NR)	Cox proportional hazards	BMI, acute lung edema, NYHA class IV, LV wall thickness, not using beta blockers, Hemoglobin <12 g/dL, Na <130mmol/L	Decrease > 35%: HR=0.38(0.14-1.00) p=0.049
Marcucci,[51] 2006	Cohort heart failure patients	n=214 mean age: 71.9yrs (9.8) 79% males	ADM Mean: NR D/C Mean: NR Cutpoint: NR	NT-proBNP, DD, TAT, IL-6, CRP	median 8.5 months HF readmission (19, 214)	Multivariate stepwise cox	age, gender, traditional cardiovascular risk factors, systolic LV function, renal failure, NYHA functional class, hemoglobin, serum sodium	Admission: HR=5.3 (2.0-13.8), p<0.001

Abbreviations: ADM = admission; BMI = body mass index; CRP = C-reactive protein; D/C = discharge; DD = ; EF = ejection fraction; ER = emergency room; HF = heart failure; HR = heart rate; IL-6 = ; LOS = length of stay; LV = left ventricular; NR=not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; TAT = ; yrs=years

Table J-21. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and morbidity – admission and discharge (all time periods) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bettencourt[45] 2004	Cohort Decompensated HF, NT-proBNP change<30%	n=49 mean age: 73.4y (NR) 49.0% males	ADM mean: NR D/C mean: NR Cutpoint: NA	NT-proBNP change <30%, NT-proBNP Increase >=30%, Volume overload at D/C	6m Death or hospital reADM (NR)	Multivariable cox regression	Volume overload at D/C	Change <30%: HR=2.03 (1.14-3.64)
	Cohort Decompensated HF, NT-proBNP Increase >=30%	n=25 mean age: 74.4y (NR) 44.0% males	ADM mean: NR D/C mean: NR Cutpoint: NA	NT-proBNP increase >=30%, NT-proBNP change <30%, volume overload at D/C	6m death or hospital reADM (NR)	Multivariable cox regression	Volume overload at D/C	Increase >35%: HR=5.96 (3.23-11.01)
Bettencourt[47] 2006	Cohort Decompensated HF patients	n=224 mean age: depressed SF=70.7y (12.6) preserved SF=74.6y (10.5) 48.21% male	ADM mean: depressed SF= 7,685 (3,664-15,280)** preserved SF= 4,512 (1,773-9,290)** D/C mean: depressed SF= 5,403 (2,160-10,408)** preserved SF= 2,285 (1,030-4,030)** Cutpoint: NR	NT-proBNP at D/C, change in NT-proBNP, serum creatinine, Hb	6m Composite (death or hospitalizations) (95, 224)	Multivariable cox regression	Change in NT-proBNP, serum creatinine, Hb	D/C HR=NR
	Cohort Cecompensated HF patients with depressed systolic function	n=161 mean age: 70.7y (12.6) 54.0% male	ADM mean: 7,685 (3,664–15,280)** D/C mean: 5,403 (2,160–10,408)** Cutpoint: >5,403	NT-proBNP at D/C, change in NT-proBNP, serum creatinine, Hb	6m Composite (death or hospitalizations) (68, 161)	Multivariable cox regression	Change in NT-proBNP, serum creatinine, Hb	D/C: HR=NS

Table J-21. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and morbidity - admission and discharge (all time periods) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bettencourt[47] 2006 (cont'd)	Cohort Decompensated HF patients with depressed systolic function, grp 2 vs. grp 1	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: less than 30 % change from baseline	Change in NT-proBNP, NT-proBNP at D/C, serum creatinine, Hb	6m Composite (death or HF hospitalizations or ED visits) (NR)	Multivariable cox regression	NT-proBNP at D/C, serum creatinine, Hb	Change <30 %: HR=3.88 (0.94, 15.98)
	Cohort Decompensated HF patients with depressed systolic function, grp 3 vs. grp 1	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: More than 30 % increase from baseline	Change in NT-proBNP, NT-proBNP at D/C, serum creatinine, Hb	6m Composite (death or hospitalizations) (NR)	Multivariable cox regression	NT-proBNP at D/C, serum creatinine, Hb	Change >30%: HR=7.79 (2.03, 29.86)
	Cohort Decompensated HF patients with preserved systolic function	n=63 mean age: 74.6y (10.5) 33.3% male	ADM mean: 4512 (1,773–9,290)** D/C mean: 2,285 (1,030–4,030)** Cutpoint: >2,285	NT-proBNP at D/C, change in NT-proBNP, serum creatinine, Hb	6m Composite (eath or hospitalizations) (27, 63)	Multivariable cox regression	change in NT-proBNP, gender, preserved, ACE inhibitor	D/C above the median: HR=2.71 (1.49, 4.92)
	Cohort Decompensated HF patients with preserved systolic function, grp 2 vs. grp 1	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: less than 30 % change from baseline	Change in NT-proBNP, NT-proBNP at D/C, gender, preserved, ACE inhibitor	6m Composite (death or HF hospitalizations or ED visits) (NR)	Multivariable cox regression	NT-proBNP at D/C, gender, preserved, ACE inhibitor	D/C: HR= 2.12 (1.17-3.82)
	Cohort Decompensated HF patients with preserved systolic function, grp 3 vs. grp 1	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: More than 30% increase from baseline	Change in NT-proBNP, NT-proBNP at D/C, gender, preserved, ACE inhibitor	6m Composite (death or HF hospitalizations or ED visits) (NR)	Multivariable cox regression	NT-proBNP at D/C, gender, preserved, ACE inhibitor	Change increase 30%: HR=3.18 (1.57-6.46)

Table J-21. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and morbidity - admission and discharge (all time periods) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Ferreira[55] 2007	Cohort Decompensated HF patients	n=304 mean age: 72.7y (11.6) 54% male	ADM mean: 7,006 (2,816-13,788)** D/C mean: 3,796 (1,618-9,620)** Cutpoint: >3,796	NT-proBNP at D/C, age, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	6m Composite (all-cause mortality or reADM) (131, 304)	Multivariable cox regression	Age, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	D/C: HR=2.02 (1.28, 3.2)
	Cohort Decompensated HF patients, grp 2 vs. grp 1	n=257 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: Decreasing by at least 30% from baseline,grp 1	Change in NT-proBNP, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	6m Composite (all-cause mortality or reADM) (NR)	Multivariable cox regression	Age, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	Change >30% decrease: HR=2.24 (1.37, 3.66)
	Cohort Decompensated HF patients, grp 3 vs. grp 1	n=209 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: More than 30% increase from baseline,grp 3	Change in NT-proBNP, age, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	6m Composite (all-cause mortality or reADM) (NR)	Multivariable cox regression	Age, LVEF, NYHA class, pulse, renal failure, anemia, ACE inhibitors	Change increase >30%: HR=3.85 (2.24, 6.63)
Siswanto[57] 2006	Cohort Patients hospitalized through the ED with HF	n=97 mean age: 55.2y (10.3) % males: 53	ADM mean: 10.283.76 (10210.61) D/C mean: 6.681.44 (7.64137) Cutpoint: decrease in NT-proBNP >35% during hospitalization	Decrease in NT-proBNP >35% during hospitalization, BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb <12 g/dL, Na <130mmol/L	6m Composite (rehospitalization and mortality) (NR)	Cox proportional hazards	BMI, acute lung edema, NYHA class IV, LV wall thickness, not using BB, Hb<12 g/dL, Na <130mmol/L	Decrease >35%: HR=0.42(0.12-0.76) p=0.010

Table J-21. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and morbidity - admission and discharge (all time periods) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pimenta[56] 2007	Cohort Acute HF patients	n=283 mean age: 72.8y (11.7) 48.0% male	ADM mean: NR D/C mean: NR Cutpoint: NR	NT-proBNP at D/C, age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	182d** Composite (all-cause mortality or reADM) (125, 283)	Multivariable cox regression	Age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	D/C: HR=NR
	Cohort Acute HF patients with normal eGFR (≥90 mL/min)	n=164 mean age: 70.4y (12.4) 61.58% male	ADM mean: 4,807 (2,089-9,847)** D/C mean: 2,575 (1,232, 6,454) Cutpoint: >2,575	NT-proBNP at D/C above median, age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	182d** Composite (all-cause mortality or reADM) (61, 164)	Multivariable cox regression	Age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	D/C above median: HR=1.64 (0.98, 2.76)
				Change in NT-proBNP (decrease by 30%), age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	182d** Composite (all-cause mortality or reADM) (61, 164)	Multivariable cox regression	Age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	Change decrease <30%: HR=2.68 (1.54, 4.68)
	Cohort Acute HF patients with reduced eGFR (RF)	n=119 mean age: mild RF= 75.6y (90.9) moderate RF = 77.9y (8.6) severe RF= 72.5y (11.9) 27.0% male	ADM mean: mild RF=10578 (4,538-20,416)** moderate RF=10,776 (5,342-31,264)** severe RF=17,789 (10,639-43,691)** D/C mean: mild RF=5,512 (2,223-11,002)** moderate RF=7,504 (4,120-17,592)** severe RF=25,010 (2,785-37,747)** Cutpoint: Above median	NT-proBNP at D/C, age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	182d** Composite (all-cause mortality or reADM) (61, 164)	Multivariable cox regression	Age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	D/C above median: HR=2.53 (1.27, 5.03)

Table J-21. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and morbidity - admission and discharge (all time periods) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pimenta[56] 2007 (cont'd)	Cohort Acute HF patients with reduced eGFR (RF)	n=119 mean age: mild RF=75.6y (90.9) moderate RF=77.9y (8.6) severe RF=72.5y (11.9) % male: 27	ADM mean: mild RF=10578 (4538-20416)** moderate RF=10776 (5342-31264)** severe RF=17789 (10639-43691)** D/C mean: mild RF=5512 (2223-11002)** moderate RF=7504 (4120-17592)** severe RF=25010 (2,785-37,747)** Cutpoint: Above median	Change in NT-proBNP, age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	182d** Composite (all-cause mortality or reADM) (61, 119)	Multivariable cox regression	Age, sex, Hb, serum Na, LVEF, systolic BP, heart rate, NYHA class	Change decrease <30% : HR=2.54 (1.49, 4.33)
Carrasco-Sanchez[73] 2011	Cohort Patients admitted with HF and preserved EF (LVEF >45%)	n=218 mean age: 75.6y (8.7) % male: 39.9	ADM mean: 3606 (1824-7123)** D/C mean: NR Cutpoint: >3606	NT-proBNP*, cystatin C, age, creatinine*, BUN*, eGFR*, Hb*, hyponatraemia, NYHA class*	12m composite (all-cause mortality and reADM) (126, 218)	Multivariable cox regression and ROC analysis	Cystatin C, age, creatinine*, BUN*, eGFR*, Hb*, hyponatraemia, NYHA class*	ADM: HR=NR, p=NS,
Michtalik[76] 2011	Cohort Patients With HF	n=217 mean age: 63.3y (14.4) % male: 50	ADM mean: 5913 (1831-10989)** D/C mean: NR Cutpoint: >50 % change	NT-proBNP, age, gender, race, and ADM creatinine level, LVEF, length of ADM	12m Composite (all-cause mortality or hospital ADM) (134, 217)	Multivariable cox regression	Age, gender, race, and ADM creatinine level, LVEF, length of ADM	Change >50%: HR=1.54 (1.05, 2.27)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CA125 = carbohydrate antigen 125; 95% CI, = confidence interval; CMP = cardiomyopathy; CRP = C-reactive protein; CV = cardiovascular; d = day(s); D/C = discharge; DM = diabetes mellitus; ED = emergency department; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; grp = group; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; ICU = intensive care unit; IL-6=interleukin-6; ln=natural log; LV = left ventricular; LVEF = left ventricular ejection fraction; m = month(s); mL/min=milliliters per minute; MI = myocardial infarction; n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RF = renal failure; ROC = receiver operating characteristic; RR = relative risk; SD = standard deviation; vs. = versus; y = year(s)

Table J-22. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and cardiovascular morbidity—admission and discharge (all time periods) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
van Kimmenade[50] 2006 PRIDE	Cohort patients admitted with AHF	n=209 mean age: 72.8y (13.6) 51% male	ADM mean: dead= 9,332 (3,864–15,717)** alive= 3,511 (1,610–9,541)** D/C mean: NR Cutpoint: NR	Log NT-proBNP*, Log galectin-3, Glomerular filtration rate*, NYHA functional classification*, age	2 months composite (all-cause mortality / recurrent HF) (77, 209)	multivariable logistic regression	Log galectin-3, Glomerular filtration rate, NYHA functional classification, age	ADM: OR = 2.92 (0.53–9.11), p=0.42
Metra[70] 2007	Cohort patients with AHF admitted to hospital	n=107 mean age: survivors= 66y (13) dead= 68y (10) 92% male	ADM mean: 4,421 (1,621 – 8,536)** D/C mean: 2,779 (967 – 6,392)** Cutpoint: ≥3,000	NT-proBNP at D/C, cTnT, NYHA class	184 days** composite (all-cause mortality or CV hospitalization) (52, 107)	multivariable Cox regression	Age, gender, BMI, SBP, HR, LVEF, sodium, cTnT, NYHA class	D/C: HR = 3.88 (3.25 - 4.52)
Perna[48] 2006	Cohort decompensated HF patients	n=76 mean age: 62.3y (15) 71% male	ADM mean: 6,234 (7,420) D/C mean: 5,146 (7,069) Cutpoint: >3,700	NT-proBNP at ADM, cTnT, SBP, HR, blood urea, previous hospitalization, LVEF	252 days composite (all-cause mortality or HF re-hospitalizations (30, 76)	multi-variable cox regression	cTnT, SBP, HR, blood urea, previous hospitalization, LVEF	ADM: HR= 5.1 (2.3, 12.2), p<0.0001
			ADM mean: 6,234 (7,420) D/C mean: 5,146 (7,069) Cutpoint: >3,700	NT-proBNP at ADM, NT-proBNP D/C, cTnT, SBP, HR, blood urea, previous hospitalization, LVEF	252 days composite (all-cause mortality or HF re-hospitalizations (30, 76)	multi-variable cox regression	NT-proBNP D/C, cTnT, SBP, HR, blood urea, previous hospitalization, LVEF	ADM: HR= 5.0 (2.3, 11.2), p<0.0001
Fernández[64] 2009	Cohort patients hospitalized for acute HF	n=138 mean age: 74y (67 - 80)** 54% male	ADM mean: Tertile 1= 2,358 (1,359–3,853)** Tertile 2= 3,571 (1,680–7,597)** Tertile 3= 5,255 (2,968–14,543)** D/C mean: NR Cutpoint: per 100 pg/dl	NT-proBNP, age, hyperlipidemia, NYHA class, DM, previous MI, anemia, cTnT, cystatin C, creatinine, MDRD	261 days** composite (all-cause mortality or HF re-ADM (60, 138)	multi-variable cox regression	age, hyperlipidemia, NYHA class, DM, previous MI, anemia, cTnT, cystatin C, creatinine, MDRD	ADM: HR=1.004 (1.001, 1.007) per 100 pg/dl

Table J-22. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of all-cause mortality and cardiovascular morbidity—admission and discharge (all time periods) in patients with decompensated heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Korewicki[77] 2011	Cohort Severe chronic HF in patients considered for heart transplantation	n=983 mean age: 49.38y (11.2) 87.8% male	ADM mean: 2,294.5 (28.0-46,128) D/C mean: NR Cutpoint: ≥ 4,302 pg/mL	NT-proBNP, NYHA class, HFSS, BMI, hs-CRP, PCWP, PASP, SBP	601 days** composite (all-cause mortality or Heart transplantation (164, 983)	multi-variable cox regression	Left atrial volume index, Pulmonary artery systolic pressure, E/E ratio	ADM: HR= 1.600 (1.074, 2.385), p<0.0001

**median

Abbreviations: ADM = admission; AF = atrial fibrillation; BMI = body mass index; CRP = C-reactive protein; cTnT = cardiac troponin T; D/C = discharge; DM = diabetes mellitus; EF = ejection fraction; HF = heart failure; HFSS = Heart Failure Survival Score; HR = heart rate; hsCRP = high-sensitivity c-reactive protein; LV = left ventricular; MDRD = Modification of Diet in Renal Disease formula; MI = myocardial infarction; NR=not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCWP = pulmocapillary wedge pressure; SBP = systolic blood pressure; yrs=years

Table J-23. Studies evaluating independent predictive value of NT-proBNP for the composite outcome of cardiovascular mortality and morbidity - admission and discharge (all time periods) in patients with decompensated heart failure

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Verdiani[67] 2008	Cohort Patients hospitalized with acutely decompensated HF	n=120 mean age: 77.8yrs (9) 56.6% male	ADM mean: 10,912 (12,239) D/C mean: 4,701 (4,898) Cutpoint: change in NT-proBNP 30%	NT-proBNP (reduction %), gender, ischemic etiology of HF, COPD, DM, depression, CRF, HT, creatinine, sodium, Hb, LVEF, NYHA, LOS	6 months composite (CV death or readmission) (52, 120)	multivariable Cox regressions	gender, ischemic etiology of HF, COPD, DM, depression, CRF, HT, creatinine, sodium, Hb, LVEF, NYHA, LOS	Change reduction <30%: HR = 2.04 (1.02 - 4.08), p=0.04
Bayes-Genis[54] 2006	Cohort decompensated HF patients	n=59, mean age: 60yrs (14) 76.3% male	ADM mean: 7,050 (6,620) D/C mean: NR Cutpoint: per 10% reduction in NT-proBNP	NT-proBNP (relative reduction at 2 weeks), clinical score, age, LVEF, NYHA class	3 months composite (CV mortality or HF hospitalizations (23, 59)	multi-variable step-wise cox regression	clinical score, age, LVEF, NYHA class	Change Decrease at 2 weeks: HR= 0.79 (0.70, 0.88), p<0.001
Park[58] 2010	Cohort decompensated HF patients	n=193 mean age: 69yrs(13) 39.3% male	ADM mean: with events= 6,634.24 (3.85) no events= 3,327.57 (3.85) D/C mean: NR Cutpoint: per log unit	logNT-proBNP, uric acid, Age, CrCl, ACE inhibitors, ARB, Diuretics	3 months composite (cardiac mortality or HF re-hospitalizations (28, 193)	multi-variable cox regression	uric acid, age, CrCl, ACE inhibitors, ARB, Diuretics	Admission: HR= 1.263 (0.897, 1.780), p=0.182
Ho[75] 2011	Cohort patients hospitalized for acute HF	n=87 mean age: 73yrs (14) 79.0% male	ADM mean: MACE (–)= 2,305 (2,202) MACE (+)= 5,084 (5,688) D/C mean: NR Cutpoint: >1,875	NT-proBNP, Left atrial volume index, Pulmonary artery systolic pressure, E/E ratio	191 days** composite (cardiac mortality or HF re-admission (34, 87)	multi-variable cox regression	Left atrial volume index, Pulmonary artery systolic pressure, E/E ratio	Admission: HR=3.751 (1.834, 7.767), p,0.0001
Dini[60] 2010	Cohort patients hospitalized for systolic HF	n=127 mean age: 68yrs (12) 73.2% male	ADM mean: 1,578 (624 – 3,283)** D/C mean: >1,586 Cutpoint: per 10% reduction in NT-proBNP	NT-proBNP, NYHA class, LVEF, Matrix metalloproteinase-9, E wave deceleration time, Matrix metalloproteinase-3, LV end-systolic volume index	24 months composite (Cardiac mortality or HF hospitalizations (58, 127)	multi-variable cox regression	NYHA class, LVEF, Matrix metalloproteinase-9, E wave deceleration time, Matrix metalloproteinase-3, LV end-systolic volume index	Admission: HR=NR, p=NS

Table J-23. Studies Evaluating independent predictive value of NT-proBNP for the composite outcome of CV mortality and morbidity - admission and D/C (all time periods) in Patients With decompensated HF (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Krackhardt[78] 2011	Cohort patients admitted with decompensated HF secondary to non-ischemic cardiomyopathy	n=155 mean age: NR % males: NR	ADM mean: 968** pg/mL D/C mean: NA Cutpoint: NA	log NT-proBNP, age, gender, NYHA, LVEF, LVEDP, LVEDD, rhythm AF, history of hypertension, diabetes, renal dysfunction	8.9 years** cardiac death/urgent cardiac transplantation (NR)	cox proportional hazards	age, gender, NYHA, LVEF, LVEDP, LVEDD, rhythm AF, history of hypertension, diabetes, renal dysfunction	Admission: HR=2.76 (1.53-4.98)

Abbreviations: ADM = admission; AF = atrial fibrillation; BMI = body mass index; CRP = C-reactive protein; cTnT = cardiac troponin T; D/C = discharge; DD = diastolic dysfunction; DM = diabetes mellitus; E/Em = E wave deceleration time, Em; EF = ejection fraction; ER = emergency room; HF = heart failure; HFSS = Heart Failure Survival Score;HR = HR; hsCRP = high-sensitivity c-reactive protein; IL-6 = interleukin-6; LOS = length of stay; LV = LV; LV = LV; MDRD = Modification of Diet in Renal Disease formula; MI = myocardial infarction; NR=not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCWP= Pulmocapillary wedge pressure; SBP = systolic blood pressure; yrs=years

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
<31d	Peacock[44] 2011 BACH	Cohort Patients with acute HF	n=466 mean age: 70.8y(14) 58.6% male	ADM mean: BNP 764 (402-1,415) D/C mean: NA Cutpoint: NA	logBNP, logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	14d 14 day mortality	Cox proportional hazards	logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	logBNP chi-square 0.1 p=0.768 c index=0.513
		Cohort Patients with acute HF	n=466 mean age: 70.8y(14) 58.6% male	ADM mean: NT-proBNP 5,165 (2,332-10,096) D/C mean: NA Cutpoint: NA	logNT-proBNP, logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	14d 14 day mortality	Cox proportional hazards	logBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	logNT-proBNP chi-square 1.8 p=0.179 c index=0.586
	Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 24h, age, cTnT, eGFR*, NYHA*	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	BNP HR=NR per 100pg/mL increase, p=significant
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 48h, age, cTnT*, eGFR*, NYHA*	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	BNP HR=NR per 100pg/mL increase, p=significant

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure (continued)

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
<31d (cont'd)	Noveanu[42] 2011 (cont'd)	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (,3068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP D/C, age, cTnT*, eGFR*, NYHA	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	BNP HR=NR per 100pg/mL increase, p=significant
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 24 hrs, age, cTnT, eGFR*, NYHA*	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	NT-proBNP HR=NR per 1000pg/mL increase, p=NS
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP at 48 hrs, age, cTnT*, eGFR*, NYHA*	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	NT-proBNP HR=NR per 1000pg/mL increase, p=NS
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3068, 14,791)** D/C mean: NR Cutpoint: NR	BNP, NT-proBNP D/C, age, cTnT*, eGFR*, NYHA	30d All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	NT-proBNP HR=NR per 1000pg/mL increase, p=0.05

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure (continued)

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
2 to 3 months	Boisot[41] 2008	Cohort Patients admitted with a diagnosis of acute decompensated HF	n=150 mean age: NR 99.0%male	ADM mean: 635 (304, 1,501)** D/C mean: 399 (174, 400)** Cutpoint: decrease of <10%	Decrease BNP <10%*, BUN, ST2 decrease	90d All-cause mortality (24, 150)	Multivariable logistic regression and ROC analysis	Age >65*, BUN, ST2 decrease, EF*, rales*, wheezing murmurs*, CAD*, MI*, AF*	Decrease BNP <10% OR=1.15 (0.36-3.63), (p=0.817) AUC=0.67, Se=0.63, Sp=0.67
		Cohort Patients admitted with a diagnosis of acute decompensated HF	n=150 mean age: NR 99.0%male	ADM mean: 5,878 (2,297, 11,918)** D/C mean: 3,580 (1,379, 10,102)** Cutpoint: decrease of <3%	Decrease in NT-proBNP <3%, BUN, ST2 decrease	90d All-cause mortality (24, 150)	Multivariable logistic regression and ROC analysis	Age >65*, BUN, ST2 decrease, EF*, rales*, wheezing murmurs*, CAD*, MI*, AF*	NT-proBNP <3% OR=0.19 (0.06-0.61) (p=0.005), NT-proBNP % change from first to last sample AUC=0.78, Se=0.71, Sp=0.23
	Peacock[44] 2011 BACH	Cohort Patients with acute HF	n=466, mean age: 70.8y(14) 58.7%male	ADM mean: BNP 764 (402-1,415) D/C mean: NR Cutpoint: NR	logBNP, logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	90d 90 day mortality	Cox proportional hazards	logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	logBNP chi-square 12.5 p<0.001 c index=0.636
		Patients with acute HF	n=466, mean age: 70.8y(14) 58.7%male	ADM mean: NT-proBNP 5,165 (2,332-10,096) D/C mean: NA Cutpoint: NA	logBNP, logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	90d 90 day mortality	Cox proportional hazards	logNT-proBNP, BUN, MR-proANP, systolic BP, pulse oximetry, creatinine, age, troponin, MR-proADM, copeptin, copeptin and MR-proADM	logNT-proBNP chi-square 25.6 p<0.001 c index=0.693

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure (continued)

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
2 to 3 months (cont'd)	Maisel[40] 2010 BACH	Cohort Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y(13.8) 62.5%male	ADM mean: NR D/C mean: NR Cutpoint: NR	logBNP, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	Age, gender, BMI, creatinine	logBNP HR=1.3 (0.9-1.9) per increase of 1 IQR, p=0.137
		Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y(13.8) 62.5%male	ADM mean: NR D/C mean: NR Cutpoint: NR	logBNP, logMR-proADM, troponin, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	logMR-proADM, troponin, age, gender, BMI, creatinine	logBNP HR=0.9 (0.6-1.4) per increase of 1 IQR, p=0.57
		Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y(13.8) 62.5%male	ADM mean: NR D/C mean: NR Cutpoint: NR	logNT-proBNP, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	Age, gender, BMI, creatinine	logNT-proBNP HR=1.5 (1.0-2.3) per increase of 1 IQR, p=0.041
		Patients with acute HF presenting at ED with dyspnea	n=568 mean age: 71.2y(13.8) 62.5%male	ADM mean: NR D/C mean: NR Cutpoint: NR	logNT-proBNP, logMR-proADM, troponin, age, gender, BMI, creatinine	90d All-cause mortality (65, 568)	Multivariable cox regression	logMR-proADM, troponin, age, gender, BMI, creatinine	log NT-proBNP HR=0.8 (0.5-1.4) per increase of 1 IQR, p=0.46

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure (continued)

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
6 to 11 months	Noveanu[42] 2011	Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 1,315 (759, 2,349)** D/C mean: NR Cutpoint: NR	BNP at 24h, age, cTnT, eGFR*, NYHA*	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.02 (1.01-1.04) per 100 pg/mL increase, Se=0.65, Sp=0.76, AUC=0.77 (0.67-0.86)
					BNP at 48h, age, cTnT*, eGFR*, NYHA	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.03 (1.01-1.06) per 100 pg/mL increase, Se=0.76, Sp=0.71, AUC=0.78 (068-0.87)
					BNP D/C, age, cTnT*, eGFR*, NYHA*	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.02 (1.01-1.03) per 100 pg/mL increase, Se=0.72, Sp=0.74, AUC=0.78 (0.67-0.88)
				ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	NT-proBNP at 24h, age, cTnT, eGFR*, NYHA*	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.01 (0.99-1.04) per 1000pg/mL increase, Se=0.69, Sp=0.77, AUC=0.73 (0.54-0.92)
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	NT-proBNP at 48h, age, cTnT*, eGFR*, NYHA*	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.03 (0.99-1.07) per 1000pg/mL increase, Se=0.72, Sp=0.81, AUC= 0.75 (0.56-0.90)
		Cohort Patients with acute decompensated HF presenting at ED	n=171 mean age: 80y(73, 85)** 60%male	ADM mean: 6,964 (3,068, 14,791)** D/C mean: NR Cutpoint: NR	NT-proBNP D/C, age, cTnT*, eGFR*, NYHA	1y All-cause mortality (60, 171)	Multivariable cox regression and ROC analysis	Age, cTnT, eGFR, NYHA	HR=1.07 (1.01-1.13) per 1000pg/mL increase, Se=0.61, Sp=0.90, AUC= 0.77 (0.63-0.91)

Table J-24. Studies evaluating independent predictive value of both BNP and NT-proBNP for the outcome of all-cause mortality in patients with decompensated heart failure (continued)

Interval	Author Year	Study Design Population	n, mean age, %male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk
6 to 11 months (cont'd)	Sakhuja[39] 2007 PRIDE	Cohort Patients with acute HF presenting to urban academic center	n=209 "increased cTnT" n=96 mean age: 74.3y(11.6) 58%male "no increased cTnT" n=113 mean age: 71.4y(14.9) 45%male	ADM mean: Increase cTnT=544**, no-increase cTnT=221** D/C mean: NR Cutpoint: 352	BNP, cTnT, age, GFR, NYHA class	12m All-cause mortality (NR)	Multivariable cox regression and ROC analysis	cTnT, age, GFR, NYHA class	HR=2.53 (1.53-6.21), p=0.008
				ADM mean: Increase cTnT = 7,703**, no-increase cTnT=2,287** D/C mean: NR Cutpoint: 3,174	NT-proBNP, cTnT, age, GFR, NYHA class	12m All-cause mortality (NR)	Multivariable cox regression and ROC analysis	cTnT, age, GFR, NYHA class	HR=2.76 (1.62-5.36), p=0.004
	Rehman[43] 2008 PRIDE	Cohort Patients with acute HF	n=346 mean age: 73y(13) 68%male	ADM mean: 494 (203, 1,180)** D/C mean: NR Cutpoint: >494	BNP, ST2, CRP, NT-proBNP, age, prior chronic HF*, BB, ACE inhibitor, NYHA*, systolic BP, creatinine	1y Mortality (97, 346)	Multivariable cox regression and ROC analysis	ST2, CRP, NT-proBNP, age, prior chronic HF, BB, ACE inhibitor, NYHA, BP, BMI, S3 gallop, rates on lung exam, BUN, creatinine, WCC, Hb, pleural effusion	HR=2.12 (1.37-3.27), p=0.001
				ADM mean: 3,578 (1,574, 9,446)** D/C mean: NR Cutpoint: >3,578	NT-proBNP, ST2, CRP, BNP, age, prior chronic HF*, BB, ACE inhibitor, NYHA*, systolic BP, creatinine	1y Mortality (97, 346)	Multivariable cox regression and ROC analysis	ST2, CRP, BNP, age, prior chronic HF, BB, ACE inhibitor, NYHA, BP, BMI, S3 gallop, rates on lung exam, BUN, creatinine, WCC, Hb, pleural effusion	HR=1.87 (1.20-2.91), p=0.006

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; AUC=area under the curve; BACH = Biomarkers in Acute Heart Failure; BB = betablocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; 95% CI, = confidence interval; CRP = C-reactive protein; cTnT = cardiac troponin T; d = day(s); D/C = discharge; ED = emergency department; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; h = hour(s); Hb = hemoglobin; HF = heart failure; HR = hazard ratio; IQR = interquartile range; m = month(s); MI = myocardial infarction; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio;

pg/mL = picograms per milliliter; PRIDE = Pro-BNP Investigation of Dyspnea in the Emergency Department; ROC = receiver operating characteristic; RR = relative risk; SD = standard deviation; WCC = white cell count; y = year(s)

Table J-25. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Vrtovec,[80] 2003	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Horwich,[81] 2006	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Ralli,[82] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Boffa,[83] 2009	√	√	X	X	X	X	√	√	√	√	√	X	?	√	√	√	√
Adlbrecht,[84] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Scardovi,[85] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	X	X	√	√
Vrtovec,[86] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	X	X	√	?
Bermingam,[87] 2011	√	√	√	?	√	√	X	√	?	√	√	?	√	?	?	√	X
Neuhold,[38] 2008	X	X	√	√	√	√	√	√	√	√	X	X	√	?	?	√	√
Kruger,[88] 2006	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Kozdag,[89] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Dries,[90] 2010	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Popescu,[91] 2007	√	√	√	?	?	√	√	√	?	?	√	?	X	√	√	√	√
Scardovi[92] 2007	√	√	√	?	?	√	√	√	?	?	√	X	X	?	?	√	√
Moerti,[93] 2009	√	√	√	?	?	√	√	?	√	√	√	√	√	√	√	√	√
Meyer,[94] 2005	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✖ = High Risk ? = unclear

Table J-26. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Vrtovec,[80] 2002	Cohort Patients with advanced heart failure	n=241 mean age: 67y(14) 59.0% male	ADM mean: Prolonged QTc = 786 (321) Normal QTc = 733 (274) D/C mean: NR Cutpoint: >1,000	BNP >1,000, QTc >440 ms, age, male, ischemic cause, NYHA IV, heart rate, SBP, DBP, LVEF, LVEDD, sodium, serum creatinine, inotropes, diuretics, digoxin, ACE inhibitors, betablockers	6m All-cause mortality (46, 241)	Multivariable cox proportional hazard regression	QTc >440 ms, age, male, ischemic cause, NYHA IV, heart rate, SBP, DBP, LVEF, LVEDD, sodium, serum creatinine, inotropes, diuretics, digoxin, ACE inhibitors, betablockers	HR=1.99 (1.18-3.36)
Ralli,[82] 2005	Cohort Patients with advanced HF	n=264 mean age: NR (17-84)** 72.0% male	ADM mean: 850.4 (956.6) D/C mean: NR Cutpoint: ≥ 485	BNP, Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	12m All-cause mortality (46, 264)	Multivariable cox proportional hazard regression	Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	RR=17.34 (2.23-134.9)
	Cohort Anemic patients with high BNP (≥485) vs. non-anemic patients with low BNP (<485)	n=108 mean age: 55y(13) 75.9% male	ADM mean: 1,052 (1,089) D/C mean: NR Cutpoint: ≥ 485	BNP, Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	12m All-cause mortality (29, 108)	Multivariable cox proportional hazard regression	Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	RR=10.36 (3.06-35.10)
	Cohort Non-anemic patients with high BNP (≥485) vs. low BNP (<485)	n=156 mean age: 53y(13) 62.9% male	ADM mean: 711 (829) D/C mean: NR Cutpoint: ≥485	BNP, Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	12m All-cause mortality (17, 156)	Multivariable cox proportional hazard regression	Hb, cTnI, age, sex, EF, NYHA class, HF etiology, PCWP, cardiac output, diabetes mellitus, serum sodium, creatinine, and albumin	RR=4.73 (1.31-17.06)

Table J-26. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Horwich,[81] 2006	Cohort Patients with HF, lean-BMI <25	n=131 mean age: 54y(15) 70.0% male	ADM mean: 747 (272-1,300)** D/C mean: NR Cutpoint: 590	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m All-cause mortality (21, 131)	Multivariable cox proportional hazard regression	gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=4.2 (1.7-10.3)
	Cohort Patients with HF, overweight-BMI 25-29.9	n=99 mean age: 53y(12) 76.0% male	ADM mean: 380 (143-856)** D/C mean: NR Cutpoint: 491	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m All-cause mortality (6, 99)	Multivariable cox proportional hazard regression	gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=16.2 (1.25-21.0)
	Cohort Patients with HF, obese-BMI≥30	n=86 mean age: 51y(11) 78.0% male	ADM mean: 332 (113-617)** D/C mean: NR Cutpoint: 343	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m All-cause mortality (10, 86)	Multivariable cox proportional hazard regression	gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=9.5 (1.5-58.4)
Boffa,[83] 2009	Cohort Patients with HF and LVEF <45%	n=79 mean age: 58y(15) 84.8% male	ADM mean: 572.9 (586.2) D/C mean: NR Cutpoint: NR	BNP, NYHA class, creatinine, IL-6, LVEF	17m All-cause mortality (14, 79)	Multivariable cox proportional hazard regression	NYHA class, creatinine, IL-6, LVEF	HR=1.001 (0.99-1.03)
Meyer,[94] 2005	Cohort Ambulatory chronic HF patients	n=75 mean age: 55y(8) 89.0% male	ADM mean: 328 (406) D/C mean: NR Cutpoint: NR	logBNP, age, gender, BMI, cholesterol (LDL/HDL), History of hypertension, smokers, diabetes mellitus	561d** All-cause mortality (NR)	Multivariable cox proportional hazard regression	age, gender, BMI, cholesterol (LDL/HDL), History of hypertension, smokers, diabetes mellitus	Chi-square=8.7129, p=0.0032

Table J-26. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Adlbrecht,[84] 2009, Berger, 2002; Gwechenberger, 2004; Berger, 2006; Sturm et al, 2000	Cohort Chronic HF outpatients	n=786 mean age: 56.6y(11.4) 82.0% male	ADM mean: 689.4 (4) D/C mean: NR Cutpoint: 689.4	BNP, MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	24m All-cause mortality (233, 786)	Multivariable cox proportional hazard regression	MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	HR=NS, p=0.390
			ADM mean: 689.4 (4) D/C mean: NR Cutpoint: per log unit	logBNP, MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	24m All-cause mortality (233, 786)	Multivariable cox proportional hazard regression	MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	HR=1.32 (1.16–1.50)
			ADM mean: 689.4 (4) D/C mean: NR Cutpoint: per IQR	BNP (inter-quartile range), MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	24m All-cause mortality (233, 786)	Multivariable cox proportional hazard regression	MR-proADM, CT-proET-1, age, gender, GFR, NYHA>II, LVEF	HR=1.60 (1.30–1.95)
Neuhold,[95] 2008	Cohort HF patients representing whole spectrum of HF based on systolic dysfunction	n=786 mean age: 57y(11) 81.0% male	ADM mean: 688 (948) D/C mean: NR Cutpoint: NR	BNP, copeptin, age, NYHA, GFR, LVEF, SBP, sodium, BMI, gender	2y All-cause mortality (233, 786)	Multivariable cox proportional hazard regression	copeptin, age, NYHA, GFR, LVEF, SBP, sodium, BMI, gender	HR=NR
Scardovi,[85] 2008	Cohort Outpatients with stable mild to moderate HF and LVEF <40 % (BNP >250 vs. ≤250)	n=156 mean age: 68y(12) 73.0% male	ADM mean: 207(90-520)** D/C mean: NR Cutpoint: >250	logBNP, LBBB, beta-blockers	2y All-cause mortality (24, 156)	Multivariable cox proportional hazard regression	LBBB, beta-blockers	HR=1.59 (1.07-2.36)
				logBNP, LBBB, beta-blockers, VE/VO2, VE/VCO2 slope, EVR	2y All-cause mortality (24, 156)	Multivariable cox proportional hazard regression	LBBB, beta-blockers, VE/VO2, VE/VCO2 slope, EVR	HR=1.10 (0.67-1.80)

Table J-26. Studies evaluating independent predictive value of BNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bermingham,[87] 2011	Cohort Non-acute HF patients attending disease management program	n=1,294 mean age: 70.6y(11.5) 64.0% male	ADM mean: 326(138-680)** D/C mean: NR Cutpoint: NR	lnBNP, beta2-agonist, age, DBP, smoking status, MI and angina, beta-blocker use, anti-platelet use	2.9y All-cause mortality (341, 1,294)	Multivariable cox proportional hazard regression	beta2-agonist, age, DBP, smoking status, MI and angina, beta-blocker use, anti-platelet use	HR=1.53 (1.33-1.75)
Moertl,[93] 2009	Cohort Patients with chronic HF	n=797 mean age: men= 57y(11) women= 57y(13) 81.9% male	ADM mean: men=2,216 (121,479)** women=217 (117-405)** D/C mean: NR Cutpoint: NR	logBNP, logNT-proBNP, logMR-proANP, NYHA, LVEF, GFR, sodium, age, SBP, ankle edema, gender, diabetes mellitus, BMI	68m** All-cause mortality (492, 797)	Multivariable cox proportional hazard regression	beta2-agonist, age, DBP, smoking status, MI and angina, beta-blocker use, anti-platelet use	HR=1.34 (1.2-1.49)
				logBNP, logNT-proBNP, logMR-proANP, NYHA, LVEF, GFR, sodium, age, SBP, ankle edema, gender, diabetes mellitus, BMI	68m** All-cause mortality (492, 797)	Multivariable cox proportional hazard regression	beta2-agonist, age, DBP, smoking status, MI and angina, beta-blocker use, anti-platelet use	HR=0.944 (0.78-1.15)

Abbreviations: ACE = angiotensin converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; 95% CI, = confidence interval; cTnl = cardiac troponin l; CT-proET-1 = C-terminal pro-endothelin-1 precursor fragment; d = day(s); DBP = diastolic blood pressure; EF = ejection fraction; EVR = enhanced ventilatory response; GFR = glomerular filtration rate; Hb = hemoglobin; HDL = high-density lipoprotein; HF = heart failure; HR = hazard ratio; IL-6 = interleukin-6; LBBB = left bundle branch block; LDL = low-density lipoprotein; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; m = month(s); MI = myocardial infarction; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; PCWP = pulmocapillary wedge pressure; RR = relative risk; SD = standard deviation; SBP = systolic blood pressure; VE/VO2 = ventilation and breathed-out O2 ratio; VE/VCO2 slope = the slope of the regression line relating VE to CO2 output during exercise; y = year(s);

Table J-27. Studies evaluating independent predictive value of BNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Vrtovec,[80] 2002	Cohort Patients with advanced HF	n=241 mean age: 67y(14) 59% male	ADM mean: Prolonged QTc = 786 (321) Normal QTc = 733 (274) D/C mean: NR Cutpoint: >1,000	BNP >1,000, QTc >440 ms, age, male, ischemic cause, NYHA IV, heart rate, SBP, DBP, LVEF, LVEDD, sodium, serum creatinine, inotropes, diuretics, digoxin, ACE inhibitors, betablockers	6m Sudden cardiac death (18, 241)	Multivariable cox proportional hazard regression	QTc >440 ms, age, male, ischemic cause, NYHA IV, heart rate, SBP, DBP, LVEF, LVEDD, sodium, serum creatinine, inotropes, diuretics, digoxin, ACE inhibitors, betablockers	HR=1.76 (1.01-3.07)
					6m Pump failure mortality (24, 241)	Multivariable cox proportional hazard regression	QTc >440 ms, age, male, ischemic cause, NYHA IV, heart rate, SBP, DBP, LVEF, LVEDD, sodium, serum creatinine, inotropes, diuretics, digoxin, ACE inhibitors, betablockers	HR=3.78 (1.63 -8.78)
Vrtovec,[86] 2008	Case-series Patients with HF & LVEF <30% with cholesterol level >150 mg/DL, NYHA class III/IV for min 2m	n=110 mean age: 63y(13) 61% male	ADM mean: 664 (220) D/C mean: NR Cutpoint: >700	BNP, absence of statin therapy, high QTVI, HF of ischemic cause, age >60y	6m Sudden cardiac death (15, 110)	Multivariable cox proportional hazard regression	Absence of statin therapy, high QTVI, HF of ischemic cause, age >60y	HR=1.03 (0.65-1.32)

Abbreviations: ADM = admission; ACE = angiotensin converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; 95% CI, = confidence interval; DBP = diastolic blood pressure; D/C = discharge; HF = heart failure; HR = hazard ratio; IL-6 = interleukin-6; LBBB = left bundle branch block; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; m = month(s); mg/DL = milligram per deciliter; n=number; NR = not reported; NYHA = New York Heart Association; pg/mL = picograms per millimeter; QTVI = QT variability index; SBP = systolic blood pressure

Table J-28. Studies evaluating independent predictive value of BNP for the outcome of cardiovascular morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bermingham[87] 2011	Cohort Non-acute HF patients attending disease management program	n=1,294 mean age: 70.6y(11.5) 64% male	ADM mean: 326(138-680)** D/C mean: NR Cutpoint: NR	lnBNP, beta2-agonist, age, diastolic BP, smoking status, MI and angina, betablocker use, anti-platelet use	2.9y HF hospitalization (NR)	Multivariable cox proportional hazard regression	Beta2-agonist, age, diastolic BP, smoking status, MI and angina, betablocker use, anti-platelet use	HR=1.53 (1.33-1.75)

Abbreviations: ADM = admission; BNP=B-type natriuretic peptide; BP=blood pressure; 95% CI,=confidence interval; D/C = discharge; HF=heart failure; HR=hazard ratio; ln=natural log; MI=myocardial infarction; n=number; NR=not reported; pg/mL=picogram per milliliter; SD=standard deviation; y=year(s)

Table J-29. Studies evaluating independent predictive value of BNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Kruger,[88] 2005	Cohort Patients with chronic HF	n=85 mean age: 59y(13) 74.0% male	ADM mean: event-free grp = 342(354) with events grp = 601(340) D/C mean: NR Cutpoint: 324	BNP, LVEF, NYHA class, age, sex, body mass index, and peak VO2	427d Composite (all-cause mortality & cardiac decompensation) (14, 85)	Multivariable cox proportional hazard regression	LVEF, NYHA class, age, sex, BMI, and peak VO2	HR=NS

Abbreviations: ADM = admission; BMI=body mass index; BNP=B-type natriuretic peptide; 95% CI,=confidence interval; d=day(s); D/C = discharge; grp=group; HR=hazard ratio; LVEF=left ventricular ejection fraction; n=number; NS=non-significant; NR=not reported; NYHA=New York Heart Association; pg/mL=picograms per milliliter; SD=standard deviation

Table J-30. Studies evaluating independent predictive value of BNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Horwich[81] 2006	Cohort Patients with HF, lean-BMI <25	n=131 mean age: 54y(15) 70% male	ADM mean: 747 (272-1,300)** D/C mean: NR Cutpoint: 590	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m Composite (death or urgent heart transplant) (56, 131)	Multivariable cox proportional hazard regression	Gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=3.3 (1.8-5.9)
	Cohort Patients with HF, overweight-BMI 25-29.9	n=99 mean age: 53y(12) 76% male	ADM mean: 380 (143-856)** D/C mean: NR Cutpoint: 491	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m Composite (death or urgent heart transplant) (25, 99)	Multivariable cox proportional hazard regression	Gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=5.4 (1.9-15.3)
	Cohort Patients with HF, obese-BMI≥30	n=86 mean age: 51y(11) 78% male	ADM mean: 332 (113-617)** D/C mean: NR Cutpoint: 343	BNP, gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	15.2m Composite (death or urgent heart transplant) (23, 86)	Multivariable cox proportional hazard regression	Gender, age, LVEF, HF etiology, NYHA class, creatinine, and hypertension	HR=11.5 (2.6-50.2)
Boffa[83] 2009	Cohort Patients with HF and LVEF<45%	n=79 mean age: 58y(15) 84.8% male	ADM mean: 572.9 (586.2) D/C Mean: NR Cutpoint: NR	BNP, NYHA class, creatinine, IL-6, LVEF	17m Composite (death or urgent heart transplant) (23, 79)	Multivariable cox proportional hazard regression	NYHA class, creatinine, IL-6, LVEF	HR=1.0 (0.99-1.01)
Kozdag[89] 2010	Cohort Patients with chronic HF	n=334 mean age: 62y(13) 65.0% male	ADM mean: 642.5 (199-1,377)** D/C mean: NR Cutpoint: >686	logBNP, age, sex, DM, HT, albumin, FT3,diuretics, spironolactone, betablockers, ACE inhibitors, ARB, LVEF,NYHA class, and RV diameter	17m Composite (sudden & HF death, cardiac transplantation, ICD shock due to ventricular fibrillation) (92, 334)	Multivariable cox proportional hazard regression	Age, sex, DM, HT, albumin, FT3,diuretics, spironolactone, betablockers, ACE inhibitors, ARB, LVEF,NYHA class, and RV diameter	HR=3.194 (1.625-6.277)

Table J-30. Studies evaluating independent predictive value of BNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Scardovi[92] 2007	Cohort Outpatients with stable chronic HF	n=244 mean age: 71y(62-76)** 77.0% male	ADM mean: 166 (77 - 403)** D/C mean: NR Cutpoint: >166	BNP, NYHA class, hemoglobin, and creatinine clearance	18m Composite (all-cause mortality, HF hospitalization) (80, 244)	Multivariable cox proportional hazard regression	NYHA class, hemoglobin, and creatinine clearance	HR=1.35 (1.12-1.63)
Popescu[91] 2007	Cohort Patients with symptomatic but stable chronic HF	n=46 mean age: 73y(10) 65.0% male	ADM mean: 206 (98–431)** D/C mean: NR Cutpoint: NR	logBNP, LAVi, advanced LVDD, LVEF, indexed LV volumes, LV mass, wall motion score index, age, gender, E/Vp ratio, E deceleration time, and TAPSE	20m Composite (all-cause mortality, HF hospitalization) (19, 46)	Multivariable cox proportional hazard regression	LAVi, advanced LVDD, LVEF, indexed LV volumes, LV mass, wall motion score index, age, gender, E/Vp ratio, E deceleration time, and TAPSE	HR=NS
Dries[90] 2010	Cohort Outpatients with predominantly systolic HF	n=756 mean age: 57y(14) 69.0% male	ADM mean: 327 (509) D/C mean: NR Cutpoint: 2-fold increase	BNP, age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	2.5y Composite (all-cause mortality, cardiac transplantation and HF hospitalization) (355, 756)	Multivariable cox proportional hazard regression	Age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	HR=1.1 (1.1-1.2) per 2-fold increase in level
	Cohort Outpatients with predominantly systolic HF, BNP tertile 2 vs. 1	n=504 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >55	BNP, age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	2.5y Composite (all-cause mortality, cardiac transplantation and HF hospitalization) (187, 504)	Multivariable cox proportional hazard regression	Age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	HR=1.8 (1.3-2.5)

Table J-30. Studies evaluating independent predictive value of BNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Dries[90] 2010 (cont'd)	Cohort Outpatients with predominantly systolic HF, BNP tertile 3 vs. 1	n=504 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >264	BNP, age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	2.5y Composite (all-cause mortality, cardiac transplantation and HF hospitalization) (232, 504)	Multivariable cox proportional hazard regression	Age, sex, race, tobacco use, creatinine, BMI, LVEF, Ischemic etiology, NYHA class	HR=2.1 (1.5-3.0)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; ARB = angiotensin receptor blockers; BMI = body mass index; BNP = B-type natriuretic peptide; 95% CI, = confidence interval; D/C = discharge; DM = diabetes mellitus; FT3 = free triiodothyronine; HF = heart failure; HR = hazard ratio; HT = hypertension; ICD = implantable cardioverter-defibrillator; IL-6 = interleukin-6; LAVi = left atrial volume indexed to body surface area; LV = left ventricular; LVDD = left ventricular diastolic dysfunction; LVEF = left ventricular ejection fraction; m = month(s); NYHA = New York Heart Association; NR = not reported; NS = non-significant; pc/mL = picograms per milliliter; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; y = year(s);

Table J-31. Studies evaluating independent predictive value of BNP for the outcome of composite of all-cause mortality and all-cause morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bermingham[87] 2011	Cohort Non-acute HF patients attending disease management program	n=1,294 mean age: 70.6y(11.5) 64.0% male	ADM mean: 326(138-680)** D/C mean: NR Cutpoint: NR	lnBNP, beta2-agonist, age, diastolic BP, smoking status, MI and angina, beta-blocker use, anti-platelet use	33m Composite (all-cause hospitalization & mortality) (653, 1,294)	Multivariable cox proportional hazard regression	beta2-agonist, age, diastolic BP, smoking status, MI and angina, beta-blocker use, anti-platelet use	HR=1.28 (1.17-1.41)

Abbreviations: BNP=B-type natriuretic peptide; BP=blood pressure; 95% CI,=confidence interval; HR=hazard ratio; ln=natural log; MI=myocardial infarction; n=number; pg/mL=picograms per milliliter; SD=standard deviation; y=year(s)

Table J-32. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Rothenburger,[96] 2004	√	√	√	X	?	√	√	NA	√	NA	√	?	√	√	√	√	√
Gardner,[97] 2003.	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Gardner,[98] 2005	√	√	√	√	√	√	√	√	?	?	√	?	√	√	√	√	√
Hartmann,[99] 2004	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Corell,[100] 2007	√	√	√	√	√	√	√	√	X	X	√	√	√	X	X	√	√
Schou,[101] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Guder,[102] 2007	√	√	√	√	√	X	√	√	√	√	√	X	√	√	√	√	√
Mikkelsen,[103] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Jankowska,[104] 2006	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Bruch,[105] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Masson,[106] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bruch,[107] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Kistorp,[108] 2005	√	√	√	X	√	√	√	√	√	√	√	√	√	√	√	√	√
George,[109] 2005	√	√	√	?	√	?	√	√	?	?	√	?	√	?	?	√	√
George,[110] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Gardner,[111] 2005	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Gardner,[112] 2005	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Sherwood,[113] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Jankowska,[114] 2010	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√	√	√
Codognotto,[115] 2010	√	√	?	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Dini,[116] 2010	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√
Berger,[117] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Tsutamoto,[118] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Nishiyama,[119] 2009	√	√	√	?	?	√	√	√	?	?	?	?	√	X	X	√	?
Al Najjar,[120] 2009	√	√	√	√	√	√	√	√	X	X	√	?	√	√	√	√	√
Frankenstein,[121] 2009	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Cleland,[122] 2009	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√

Table J-32. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (continued)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Charach,[123] 2009	√	√	√	√	√	√	√	√	?	?	√	?	√	X	X	√	√
Zielinski,[124] 2009	√	√	√	√	?	√	√	√	√	√	√	√	X	X	X	√	√
Poletti,[125] 2008	√	√	X	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Epelman,[126] 2009	√	√	√	√	X	√	√	√	√	√	√	X	X	√	√	√	√
Dini,[127] 2009	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Bayes-Genis,[128] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Frankenstein,[129] 2009	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Kubanek,[130] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Wedel,[131] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Pfisterer,[132] 2009	√	√	√	√	√	√	√		√	NA	√	√	√	√	√	√	√
Koc,[133] 2009	X	√	√	√	√	√	√	NA	√	NA	√	?	X	√	X	√	√
Michowitz,[134] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Honold,[135] 2008	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	√
Tsutamoto,[136] 2008	√	√	√	√	√	√	√	NA	√	NA	√	?	√	X	X	√	√
Hinderliter,[137] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Frankenstein,[138] 2008	√	√	√	√	√	√	√	NA	√	NA	√	X	√	√	√	√	√
Kallistratos,[139] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
Masson,[140] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X
Grewal,[141] 2008	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Bruch,[142] 2008	√	√	√	√	√	√	√	√	√	√	√	X	√	?	?	√	√
Dini,[143] 2008	√	√	√	?	?	√	√	√	?	?	√	√	√	X	X	√	√
Amir,[144] 2008	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pascual-Figal,[145] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Moertl,[146] 2008	√	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√
Koc,[147] 2008	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Pfister,[148] 2008	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Gardner,[149] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Tsutamoto,[150] 2007	√	√	√	?	?	√	√	?	?	?	?	?	√	X	X	√	√

Table J-32. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (continued)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
vonHaehling,[151] 2007	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Schou,[152] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Frankenstein,[153] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Kempf,[154] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Michowitz,[155] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	?
Bayes-Genis,[156] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Yin,[157] 2007	√	√	√	√	√	√	√	√	√	√	√	X	X	X	X	√	√
Petretta,[158] 2007	√	√	√	√	√	√	√	√	√	√	√	X	√	√	X	√	√
Tsutamoto,[159] 2007	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
MacGowan,[160] 2010	√	√	?	√	√	√	√	√	√	√	√	?	X	?	?	√	√
Song,[161] 2010	√	√	√	√	√	√	√	X	√	√	√	√	X	√	√	√	√
Jankowska,[162] 2010	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	X
Jankowska,[163] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Tang,[164] 2011	√	√	√	√	√	√	√	√	√	√	√	√	X	X	X	√	X
Schierbeck,[165] 2011	√	√	√	?	?	√	√	√	?	?	√	X	√	√	√	√	√
Raposeiras-Roubin,[166] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
von Haehling,[167] 2010	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√	√
van den Broek,[168] 2011	√	√	√	?	?	√	√	X	√	√	√	X	√	√	√	√	√
Kawahara,[169] 2011	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Pfister,[170] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Frankenstein,[171] 2011	√	√	√	X	?	√	√	√	?	?	√	X	√	√	√	√	√
Bajraktari,[172] 2011	√	√	√	?	√	√	√	√	√	√	√	?	X	X	X	√	√
Carlsen,[173] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
Broch,[174] 2012	√	√	√	?	?	√	√	√	√	√	√	√	√	?	√	u	√
Tziakas,[175] 2012	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bayes-Genis,[176] 2012	?	?	?	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Franke,[177] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	X	√	√	√	√
Jungbauer,[178] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Table J-32. Risk of bias for prognostic studies using the Hayden Criteria for stable population assessing NT-proBNP (continued)

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Anand,[179] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	X	X	√	√
de Antonio,[180] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Balling,[181] 2012	√	√	√	√	√	√	√		?	?	√	√	√	√	√	√	√
Al-Najjar,[182] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√
Christensen,[183] 2012	√	√	√	?	?	√	√	√	?	?	√	√	√	√	√	√	√
Moertl,[93] 2009	√	√	√	?	?	√	√	?	√	√	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Hartmann[99] 2004	Cohort Secondary analysis of RCT data Patients with severe chronic HF (LVEF <25% and symptoms at rest or on minimal exertion)	n=1,011 mean age: 62.7y(10.9) 81.0% male	ADM mean: 1,767(748 – 3,927)** D/C mean: NR Cutpoint: >1,767	NT-proBNP, treatment group, LVEF, age, sex, cause of HF, creatinine, SBP, recent hospitalization, high-risk combination	159d* All-cause mortality (78, 1,011)	Multivariable cox regression	Treatment group, LVEF, age, sex, cause of HF, creatinine, SBP, recent hospitalization, high-risk combination	RR=2.17 (1.33 - 3.54)
Amir[144] 2008	Cohort Patients referred to outpatient HF center (NYHA class II-IV)	n=70 mean age: 69y(13) 75.7% male	ADM mean: 2,849 (4, 211) D/C mean: NR Cutpoint: >1,958	NT-proBNP (tertiles), age, MBI, LVEF, NYHA, QRS width, ischemic etiology, AF, blood urea level, creatinine, Hb, hs-CRP	6m All-cause mortality (8, 70)	Multivariable logistic regression	Age, MBI, LVEF, NYHA, QRS width, ischemic etiology, atrial fibrillation, blood urea level, creatinine, Hb, hs-CRP	OR=7.6 (1.4 - 40.8)
Gardner[97] 2003	Cohort Patients with advanced HF referred to the Cardiopulmonary Transplant Unit (LVEF ≤35%, NYHA II-IV)	n=142 mean age: 50.4y(10.5) 82.4% male	ADM mean: 1490 (511, 3,887)** D/C mean: NR Cutpoint: >1,490	NT-proBNP, SBP, LVEF, RVEF, peak VO2, HFSS, sodium	374d** All-cause mortality (20, 142)	Multivariable cox regression	SBP, LVEF, RVEF, peak VO2, HFSS, sodium	HR=NR, chi-square=6.03 (p=0.01)
Gardner[112] 2005	Cohort Patients with advanced HF	n=97 mean age: 50.9y(10.5) 86.6% male	ADM mean: 1,548 (604, 4,127)** D/C mean: NR Cutpoint: >1,548	NT-proBNP, RA pressure, PA systolic pressure, PA wedge pressure, cardiac index, LVEF	370d** All-cause mortality (17, 97)	Multivariable cox proportional hazard regression	RA pressure, PA systolic pressure, PA wedge pressure, cardiac index, LVEF	HR=NR, chi-square=13.8, p=0.0002

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Berger[117] 2010	RCT HF patients, NYHA II/IV, cardiothoracic ratio>0.5, LVEF<40%	n=278 mean age: urgent care=71y(13) Nurse MC=73y(11) Intensive BM=70y(12) 67.6% male	ADM mean: urgent care=2,469 (355–15,603)** Nurse MC=2,216 (355–18,487)** Intensive BM=2,216 (355–9,649)** D/C mean: NR Cutpoint: NR	NT-proBNP, LVSD, diabetes, chronic obstructive lung disease, age	12m Mortality (76,278)	Multivariable cox proportional hazard regression	LVSD, diabetes, chronic obstructive lung disease, age	HR=NR
von Haehling[167] 2009	Cohort Patients with chronic HF	n=501 mean age: 63y(11) 92.0% male	ADM mean: 878 (348 – 2,480)** D/C mean: NR Cutpoint: per SD increase	log10NT-proBNP, log10MR-proADM, age, LVEF, NYHA class, creatinine	12m All-cause mortality (70, 501)	Multivariable cox proportional hazard regression	log10MR-proADM, age, LVEF, NYHA class, creatinine	HR=1.43 (0.89 - 2.3) per SD increase
Al-Najjar[182] 2012	Cohort Patients from a community HF clinic who underwent cardiopulmonary exercise testing	n=411 mean age: 65.7y(10.8) 81.4% male	ADM mean: 118 (56-287)** pmol/L D/C mean: NR Cutpoint: NR	log NT-proBNP, age, make, BMI, heart rate at rest, heart rate at peak exercise, 95% CI, index, Delta heart rate, exercise time, peak VO2 slope, LV impairment, LVEDD, loop diuretic, aldosterone antagonist, ACE inhibitor, BB, digoxin, SR, AF, QRS duration	1y All-cause mortality (NR)	Multivariable cox proportional hazard regression	Age, make, BMI, heart rate at rest, heart rate at peak exercise, 95% CI, index, Delta heart rate, exercise time, peak VO2 slope, LV impairment, LVEDD, loop diuretic, aldosterone antagonist, ACE inhibitor, BB, digoxin, SR, AF, QRS duration	HR=NR chi-square= 20.2 p<0.001

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Michowitz[155] 2007	Cohort Patients with CHF attending outpatient clinic (NYHA class II - IV)	n=107 mean age: 71.3y(10.1) 78.5% male	ADM mean: 1942 (2626) D/C mean: NR Cutpoint: per unit increase	NT-proBNP, age, gender, NYHA, LVEF, hyperlipidemia, smoking, HTN, DM, IHD, EPCs, hsCRP, VEGF	17m All-cause mortality (21, 107)	Multivariable cox proportional hazard regression	Age, gender, NYHA, LVEF, hyperlipidemia, smoking, HTN, DM, IHD, EPC, hsCRP, VEGF	HR=1.043 (0.952-1.143) per unit increase
	Cohort Patients with systolic HF	n=78 mean age: NR % male NR	ADM mean: NR D/C mean: NR Cutpoint: per unit increase	NT-proBNP, age, gender, NYHA, LVEF, hyperlipidemia, smoking, HTN, DM, IHD, EPC, hsCRP, VEGF	17m All-cause mortality (NR)	Multivariable cox proportional hazard regression	Age, gender, NYHA, LVEF, hyperlipidemia, smoking, HTN, DM, IHD, EPC, hsCRP, VEGF	HR=1.16 (1.042-1.291) per unit increase
Gardner[111] 2005	Cohort Patients with advanced chronic HF, LVEF≤35%, NYHA functional class II to IV	n=182 mean age: 50.6y(10.5) 79.1% male	ADM mean: 1505 (517-4015)** D/C mean: NR Cutpoint: >1505	NT-proBNP, peak VO2, Na, creatinine, HFSS, HR, BP, LVEF, Hb, anemia, hematocrit	554d** All-cause death (30, 182)	Multivariable cox proportional hazard regression	Peak VO2, Na, creatinine, HFSS, HR, BP, LVEF, Hb, anemia, hematocrit	HR=NR, chi-square=14.2, p<0.001
Dini[143] 2008	Cohort Patients with LV systolic HF, EF ≤45% with moderate to severe MR	n=142 mean age: 71y(11) 78.0% male	ADM mean:3283 (585) D/C Mean: NR Cutpoint: ≥3283	NT-proBNP, RV fractional area change <32%, LVEF, Age >70*, NYHA, AF, gender, E/Em, EGFR	20m** All-cause mortality (46, 142)	Multivariable cox proportional hazard regression	RV fractional area change <32%, LVEF, Age >70*, NYHA, AF, gender, E/Em, EGFR	HR=2.58 (1.24 - 5.37)
Gardner[149] 2007 Gardner, 2003	Cohort Patients with advanced HF referred to the Cardiopulmonary Transplant Unit (LVEF ≤35%, NYHA II-IV)	n=182 mean age: 51.3y(10.5) 80.2% male	ADM mean: 1506 (517-4014)** D/C mean: NR Cutpoint: >1506	NT-proBNP, SBP, LVEF (%), peak VO2, Na, urea, MDRD-1	642d** All-cause mortality (40, 182)	Multivariable cox proportional hazard regression	SBP, LVEF (%), peak VO2, Na, urea, MDRD-1	HR=2.5 (1.0-6.2)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Gardner[98] 2005	Cohort Patients with advanced HF referred to the Cardiopulmonary Transplant Unit (LVEF ≤35%, NYHA II-IV)	n=150 mean age: 50.4y(10.2) 82.7% male	ADM mean: 1494 (530-3930)** D/C mean: NR Cutpoint: >1494	NT-proBNP, Endothelin-1, TN factor-α, Adrenomedullin	666d** All-cause mortality (25, 150)	Multivariable cox proportional hazard regression	Endothelin-1, TN factor-α, Adrenomedullin	HR=NR, chi-square=26.95 (p=0.0001)
Masson[106] 2006 Cohn, 2001	Cohort Secondary analysis of RCT data Patients with stable symptomatic HF (LVEF <40%)	n=3,916 mean age: NR 80.2% male	ADM mean: 895 (375- 1985)** D/C mean: NR Cutpoint: >895	NT-proBNP (deciles), age, BMI, NYHA, LVEF, LVIDD, AF, SBP, BB, ischemic etiology, HR, digoxin, Diuretics, ACE inhibitors, creatinine	23m All-cause mortality (758, 3916)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, BB, ischemic etiology, AF, SBP, HR, digoxin, Diuretics, ACE inhibitors, creatinine	HR=2.07 (1.76-2.46)
	Cohort Patients with NT-proBNP level in 10th decile (>3863) vs. 1st decile (<173)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >3863	NT-proBNP (deciles), age, BMI, NYHA, LVEF, LVIDD, AF, SBP, BBs,ischemic etiology, heart rate, digoxin, diuretics, ACE inhibitors, creatinine	23m All-cause mortality (NR)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, SBP, heart rate, digoxin, Diuretics, ACE inhibitors, beta-blockers, creatinine	HR=4.02 (2.63-6.11)
Rothenburger[96] 2004	Cohort Patients with chronic HF due to LVSD associated with CAD or DCM, NYHA class 3 and class 4	n=276 mean age: NYHA 3= 53y(13) NYHA 4= 54y(10) 67% male	ADM mean: NYHA 3= 1800 (452) NYHA 4= 3800 (499) D/C mean: NR Cutpoint: NR	NT-proBNP, HFSS, NYHA, age, CAD, creatinine, Na, heart rate, QRS, CO, cardiac index, EF, FS, LVEDD, LVESD	2y All-cause mortality (28, 276)	Multivariable logistic regression	HFSS, NYHA, age, CAD, creatinine, Na, heart rate, QRS, CO, cardiac index, EF, FS, LVEDD, LVESD	OR=NR

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
George[110] 2005	Case-series Outpatients from CHF clinic (NYHA class II to IV)	n=188 mean age: 71.4y(11.8) 77.1% male	ADM mean:1556** D/C mean: NR Cutpoint: >1556	NT-proBNP, NYHA, EPO, Hb	24m All-cause mortality (38, 188)	Multivariable cox proportional hazard regression	NYHA, EPO, Hb	HR=NR, chi-square=13.6 (p<0.001)
Jungbauer[178] 2011	Cohort Patients with HF	n=149 mean age: 61.8y(11.6) 87.2% male	ADM mean: 2560 (602-2820)** D/C mean: NR Cutpoint: >900	NT-proBNP, age, sex, LVEF, NYHA, hs-cTnT	757d All-cause mortality (NR)	Multivariable logistic regression	age, sex, LVEF, NYHA, hs-cTnT	OR=2.7 (1.3-5.7)
Dini[116] 2010	Cohort Chronic systolic HF outpatients, LVEF ≤45%	n=489 mean age: 69y(12) 82.0% male	ADM mean: 1522 (2948) D/C mean: NR Cutpoint: 2,466	NT-proBNP, LV ESVi, LVEF, NYHA, PASP, LVEDVi, LA area, AF, moderate-to-severe MR, age>70y, restrictive mitral flow, gender, CAD	25m** All-cause mortality (89, 489)	Multivariate cox regression	LV ESVi, LVEF, NYHA, PASP, LVEDVi, LA area, AF, moderate-to-severe MR, age>70y, restrictive mitral flow, gender, CAD	HR=3.05 (1.81-5.15)
Güder[102] 2008	Cohort Patients with chronic HF	n=294 mean age: 66.2y(12.4) 66.6 % male	ADM mean: 1,020 (178, 13,572)** D/C mean: NR Cutpoint: per tertile	NT-proBNP, age, sex, NYHA class, high C-reactive protein, hypercholesterolemia, ACE inhibitors, serum Na	803d** All-cause mortality (79, 294)	Multivariate cox regression	Age, sex, NYHA class, high C-reactive protein, hyper-cholesterolemia, ACE inhibitors, serum Na	HR=2.16 (1.53-3.05) HR=1.61 (1.248-2.118) per SD increase

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Masson[140] 2008	Case-series Patients with stable symptomatic HF	n=1742 mean age: 63y(11) 80.6% male	ADM mean: 861 (368–1,803)** D/C mean: NR Cutpoint: per unit log	Baseline logNT-proBNP, age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (267, 1724)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.403 (1.241–1.585) per 1 increment on log scale HR=1.993 (1.616-2.459) per 1 increment on log scale
	Case-series Patients with stable symptomatic HF, baseline NT-proBNP quartile Q1	n=436 mean age: NR % male: NR	ADM mean: 199 (12–368)** D/C mean: NR Cutpoint: NR	Baseline NT-proBNP (Q1), age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (34, 436)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.143 (1.025–1.274) per increments of 1 unit (%) of changes in NT-proBNP

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Masson[140] 2008 (cont'd)	Case-series Patients with stable symptomatic HF, baseline NT-proBNP quartile Q2	n=435 mean age: NR % male: NR	ADM mean: 571 (369–859)** D/C mean: NR Cutpoint: NR	Baseline NT-proBNP (Q2), age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (44, 435)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.390 (1.075–1.798) per increments of 1 unit (%) of changes in NT-proBNP
	Case-series Patients with stable symptomatic HF, baseline NT-proBNP quartile Q3	n=436 mean age: NR % male: NR	ADM mean: 1210 (862–1803)** D/C mean: NR Cutpoint: NR	Baseline NT-proBNP (Q3), age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (79, 436)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.615 (1.405–1.865) per increments of 1 unit (%) of changes in NT-proBNP
	Case-series Patients with stable symptomatic HF, baseline NT-proBNP quartile Q4	n=435 mean age: NR % male: NR	ADM mean: 2982 (1807–24428)** D/C mean: NR Cutpoint: NR	Baseline NT-proBNP (Q4), age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (110, 435)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF,LV diameter, Rx of digoxin and diuretics	HR=1.352 (1.060–1.724) per increments of 1 unit (%) of changes in NT-proBNP
	Case-series Patients with stable symptomatic HF, high to low (NT-proBNP >1,078 at baseline to <1,078 at 4m) vs. low to low (NT-proBNP <1,078 at baseline and 4m)	n=1,029 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	Change in NT-proBNP level, age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (89, 1,029)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=0.614 (0.290-1.302), p=0.2036
		n=1,018 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	Change in NT-proBNP level, age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (104, 1018)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.699 (1.051-2.745)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Masson[140] 2008 (cont'd)		n=1,503 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	Change in NT-proBNP level, age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	25m** All-cause mortality (234, 1503)	Multivariate cox regression	Age, BMI, serum creatinine, ischemic etiology of HF, NYHA class, LVEF, LV diameter, Rx of digoxin and diuretics	HR=1.877 (1.180-2.986)
von Haehling[151] 2007	Cohort Patients with chronic HF	n=525 mean age: 61y(12) 94.0% male	ADM mean: 1,671 (625, 3,933)** D/C mean: NR Cutpoint: per SD increase	NT-proBNP, MR-proANP, Age, LVEF, NYHA class, creatinine, BMI	28m All-cause mortality (171, 525)	Multivariate cox regression	MR-proANP, age, LVEF, NYHA class, creatinine, BMI	HR=1.17 (1.04 - 1.31) per SD increase
Schou[101] 2008	Cohort HF patients with LVEF <45% referred to HF clinic	n=345 mean age: BNP ≤1,381: 69y**(NR) BNP >1,381: 75y**(NR) 69.5% male	ADM mean: 1,381** D/C mean: NR Cutpoint: >1,381	NT-proBNP, eGFR, age, BMI, NYHA, LVEF	28m** All-cause mortality (70, 345)	Multivariate cox regression	eGFR, age, BMI, NYHA, LVEF	HR=2.4 (1.41-4.10)
			ADM mean: 1,381** D/C mean: NR Cutpoint: per doubling level	log2NT-proBNP, eGFR, age, BMI, NYHA, LVEF	28m** All-cause mortality (70, 345)	Multivariate cox regression	eGFR, age, BMI, NYHA, LVEF	HR=1.56 (1.32-1.85) per doubling plasma NT-proBNP level
Schou[152] 2007	Cohort Systolic HF patients, LVEF ≤45%	n=345 mean age: anemia: 75y**(NR) non-anemic: 69y**(NR) % male 68.1	ADM mean: NR D/C mean: NR Cutpoint: >1,381	NT-proBNP, eGFR, age, BMI, NYHA, LVEF	28m** All-cause mortality (70, 345)	Multivariate cox regression	eGFR, age, BMI, NYHA, LVEF	HR=3.01 (1.84-5.41)
				NT-proBNP, anemia, eGFR, age, BMI, NYHA, LVEF	28m** All-cause mortality (70, 345)	Multivariate cox regression	anemia, eGFR, age, BMI, NYHA, LVEF	HR=2.68 (1.58-4.55)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Christensen[183] 2012	Cohort Patients with chronic HF	n=194 mean age: 69y(10) 72.0% male	ADM mean: NR D/C mean: NR Cutpoint: per SD increase	NT-proBNP, a-Defensins, age, gender, LVEF, NYHA, creatinine clearance	30m** All-cause mortality (43, 194)	Multivariate cox regression	a-Defensins, age, gender, LVEF, NYHA, creatinine clearance	HR=1.79 (1.30-2.45) per 1 SD increase
Kistorp[108] 2005	Cohort Patients with systolic chronic HF	n=195 mean age: 69.3y(10.3) 71.8% male	ADM mean: 2,508 (875-5,041)** D/C mean: NR Cutpoint: NR	NT-proBNP, adiponectin, BMI, age, LVEF<25%, SBP, creatinine clearance, duration of chronic HF	2.6y** Mortality (46,195)	Multivariate cox regression	Adiponectin, BMI, age, LVEF<25%, SBP, creatinine clearance, duration of chronic HF	HR=2.01 (1.44-3.05)
				NT-proBNP, adiponectin (2 upper tertiles vs. lowest), BMI (2 upper tertiles vs. lowest), age, LVEF<25%, SBP, creatinine clearance, duration of chronic HF	2.6y** Mortality (46,195)	Multivariate cox regression	Adiponectin (2 upper tertiles vs. lowest), BMI (2 upper tertiles vs. lowest), age, LVEF<25%, SBP, creatinine clearance, duration of chronic HF	HR=1.62 (1.09-2.39)
Tsutamoto[159] 2007	Cohort Patients with systolic chronic HF	n=449 mean age: 62.2y(12.3) 81.0% male	ADM mean: 1,125.1 D/C mean: NR Cutpoint: >633	logNT-proBNP, gender, eGFR, diabetes, hyperlipidemia Log adiponectin, cardiac index, LVEF	2.7y** All-cause mortality (47, 449)	Multivariate cox regression	gender, eGFR, diabetes, hyperlipidemia Log adiponectin, cardiac index, LVEF	HR=NR, chi-square =18.322, p=0.0001
Wedel[131] 2009 CORONA study	Case-series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3342 mean age: 72.5y(7.1) 75.0% male	ADM mean:166 (70-358)** D/C mean: NR Cutpoint: per log unit	logNT-proBNP, NYHA, intermittent claudication, diabetes, heart rate	32m** Sudden death (407, 3342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.69 (1.52-1.88)
					32m** Total mortality (934, 3324)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.60 (1.49-1.71)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cleland[122] 2009 CORONA	Case-series Secondary analysis of RCT data Chronic HF patients, ≤60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3664 mean age: T1: 70.8y(6.7) T2: 72.7y(7) T3: 74.5y(7.2) 67.6% male	ADM mean: T1=47(26-78)** pmol/L T2=173 (133-220)** pmol/L T3=486 (367-776)** pmol/L D/C mean: NR Cutpoint: per log unit	logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, SBP/10, creatinine, BMI, heart rate, gender, triglycerides	32m** All-cause mortality (934, 3663)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, SBP/10, creatinine, BMI, heart rate, gender, triglycerides	HR=1.597 (NR)
					32m** Sudden death (407, 3664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, SBP/10, creatinine, BMI, heart rate, gender, triglycerides	HR=1.688 (NR)
Tsutamoto[150] 2007 Tsutamoto, 2006	Cohort Patients with chronic HF	n=353 mean age: 62.4y(13) 90.0% male	ADM mean: 601 (229-1,249)** D/C mean: NR Cutpoint: >601	logNT-proBNP, age, gender, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	2.8y All-cause mortality (35, 353)	Multivariate cox regression	Age, gender, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	HR=NR, chi-square=35.439, p<0.0001
Corell[100] 2007 Galatius, 2002	Cohort HF patients with LVEF <45% referred to HF clinic	n=245 mean age: 70.1y(9.9) 72.0% male	ADM mean: NR D/C mean: NR Cutpoint: per SD increase	logNT-proBNP, age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	996d** All-cause mortality (55, 245)	Multivariate cox regression	Age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	HR=3.6 (2.2-5.8) per 1 SD increase
	Cohort HF patients with AF	n=63 mean age: 73y(9) 77.8% male	ADM mean: 2528 (1,209-4,293)** D/C mean: NR Cutpoint: per SD increase	logNT-proBNP, age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	996d** All-cause mortality (19, 63)	Multivariate cox regression	Age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	HR=4.0 (1.6-10.2) per 1 SD increase
	Cohort HF patients with SR	n=182 mean age: 69y(10) 70.3% male	ADM mean: 899(311-2,183)** D/C mean: NR Cutpoint: per SD increase	logNT-proBNP, age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	996d** All-cause mortality (36, 182)	Multivariate cox regression	Age, sex, LVEF, NYHA, plasma creatinine, AF/SR, heart rate, BB, ACE inhibitor or ARB	HR=3.5 (1.8-6.48) per 1 SD increase

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bayes-Genis[176] 2011	Cohort Ambulatory patients with HF	n=891 mean age: 70.2y(60.5 - 77.2)** 71.6% male	ADM mean:1,376 (527.1 – 3,024)** D/C mean: NR Cutpoint: >1,829	NT-proBNP, ST2, age, gender, ischemic etiology, LVEF, NYHA, eGFR, BMI, DM, ACE inhibitor or ARB treatment, BB, Na, Hb	33.4m** All-cause mortality (244, 891)	Multivariate cox regression	ST2, age, gender, ischemic etiology, LVEF, NYHA, eGFR, BMI, DM, ACE inhibitor or ARB treatment, BB, Na, Hb	HR=1.241 (1.089-1.413) on a continuous scale
Jankowska[104] 2006	Cohort Male chronic HF cases, median LVEF<33%	n=208 mean age: 63y(54-71)** 100% male	ADM mean:1,825 (729-4,216)** D/C mean: NR Cutpoint: per 500 pg/mL increase	NT-proBNP, age, NYHA, LVEF, GFR, Hb, TT, DHEAS, IGF-1, eFT	3y All-cause mortality (75, 208)	Multivariate cox regression	Age, NYHA, LVEF, GFR, Hb, TT, DHEAS, IGF-1, eFT	HR=1.03 (1.01-1.04) per unit increase
	Cohort Male chronic HF cases, median LVEF<33%	n=208 mean age: 63y(54-71)** 100% male	ADM mean:1,825 (729-4216)** D/C mean: NR Cutpoint: per 500 pg/mL increase	NT-proBNP, age, NYHA, LVEF, GFR, Hb, and number of anabolic deficiencies	3y All-cause mortality (75, 208)	Multivariate cox regression	Age, NYHA, LVEF, GFR, Hb, and number of anabolic deficiencies	HR=1.02 (0.99-1.04) per unit increase
Frankenstein[121] 2009	Cohort Patients with stable chronic systolic HF	n=690 mean age: BMI 20-24.9: 65y(10) BMI 25-29.9: 64y(10) BMI >30: 63y(10) 89.0% male	ADM mean: BMI 20-24.9: 1,294 BMI 25-29.9: 1,268 BMI >30: 1,282 D/C mean: NR Cutpoint: per log unit	logNT-proBNP (continuous), age, BP, BB, MDRD, dCMP, gender, BMI group, BMI (kg/m2)	3y All-cause mortality (182,690)	Multivariable cox proportional hazard regression	Age, BP, BB, MDRD, dCMP, gender, BMI group, BMI (kg/m2)	HR=1.48 (1.12-1.95)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Frankenstein[129] 2009	Cohort Chronic stable HF due to LVSD, >65y	n=443 mean age: 73.1y(6.0) 83% male	ADM mean: 1351(538-2772)** D/C mean: NR Cutpoint: NR	log NT-proBNP, age, gender, creatinine, eitology of chronic HF	3y All-cause mortality (90,443)	Multivariable cox proportional hazard regression	Age, gender, creatinine, eitology of chronic HF	HR=1.012 (1.006-1.018)
	Cohort Chronic stable HF due to LVSD, <65y	n=443 mean age: 53.7y(8.6) 83% male	ADM mean: 1361(538-2753)** D/C mean: NR Cutpoint: NR	log NT-proBNP, age, gender, creatinine, eitology of chronic HF	3y All-cause mortality (72,443)	Multivariable cox proportional hazard regression	Age, gender, creatinine, eitology of chronic HF	HR=1.017 (1.012-1.022)
Codognotto[115] 2010	Cohort Hemodialysis patients in NYHA I/II	n=50 mean age: 68y(26-80)** 72% male	ADM mean: 9,719(1,584-27,495)** D/C mean: 10,937(880-36,460)** Cutpoint: 1,000	NT-proBNP (pre D/C), troponin T, C-reactive protein, LA volume, EF, diastolic pattern	3y All-cause mortality (13, 50)	Multivariable cox proportional hazard regression	Troponin T, C-reactive protein, LA volume, EF, diastolic pattern	HR=4.1 (1.02-16.8)
Frankenstein[138] 2008	Cohort Patients with stable chronic systolic HF	n=618 mean age: Grp 1= 64y(11) Grp 2= 62y(11) Grp 3= 62y(11) 90% male	ADM mean: Grp 1= 502 (724–3,569)** Grp 2= 1,110 (387–2,597)** Grp 3= 623 (247–1,496)** D/C mean: NR Cutpoint: NR	NT-proBNP, MDRD, Age, gender, BMI, DM, SBP, LVEF, NYHA class, heart rate, 6MWT, dCMP	37m** All-cause mortality (110, 618)	Multivariable cox proportional hazard regression	MDRD, Age, gender, BMI, DM, SBP, LVEF, NYHA class, heart rate, 6MWT, dCMP	HR=1.011 (1.009–1.014) per 100 pg/mL

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Kubanek[130] 2009	Cohort Patients with chronic HF and LVEF<45%	n=354 mean age: 72y(64-78)** 75% male	ADM mean: 1683 (617-4364)** D/C mean: NR Cutpoint: per log unit	log-NT-proBNP (baseline), ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, mitral regurgitation, 6 min walk, BBs, furosemide, statins, anemia, Na, bilirubin, albumin, eGFR	38.8m** All-cause mortality (125, 354)	Multivariable cox proportional hazard regression	Ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, mitral regurgitation, 6 min walk, BBs, furosemide, statins, anemia, Na, bilirubin, albumin, eGFR	HR=2.71 (1.94-3.78) per 1 log unit
	Cohort Patients alive at 6m followup (2nd assessment)	n=318 mean age: 72y(64, 78)** 76% male	ADM mean: 393 (586-3701)** D/C mean: NR Cutpoint: per log unit	log-NT-proBNP (followup), ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, mitral regurgitation, 6 min walk, BBs, furosemide, statins, anemia, Na, bilirubin, albumin, eGFR	38.8m** All-cause death (89, 318)	Multivariable cox proportional hazard regression	Ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, mitral regurgitation, 6 min walk, BBs, furosemide, statins, anemia, Na, bilirubin, albumin, eGFR	HR=2.45 (1.50-4.01) per 1 log unit
Kempf[154] 2007	Cohort Outpatients with chronic HF	n=455 mean age: 64y(57-71)** 90.5% male	ADM mean: 801 (306-2,308)** D/C mean: NR Cutpoint: NR	lnNT-proBNP, GDF-15, LVEF, age, gender, NYHA, creatinine, uric acid, Hb	40m** All-cause mortality (117, 455)	Multivariable cox proportional hazard regression	GDF-15, LVEF, age, gender, NYHA, creatinine, uric acid, Hb	HR=1.17 (0.96-1.43) per unit increase in the ln scale
Tsutamoto[136] 2008 Tsutamoto, 2008	Cohort Patients with chronic HF	n=356 mean age: 62.6y(13) 78.9% male	ADM mean: 600 (226-1,250)** D/C mean: NR Cutpoint: >796	logNT-proBNP, age, sex, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	3.5y All-cause mortality (40, 356)	Multivariable cox proportional hazard regression	Age, sex, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	HR=NR, chi-square=2.195, p=0.0282
Schierbeck[165] 2011	Cohort HF outpatients, age 18+	n=148 mean age: 68y(NR) 68.9% male	ADM mean: NR D/C mean: NR Cutpoint: NR	logNT-proBNP, PTH upper median, 25_OHD, age, vitamin D insufficiency	3.5y All-cause mortality (53, 148)	Multivariable cox proportional hazard regression	PTH upper median, 25_OHD, age, vitamin D insufficiency	RR=1.52 (1.19-1.93)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Antonio[180] 2012	Cohort Ambulatory patients with HF	n=876 mean age: 68y(12.3) 71.9% male	ADM mean: 3,212 (6,779) D/C mean: NR Cutpoint: 1,720	logNT-proBNP, ln (hs-cTnT), age, gender, ischemic etiology, BB, LVEF, NYHA, eGFR, BMI, DM, ACE inhibitor or ARB treatment, Na, Hb	41.4m** All-cause mortality (311, 876)	Multivariable cox proportional hazard regression	ln (hs-cTnT), age, gender, ischemic etiology, LVEF, NYHA, eGFR, BMI, DM, ACE inhibitor or ARB treatment, BB, Na, Hb	HR=1.21 (1.07-1.37) on a continuous log scale
Charach[123] 2009	Cohort Outpatients with severe chronic HF treated in medical center	n=284 mean age: 71.2y(11.31) 76% male	ADM mean: 3,772 (5,715.34) D/C mean: NR Cutpoint: NR	NT-proBNP, age, DM, gender, weight, NYHA, hyperlipidemia, smoking, HTN, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	3.7y All-cause mortality (105, 284)	Multivariable cox proportional hazard regression	Age, gender, weight, hyperlipidemia, smoking, HTN, DM, NYHA, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	HR=1.055 (1.021-1.089)
Vazquez[128] 2009	Cohort Ambulatory patients with chronic HF, NYHA class II/III	n=992 mean age: 65y(12) 72.4% male	ADM mean: NR D/C mean: NR Cutpoint: 1,000	NT-proBNP>1.000 ng/L, prior AVE, LA size, LV end-diastolic diameter, grade 3/4 mitral regurgitation, LVEF≤35%, restrictive filling pattern, AF, LBBB or IVCD, non-sustained VT and frequent VPBs, eGFR, troponin-positive	44m** Sudden death (90,992)	Multivariable cox proportional hazard regression	Prior AVE, LA size, LV end-diastolic diameter, grade 3/4 mitral regurgitation, LVEF≤35%, restrictive filling pattern, AF, LBBB or IVCD, non-sustained VT and frequent VPBs, eGFR, troponin-positive	HR=1.82 (1.14-2.92)
Hinderliter[137] 2008	Cohort Patients with clinically stable HF recruited from HF clinics (LVEF ≤40%)	n=211 mean age: 57y(12) 69% male	ADM mean: 1675 (2657) D/C mean: NR Cutpoint: NR	Change in NT-proBNP, age, LVEF, LVDV, deceleration time, MR area, LA volume index, tricuspid annular excursion, TR area, RA volume index	4y** All-cause mortality (71, 211)	Multivariable cox proportional hazard regression	Age, LVEF, LVDV, deceleration time, MR area, LA volume index, tricuspid annular excursion, TR area, RA volume index	HR=2.202 (1.65-2.48) for a change of 2000 pg/mL

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Anand[179] 2011	Cohort HF patients with Preserved Ejection	n=3,480 mean age: NR % male: NR	ADM mean: 869(1,746) D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, COPD, HT, AF, DM, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (695, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.57 (1.45-1.71) per log unit
			ADM mean: 869(1,746) D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, HT, AF, DM, COPD, ischemic etiology, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (695, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR= 2.04 (1.68-2.47)
	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, “Q2 vs. Q1”	n=1,638 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (180, 1,638)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, HR, COPD, BMI, SBP, Hb level, eGFR, EF, serum albumin, Na, and neutrophil count	HR=1.55 (1.14-2.98) per log unit

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Anand[179] 2011 (cont'd)	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, "Q3 vs. Q1"	n=1,645 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (247, 1,645)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, HRCOPD, BMI, SBP, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=2.05 (1.53-2.75) per log unit
	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, "Q4 vs. Q1"	n=1,639 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (402, 1,639)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=3.68 (2.74-4.95) per log unit
	Cohort HF patients with Preserved Ejection, Irbesartan vs. placebo, below NT-proBNP median	n=1,737 mean age: placebo: 70y(6.5) Irbesartan: 70y(6.4) 35% male	ADM mean: NR D/C mean: NR Cutpoint: <339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (189, 1737)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, HR, COPD, BMI, SBP, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=0.75 (0.56-0.99), p=0.046
		n=1,737 mean age: placebo: 74y(7.1) Irbesartan: 73y(6.9) 43.5% male	ADM mean: NR D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, heart rate, Hb level, EF, eGFR, serum albumin, Na, neutrophil count	49.5m All-cause mortality (546, 1737)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, SBP, HR, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.03 (0.87-1.22), p=0.71
Al-Najjar[120] 2009	Cohort Patients referred to a specialist HF clinic (LVEF <45%)	n=1087 mean age: 71.9y (64.6-77.8)** 74.3% male	ADM mean: 156(62.1, 398.7)** pmol/L D/C mean: NR Cutpoint: NR	logNT-proBNP, age, normalized RDW, WCC, Na, urea, RDW, creatinine, Hb, NYHA, loop diuretic, severity of LV dysfunction, SR, IHD, BMI, diabetes, gender	52m** All-cause mortality (440, 1087)	Multivariable cox proportional hazard regression	Age, normalized RDW, WCC, DM, Na, urea, RDW, creatinine, Hb, NYHA, loop diuretic, severity of LV dysfunction, SR, IHD, BMI, gender	HR=2.06 (1.68-2.52)

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Michowitz[134] 2008	Cohort Patients with clinically controlled CHF attending the outpatient clinic	n=285 mean age: 71.2y(11.3)** 75.4% male	ADM mean: NR D/C mean: NR Cutpoint: per unit increase	NT-proBNP, age, weight, gender, NYHA, LVEF, hyperlipidemia, smoking, diabetes, ischemic heart disease, MPO	53.5m** All-cause mortality (106, 285)	Multivariable cox proportional hazard regression	Age, weight, gender, NYHA, LVEF, hyperlipidemia, smoking, diabetes, ischemic heart disease, MPO	HR=1.006 (1.004-1.009) per unit increase
Balling[181] 2012	Cohort Patients referred for HF management in a single HF clinic	n=340 mean age: tertile 1: 69.2y(11.1) tertile 2: 70.6y(11) tertile 3: 74.2y(9.5) 76% male	ADM mean: tertile 1: 162 (223) tertile 2: 216(303) tertile 3: 533(1,033) D/C mean: NR Cutpoint: NR	logNT-proBNP, age, sex, IHD, SBP, heart rate, plasma Na, eGFR, LVEF <0.3 vs. >aZ0.3, loop diuretic dose, NYHA functional class	55m** All-cause mortality (165, 340)	Multivariable cox proportional hazard regression	Age, sex, IHD, SBP, heart rate, plasma Na, eGFR, LVEF <0.3 vs. >aZ0.3, loop diuretic dose, NYHA functional class	HR=2.7(1.8-3.9), p<.0001
Carlsen[173] 2012 Copenhagen Hospital Heart Failure Study	Cohort Patients with clinically controlled HF attending the outpatient clinic	n=433 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: NR	NT-proBNP, age, sex, HF, MI, angina, SBP, DM, diastolic BP, HTN, AF, cancer, Na, Hb, COPD, ever smoked, pulse, loop diuretic D/C, creatinine	5y All-cause mortality (NR)	Multivariable cox proportional hazard regression	Age, weight, gender, NYHA, LVEF, hyperlipidemia, smoking, diabetes, ischemic heart disease, MPO	HR=NR

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Frankenstein[171] 2011	Cohort Systolic dysfunction (EF <40%), derive sample	n=636 mean age: 55.5y(11.7) 81% male	ADM mean: NR D/C mean: NR Cutpoint: 738	NT-proBNP, BB, age, sex	67m** All-cause mortality (151, 636)	Multivariable cox proportional hazard regression	BB, age, sex	HR=1.889 (1.347 – 2.649) per 100 pg/mL
			ADM mean: Male : 687 Female : 751 D/C mean: NR Cutpoint: NR	NT-proBNP, BB, age, sex	67m** All-cause mortality (151, 636)	Multivariable cox proportional hazard regression	BB, age, sex	HR=2.030 (1.434 – 2.873) per 100 pg/mL
			ADM mean: No BB : 708 bbl : 808 D/C mean: NR Cutpoint: NR	NT-proBNP, BB, age, sex	67m** All-cause mortality (151, 636)	Multivariable cox proportional hazard regression	BB, age, sex	HR=2.197 (1.563 – 3.008) per 100 pg/mL
Frankenstein[171] 2011	Cohort Systolic dysfunction (EF <40%), validation sample	n=676 mean age: 73.8y(9.9) 76% male	ADM mean: NR D/C mean: NR Cutpoint: 738	NT-proBNP, BB, age, sex	67m** All-cause mortality (160, 676)	Multivariable cox proportional hazard regression	BB, age, sex	HR=1.889 (1.347 – 2.649) per 100 pg/mL
			ADM mean: Male=687 Female=751 D/C mean: NR Cutpoint: NR	NT-proBNP, BB, age, sex	67m** All-cause mortality (160, 676)	Multivariable cox proportional hazard regression	BB, age, sex	HR=2.967 (1.909 – 4.611) per 100 pg/mL
			ADM mean: No BB:708 BB:808 D/C mean: NR Cutpoint: NR	NT-proBNP, BB, age, sex	67m** All-cause mortality (160, 676)	Multivariable cox proportional hazard regression	BB, age, sex	HR=3.014 (1.954 – 4.651) per 100 pg/mL

Table J-33. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Moertl[93] 2009 Unidentified previous study	Cohort Patients with chronic HF	n=797 mean age: Men:57y(11) Women:57y(13) 81.9% male	ADM mean: Men:2,216 (121, 479)** Women:217 (117, 405)** D/C mean: NR Cutpoint: NR	logNT-proBNP, NYHA, LVEF, GFR, Na, age, SBP, ankle edema, gender, DM, BMI	68m** All-cause mortality (492, 797)	Multivariable cox proportional hazard regression	NYHA, LVEF, GFR, Na, age, SBP, ankle edema, gender, DM, BMI	HR=1.4 (1.25-1.56)
				logNT-proBNP, logMR-proANP, logBNP, NYHA, LVEF, GFR, Na, age, SBP, ankle edema, gender, DM, BMI	68m** All-cause mortality (492, 797)	Multivariable cox proportional hazard regression	logMR-proANP, logBNP, NYHA, LVEF, GFR, Na, age, SBP, ankle edema, gender, DM, BMI	HR=1.136 (0.94-1.37)
Frankenstein[153] 2007	Cohort Systolic HF patients who had cardiac transplant evaluation	n=513 mean age: 54.7y(10.5) 83% male	ADM mean: 1,387 (587, 3,064)** D/C mean: NR Cutpoint: NR	NT-proBNP, NYHA, LVEF, pVO2, 6MWT, BBL, noradrenaline, adrenaline, ANP	91m All-cause mortality (202, 513)	Multivariable cox proportional hazard regression	NYHA, LVEF, pVO2, 6MWT, BBL, noradrenaline, adrenaline, ANP	HR=NR, p<0.001
Broek[168] 2011 CHS	Cohort Community-based subjects with HF (aged ≥65 years)	n=208 mean age: 75.2y(6.1) 49% male	ADM mean: depression: 496 (159, 1,632)** No depression: 520 (148, 1,716)** D/C mean: NR Cutpoint: >190	NT-proBNP, age, gender, race, SBP, cholesterol, DM, BMI, smoking, reduced physical activity, LVEF, LV hypertrophy, CHD at baseline	14y All-cause mortality (168, 208)	Multivariable cox proportional hazard regression	Age, gender, race, SBP, cholesterol, DM, BMI, smoking, reduced physical activity, LVEF, LV hypertrophy, CHD at baseline	HR=2.19 (1.40-3.43)

Abbreviations: 25_OHD = 25-hydroxyvitamin D; 6MWT = 6 minute walk test; ACE = angiotensin converting enzyme; AF = atrial fibrillation; SR = sinus rhythm; ANP = A-type natriuretic peptide; APO A-I = apolipoprotein A1; AVE = atherosclerotic vascular event; BB = betablocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHD = chronic heart disease; CHF = congestive heart failure; CHS = Cardiovascular Health Study; 95% CI, = confidence interval; CO = cardiac output; COPD = chronic obstructive pulmonary disease; d = day(s); DCM = dilative cardiomyopathy; dCMP = deoxycytidine monophosphate; DHEAS = dehydroepiandrosterone sulfate; DM = Diabetes Mellitus; E/Em = E wave deceleration time, Em; EF = ejection fraction; eFT = estimated free testosterone; eGFR = estimated glomerular filtration rate; EPCs = endothelial progenitor cells; EPO = erythropoietin; FS = shortening fraction; GDF-15 = growth differentiation factor-15; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HFSS = Heart Failure Survival Score; HR = hazard ratio; hsCRP = high-sensitivity c-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; HTN = hypertension; IGF-1 = insulin-like growth factor-1; IHD = idiopathic heart disease; IVCD = intraventricular conduction delay; kg/m2 = kilograms per meter squared; LBBB = left bundle branch block; LDL = low-density lipoprotein; ln=natural log; LV = left ventricular; LV ESVi = left ventricular end-systolic volume index; LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVIDD = left ventricular internal diastolic dimension; LVSD = left ventricular systolic dysfunction; m = month(s); MDRD = Modification of Diet in Renal Disease formula; MR = mitral regurgitation; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; n=number; Na = sodium; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; PA = pulmonary artery; PASP = pulmonary artery systolic pressure; pg/mL = picograms per milliliter; PTH = parathyroid hormone; QRS = quick release system; RA = right atrial; RDW = red blood cell distribution width; RR = relative risk; RVEF = right ventricular ejection fraction; Rx = prescription; SD = standard deviation; TN factor-α = tumor necrosis factor-alpha; TR = tricuspid regurgitation; TT = total testosterone; VEGF = vascular endothelial growth factor; VO2 = oxygen ventilation; VPBs = ventricular premature beats; vs. = versus; VT = ventricular tachycardia; WCC = white cell count; y = year(s)

Table J-34. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Jankowska,[163] 2011	Cohort Patients with systolic chronic HF	n=491 mean age: 63y(11) 91.0% male	ADM mean: 875 (347, 2,465)** D/C mean: NR Cutpoint: >2,465	log10NT-proBNP, CT-proET-1 (log), NYHA, LVEF, age, serum creatinine	12m CV mortality (70, 491)	Multivariable cox regression	CT-proET-1 (log), NYHA, LVEF, age, serum creatinine	HR=3.36 (2.40-4.71)
Tziakas,[175] 2012	Cohort Patients with acute decompensation of chronic HF admitted to Coronary Care Unit	n=219 mean age: cardiac event: 68.5y(11) No cardiac event: 69.5y(13) 64.3% male	ADM mean: cardiac event: 4,241.5 (6,130) No cardiac event:1,213(2,438) D/C mean: NR Cutpoint: >3,357	D/C NT-proBNP, age, sex, systolic BP, heart rate, BMI, NYHA, underlying etiologies, accompanying disease, echocardiographic data, mediation during followup, laboratory results	12m CV mortality (56, 196)	Multivariable cox regression	Age, sex, systolic BP, heart rate, BMI, NYHA, Underlying etiologies, accompanying disease, echocardiographic data, mediation during followup, laboratory results.	HR=0.43 (0.23-0.79), p=0.007
Petretta,[158] 2007	Cohort Chronic HF patients without cachexia referred to institution	n=82 mean age: 61y(13) 74.0% male	ADM mean: 844 (220.2, 2,755.5)** D/C mean: NR Cutpoint: per log unit	NT-proBNP, NYHA, heart rate, IGF-I, log IGF-I/GH ratio	18.4m CV mortality (70, 491)	Multivariable cox regression	NYHA, heart rate, IGF-I, log IGF-I/GH ratio	HR=1.02 (1.01 - 1.03) per unit increase p<0.001
			ADM mean: 844 (220.2, 2,755.5)** D/C mean: NR Cutpoint: >844	logNT-proBNP, NYHA, heart rate, IGF-I, log IGF-I/GH ratio	18.4m CV mortality (70, 491)	Multivariable cox regression	NYHA, heart rate, IGF-I, log IGF-I/GH ratio	HR = 9.79 (3.02 - 31.8) p<0.001
Raposeiras-Roubin,[166] 2011	Cohort Patients with chronic HF	n=106 mean age: 72y (63, 78.5)** 67.3% male	ADM mean: 2,669.8 (3,274.5) D/C mean: NR Cutpoint: NR	NT-proBNP, sRAGE, SHFS, HDL, Hb, creatinine, GFR	1.3y** Cardiac mortality (11, 106)	Multivariable cox regression	sRAGE, SHFS, HDL, Hb, creatinine, GFR	HR=1.039 (1.014 - 1.065) per 100 pg/mL

Table J-34. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Koc,[147] 2008	Case series Patients with LVSD (LVEF <45%)	n=75 mean age: 53.4 (8.8) 67.3% male	ADM mean: NYHA 1: 266(233) NYHA 2: 979(841) NYHA 3: 3,845(2,094) D/C mean: NR Cutpoint: NT-proBNP at rest for each 50 pg/mL	NT-proBNP at rest (for each 50 pg/mL), absolute change of NT-proBNP (for each 20 pg/mL), LVEDV (for each 10 mL), LVESV (for each 10 mL)	750d Cardiac mortality (14, 75)	Multivariable logistic regression	Absolute change of NT–BNP (for each 20 pg/mL), LVEDV (for each 10 mL), LVESV (for each 10 mL)	OR=0.912 (0.656-1.269)
			ADM mean: NYHA1: 266(233) NYHA2: 979(841) NYHA3: 3,845(2,094) D/C mean: NR Cutpoint: NT-proBNP at rest for each 20 pg/mL	NT-proBNP at rest (for each 20 pg/mL), absolute change of NT–BNP (for each 20 pg/mL), LVEDV (for each 10 mL), LVESV (for each 10 mL)	750d Cardiac mortality (14, 75)	Multivariable logistic regression	Absolute change of NT–BNP (for each 20 pg/mL), LVEDV (for each 10 mL), LVESV (for each 10 mL)	OR=1.106 (1.022-1.197)
Poletti,[125] 2009	Cohort Chronic HF patients with LVSD, EF=31(8)%	n=147 mean age: 64y(12) 80.5% male	ADM mean: Normal breathing: 448.5(147-1,599)** Cheyne-Stokes: 2,575(814-3,320)** D/C mean: NR Cutpoint: NR	Increased NT-proBNP, daytime CS, age, AF, higher NYHA, EF	30m** CV mortality (17,147)	Multivariable cox regression	Daytime CS, age, AF, higher NYHA, EF	HR=2.98 (1.35-6.56)
Tsutamoto,[118] 2010 Tsutamoto, 2006; 2007	Cohort Patients with systolic chronic HF	n=258 mean age: 63.8y(12.8) 78.7% male	ADM mean: 522 (215-1,240)** D/C mean: NR Cutpoint: >627	NT-proBNP, age, NYHA class, ischemic heart disease, LVEDP, LVEF, cTnT, hs-cTnI	2.6y Cardiac mortality (20, 258)	Multivariable cox regression	Age, NYHA class, Ischemic heart disease, LVEDP, LVEF, cTnT, hs-cTnI	HR=4.7 (1.5-14.4)

Table J-34. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cleland,[122] 2009 CORONA	Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3,664 mean age: T1:70.8y(6.7) T2: 72.7y(7) T3:74.5y(7.2) 67.7% male	ADM mean: T1:47(26-78)** pmol/L T2:173(133-220)** pmol/L T3:486(367-776)** pmol/L D/C mean: NR Cutpoint: per log unit	logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatinine, BMI, heart rate, gender, triglycerides	32m** Worsening HF death (230, 3664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatinine, BMI, heart rate, gender, triglycerides	HR=1.986 (NR)
Wedel,[131] 2009 CORONA study	Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3,342 mean age: 72.5y(7.1) 75.0% male	ADM mean: 166 (70-358)** D/C mean: NR Cutpoint: per log unit	log NT-proBNP, NYHA, intermittent claudication, diabetes, heart rate	32m** Death from HF (230, 3,342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.99 (1.71-2.30)
					32m** CV mortality (725, 3,342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.74 (1.60-1.88)
Bayes-Genis,[156] 2007 MUSIC Study	Cohort Patients with HF referred to specialist HF clinics	n=494 mean age: 63y(11) 78.0% male	ADM mean: NR D/C mean: NR Cutpoint: >908	NT-proBNP, indexed LA size >26mm/m2, history of MI, peripheral edema, DM, Hb, NYHA, AF	36m Sudden cardiac death (50, 494)	Multivariable cox proportional hazard regression	Indexed LA size >26mm/m2, history of MI, peripheral edema, DM, Hb, NYHA, AF	HR=3.1 (1.5 - 6.7)
Sherwood,[113] 2007	Cohort HF outpatients, EF of ≤40%	n=204 mean age: 56.8y(12.2) 67.3% male	ADM mean: 1,477 (1,810) D/C mean: NR Cutpoint: 1,000	NT-proBNP, age, HF etiology, LVEF, BDI score, antidepressant	3y** CV mortality (54,204)	Multivariable cox proportional hazard regression	Age, HF etiology, LVEF, BDI score, antidepressant	HR=1.42 (1.42-1.24)
Schierbeck,[165] 2011	Cohort HF outpatients, age 18+	n=148 mean age: 68y(NR) 68.9% male	ADM mean: NR D/C mean: NR Cutpoint: NR	logNT-proBNP, PTH upper median, 25 OHD, age, vitamin D insufficiency	3.5y Cardiac mortality (44, 148)	Multivariable cox proportional hazard regression	PTH upper median, 25_OHD, age, vitamin D insufficiency	HR=NR

Table J-34. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Vazquez,[128] 2009	Cohort Ambulatory patients with chronic HF, NYHA class II/III	n=992 mean age: 65y(12) 72.4% male	ADM mean: NR D/C mean: NR Cutpoint: 1,000	NT-proBNP>1.000 ng/L, prior AVE, LA size, LVEDD, grade 3/4 MR, LVEF≤35%, restrictive filling pattern, AF, LBBB or IVCD, non-sustained VT and frequent VPBs, eGFR, troponin-positive	44m** Cardiac mortality (213, 992)	Multivariable cox proportional hazard regression	Prior AVE, LA size, LVEDD, grade 3/4 MR, LVEF≤35%, restrictive filling pattern, AF, LBBB or IVCD, non-sustained VT and frequent VPBs, eGFR, troponin-positive	HR=2.15 (1.54-3.01)
					44m** Pump-failure death (123, 992)	Multivariable cox proportional hazard regression	prior AVE, LA size, LVEDD, grade 3/4 MR, LVEF≤35%, restrictive filling pattern, AF, LBBB or IVCD, non-sustained VT and frequent VPBs, eGFR, troponin-positive	HR=2.87 (1.80-4.57)
Hinderliter,[137] 2008	Cohort Patients with clinically stable HF recruited from HF clinics (LVEF ≤40%)	n=211 mean age: 57y(12) 69.0% male	ADM mean: 1 675 (2 657) D/C mean: NR Cutpoint: NR	change in NT-proBNP, age, LVEF, LVEDV, deceleration time, MR area, LA volume index, tricuspid annular excursion, TR area, RA volume index	4y** Progressive HF mortality (23, 211)	Multivariable cox proportional hazard regression	Age, LVEF, LVEDV, deceleration time, MR area, LA volume index, tricuspid annular excursion, TR area, RA volume index	HR=NR
					4y** Sudden cardiac death (31, 211)	Multivariable cox proportional hazard regression	Age, LVEF, LVEDV, deceleration time, MR area, LA volume index, tricuspid annular excursion, TR area, RA volume index	HR=NR
Kawahara,[169] 2011	Cohort Stable outpatients with non-ischemic chronic HF	n=95 mean age: 62.3y(9.9) 84.2% male	ADM mean: 603.9 (154, 1,257)** D/C mean: 596.9 (182, 1,006)** Cutpoint: >711	Baseline NT-proBNP, discharge NT-proBNP, hs-cTnI, age, NYHA class, creatinine, gender, LVEF	4.25y** Cardiac mortality (27, 95)	Multivariable cox proportional hazard regression	Discharge NT-proBNP, hs-cTnI, age, NYHA class, creatinine, gender, LVEF	HR=6.8 (2.2 - 20.9)

Table J-34. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Nishiyama,[119] 2009 Tsutamoto, 2008	Cohort Patients with systolic chronic HF	n=107 mean age: 63.6y(13) 85.0% male	ADM mean: 600 (233, 1,184)** D/C mean: NR Cutpoint: NR	logNT-proBNP, age, sex, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	4.3y Cardiac mortality (13,107)	Multivariable cox proportional hazard regression	Age, sex, NYHA class, ischemic heart disease, LVEDP, LVEF, norepinephrine	HR=5.3 (1.31–18.02)
Broek,[168] 2011 CHS	Cohort Community-based subjects with HF (aged ≥65 years)	n=208 mean age: 75.2y(6.1) 49.0% male	ADM mean: depression=496 (159, 1,632)** No depression=520 (148, 1,716)** D/C mean: NR Cutpoint: >190	NT-proBNP, age, gender, race, systolic BP, cholesterol, DM, BMI, smoking, reduced physical activity, LVEF, left ventricular hypertrophy, CHD at baseline	14y CV mortality (97, 208)	Multivariable cox proportional hazard regression	Age, gender, race, SBP, cholesterol, DM, BMI, smoking, reduced physical activity, LVEF, left ventricular hypertrophy, CHD at baseline	HR=2.70 (1.47-4.95)

Abbreviations: 25_OHD = 25-hydroxyvitamin D; AF = atrial fibrillation; ADM = admission; APO A-I = apolipoprotein A1; AVE = atherosclerotic vascular event; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; CHD = chronic heart disease; 95% CI, = confidence interval; CS = Cheyne-Stokes; cTnT = cardiac troponin T; CT-proET-1 = C-terminal pro-endothelian-1 precursor fragment; CV = cardiovascular; d = day(s); D/C = discharge; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GH = growth hormone; Hb = hemoglobin; HDL = high-density lipoprotein; HF = heart failure; HR = hazard ratio; hs-cTnT = high-sensitivity cardiac troponin T; IGF-I = insulin-like growth factor-I; IVCD = intraventricular conduction delay; LA = left atrial; LBBB = left bundle branch block; LVESV = left ventricular end-systolic volume; LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; m = month(s); mm/m2 = millimeter per meter squared; MI = myocardial infarction; MR = mitral regurgitation; n=number; ng/L = nanograms per liter; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pmol/L = picomol per liter; pg/mL = picograms per milliliter; PTH = parathyroid hormone; RA = right atrial; SD = standard deviation; SHFS = Seattle Heart Failure Score; sRAGE = soluble receptor for advanced glycogen end products; TR = tricuspid regurgitation; VPBs = ventricular premature beats; VT = ventricular tachycardia; y = year(s)

Table J-35. Studies evaluating independent predictive value of NT-proBNP for the outcome of all-cause morbidity in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pfister[170] 2011	Cohort Patients with chronic systolic HF	n=125 mean age: 57y(47-66)** 77.6% male	ADM mean: with WRF : 2,870 (1,063-4,765)** no WRF : 547 (173-1,454)** D/C mean: NR Cutpoint: per SD increase	logNT-proBNP, age, NYHA class, LVEF, DM, furosemide equivalent dose, eGFR	18m WRF (28, 125)	Multivariable logistic regression	Age, NYHA class, LVEF, DM, furosemide equivalent dose, eGFR	OR=3.6 (1.9-7.0) per SD increase
Schou[101] 2008	Cohort HF patients with LVEF <45% referred to HF clinic	n=345 mean age: BNP <1,381 : 69y**(NR) BNP >1,381 : 75y**(NR) 69.5% male	ADM mean: 1,381** D/C mean: NR Cutpoint: >1,381	NT-proBNP, eGFR, age, BMI, NYHA, LVEF	28m** Hospitalization (201, 345)	Multivariate cox regression	eGFR, age, BMI, NYHA, LVEF	HR=1.71 (1.24-2.36)
			ADM mean: 1,381** D/C mean: NR Cutpoint: per doubling level	log2NT-proBNP, eGFR, age, BMI, NYHA, LVEF	28m** Hospitalization (201, 345)	Multivariate cox regression	eGFR, age, BMI, NYHA, LVEF	HR=1.19 (1.09-1.31) per doubling plasma NT-proBNP level

Abbreviations: ADM = admission; BMI = body mass index; 95% CI, = confidence interval; D/C = discharge; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; equiv = equivalent; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; m = month(s); n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; SD = standard deviation; WRF = worsening renal function; y = year(s)

Table J-36. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular morbidity in patients with stable heart failure

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Berger[117] 2010	RCT HF patients, NYHA II/IV, cardiothoracic ratio>0.5, LVEF<40%	n=278 mean age: usual care: 71y(13) MC: 73y(11) BM: 70y(12) 67.6% male	ADM mean: usual care: 2,469 (355, 15,603)** MC: 2,216 (355, 18,487)** BM: 2,216 (355, 9,649)** D/C mean: NR Cutpoint: NR	NT-proBNP, LVSD, diabetes, chronic obstructive lung disease, age	12m First HF hospitalization (78, 278)	Multivariable cox proportional hazard regression	LVSD, diabetes, COPD, age	HR=NR
Mikkelsen[103] 2006	Cohort Patients with HF	n=80 mean age: Systolic HF: 70y(58-78)** HFPSF: 68y(53-77)** 50.0% male	ADM mean: Systolic HF: 2,285 (595, 6,395)** HFPSF: 199 (92, 500)** D/C mean: NR Cutpoint: NR	logNT-proBNP, age, sex, BMI, FEV1/FVC, Tei index	12m NYHA class increased or unchanged (47, 80)	Multivariable logistic regression	Age, sex, BMI, FEV1/FVC, Tei index	OR=0.49 (0.31-0.78), p=0.003
Michowitz[155] 2007	Cohort Patients with CHF attending outpatient clinic (NYHA class II - IV)	n=107 mean age: 71.3y(10.1) 78.5% male	ADM mean: 1,942 (2,626) D/C mean: NR Cutpoint: per unit increase	NT-proBNP, age, gender, NYHA, LVEF, hyperlipidemia, smoking, hypertension, DM, IHD, EPCs, hsCRP, VEGF	17m HF hospitalization (26, 107)	Multivariable cox proportional hazard regression	Age, gender, NYHA, LVEF, hyperlipidemia, smoking, hypertension, DM, IHD, EPC, hsCRP, VEGF	HR=1.069 (1.004-1.139) per unit increase p=0.03
Bruch[142] 2008	Cohort Patients with stable chronic HF	n=341 mean age: 57y(12) 79.0% male	ADM mean: 2,155 (4,455) D/C mean: NR Cutpoint: ≥1,474	NT-proBNP, eGFR, NYHA class, serum sodium, LVEF	620d Chronic HF rehospitalization (64, 341)	Multivariable cox proportional hazard regression	eGFR, NYHA class, serum sodium, LVEF	HR=1.26 (1.034-1.548)

Table J-36. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular morbidity in patients with stable heart failure (continued)

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Masson[103], 2006 Cohn, 2001	Cohort Patients with stable symptomatic HF (LVEF <40%)	n=3,916 mean age: NR 80.2% male	ADM mean: 895 (375, 1,985)** D/C mean: NR Cutpoint: >895	NT-proBNP, age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	23m HF hospitalization (634, 3,916)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	HR=2.66 (2.19-3.22)
	Cohort Patients with NT-proBNP level in 10th decile (>3,863) vs. 1st decile (<173)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >3,863	NT-proBNP (deciles), age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	23m HF hospitalization (NR)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	HR=7.51 (4.30-13.11)
Rothenburger[96] 2004	Cohort Patients with chronic HF due to LVSD associated with CAD or DCM presenting to interdisciplinary	n=550 mean age: DCM: 55y(11) CAD: 57y(8) 74.5% male	ADM mean: Heart transplant= 2,293** No heart transplant= 493** D/C mean: NR Cutpoint: >1,000	NT-proBNP, HFSS, NYHA, age, CAD, creatinine, sodium, heart rate, QRS, CO, cardiac index, EF, FS, LVEDD, LVESD	2y Decision for cardiac transplantation (254, 550)	Multivariable logistic regression	HFSS, NYHA, age, CAD, creatinine, sodium, heart rate, QRS, CO, cardiac index, EF, FS, LVEDD, LVESD	OR=10.6 (3.7 - 14.5)
George[110] 2005	Case series Outpatients from CHF clinic (NYHA class II to IV)	n=188 mean age: 71.4y(11.8) 77.1% male	ADM mean:1,556** D/C mean: NR Cutpoint: >1,556	NT-proBNP, NYHA, EPO, hemoglobin	24m CHF hospitalization (43, 188)	Multivariable cox proportional hazard regression	NYHA, EPO, hemoglobin	HR=NR, chi-square=11.2 (p<0.001)

Table J-36. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular morbidity in patients with stable heart failure (continued)

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Wedel[131] 2009 CORONA study	Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3342 mean age: 72.5y(7.1) 75.0% male	ADM mean: 166 (70-358)** D/C mean: NR Cutpoint: per log unit	logNT-proBNP, NYHA, intermittent claudication, diabetes, heart rate	31m** First CV hospitalization (1452, 3,342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.36 (1.29-1.44)
				logNT-proBNP, NYHA, intermittent claudication, diabetes, heart rate	31m** First HF hospitalization (823, 3,342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.73 (1.60-1.87)
				logNT-proBNP, NYHA, intermittent claudication, diabetes, heart rate	31m** Coronary endpoint (741, 3,342)	Multivariable cox proportional hazard regression	NYHA, intermittent claudication, diabetes, heart rate	HR=1.47 (1.36-1.59)
Kubanek[130] 2009	Cohort Patients with chronic HF and LVEF<45%	n=354 mean age: 72y(64-78)** 75.0% male	ADM mean: 1,≤683 (617-4,364)** D/C mean: NR Cutpoint: per log unit	Log-NT-proBNP (baseline), ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, MR, 6MWT, BB, furosemide, statins, anemia, sodium, bilirubin, albumin, eGFR	38.8m** First unplanned CV hospitalization (213, 354)	Multivariable cox proportional hazard regression	Ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, MR, 6MWT, BB, furosemide, statins, anemia, sodium, bilirubin, albumin, eGFR	HR=3.16 (2.24-4.46) per 1 log unit
	Cohort Patients alive at 6m followup (2nd assessment)	n=318 mean age: 72y(64, 78)** 76.0% male	ADM mean: 393 (586-3701)** D/C mean: NR Cutpoint: per log unit	Log-NT-proBNP (followup), ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, MR, 6MWT, BB, furosemide, statins, anemia, sodium, bilirubin, albumin, eGFR	38.8m** First unplanned CV hospitalization (NR, 318)	Multivariable cox proportional hazard regression	Ischemic etiology, weight, NYHA class, diastolic BP, heart rate, QRS duration, LVEDD, MR, 6MWT, BB, furosemide, statins, anemia, sodium, bilirubin, albumin, eGFR	HR=3.11 (2.10-4.59) per 1 log unit

Table J-36. Studies evaluating independent predictive value of NT-proBNP for the outcome of cardiovascular morbidity in patients with stable heart failure (continued)

Author Year Companion	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Charach[123] 2009	Cohort Outpatients with severe chronic HF treated in medical center	n=284 mean age: 71.2y(11.31) 76.0% male	ADM mean: 3772 (5715.34) D/C mean: NR Cutpoint: NR	NT-proBNP, age, gender, weight, hyperlipidemia, smoking, HT, DM, NYHA, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	3.7y Time to first HF hospitalization (NR)	Multivariable cox proportional hazard regression	Age, gender, weight, hyperlipidemia, smoking, HT, DM, NYHA, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	HR=1.01 (0.96-1.05)

Abbreviations: 6MWT = 6 minute walk test; ACE = angiotensin converting enzyme; AF = atrial fibrillation; ADM = admission; BB = betablocker; BM = NT-proBNP-guided, intensive management; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; 95% CI, = confidence interval; CMP = cardiomyopathy; CO = cardiac output; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; d = day(s); D/C = discharge; DCM = dilative cardiomyopathy; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EPCs = endothelial progenitor cells; EPO = erythropoietin; FEV1/FVC = forced expiratory volume in 1 second/forced vital capacity; FS = shortening fraction; HF = heart failure; HFPSF = heart failure with preserved systolic function; HFSS = Heart Failure Survival Score; HR = hazard ratio; hsCRP = high-sensitivity c-reactive protein; HT = hypertension; IHD = idiopathic heart disease; LDL = low-density lipoprotein; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVIDD = left ventricular internal diastolic dimesion; LVSD = left ventricular systolic dysfunction; m = month(s); MC = multidisciplinary care; MR = mitral regurgitation; n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; QRS = quick release system; SD = standard deviation; VEGF = vascular endothelial growth factor; vs. = versus; y = year(s);

Table J-37. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and all-cause morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Hartmann,[99] 2004	Cohort Secondary analysis of RCT data Patients with severe chronic HF (LVEF <25% and symptoms at rest or on minimal exertion)	n=1,011 mean age: 62.7y(10.9) % male: 81	ADM mean: 1,767 (748 – 3,927)** D/C mean: NR Cutpoint: >1,767	NT-proBNP, treatment group, LVEF, age, sex, cause of HF, creatinine, systolic BP, recent hospitalization, high-risk combination	159d** All-cause mortality or hospitalization (293, 1,011)	Multivariable cox proportional hazard regression	Treatment group, LVEF, age, sex, cause of HF, creatinine, systolic BP, recent hospitalization, high-risk combination	RR=2.11 (1.54-2.90)
Masson,[106] 2006 VAL-HeFT	Cohort Secondary analysis of RCT data Patients with stable symptomatic HF (LVEF <40%)	n=3,916 mean age: NR % male: 80.2	ADM mean: 895 (375-1,985)** D/C mean: NR Cutpoint: >895	NT-proBNP (deciles), age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, atrial fibrillation, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	23m Composite (mortality and morbidity) (1,194, 3,916)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	HR=2.20 (1.92-2.51)
	Cohort Patients with NT-proBNP level in 10th decile (>3,863) vs. 1st decile (<173)	n=NR mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >3,863	NT-proBNP (deciles), age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	23m Composite (mortality and morbidity) (NR)	Multivariable cox proportional hazard regression	Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, systolic BP, heart rate, digoxin, diuretics, ACE inhibitors, BB, creatinine	HR=4.74 (3.36-6.70)
Sherwood,[113] 2007	Cohort HF outpatients, EF<=40%	n=204 mean age: 56.8y(12.2), % male: 68.1	ADM mean: 1,477(1,810) D/C mean: NR Cutpoint: >1,000	NT-proBNP, age, HF etiology, LVEF, BDI score, antidepressant	3y** All-cause mortality or hospitalizations (145,204)	Multivariable cox proportional hazard regression	Age, HF etiology, LVEF,BDI score, antidepressant	HR=1.23 (1.12-1.35)

Abbreviations: ACE = angiotensin converting enzyme; AF = atrial fibrillation; ADM = admission; BB = betablockers; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; d = day(s); D/C = discharge; EF = ejection fraction; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; m = month(s); n=number; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; RR = relative risk; SD = standard deviation; vs. = versus; y = year(s)

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Yin,[157] 2007	Cohort Patients with advanced chronic HF	n=152 mean age: 56y(14) 77% male	ADM mean: event-free grp =1,567.0 (540.5-2,599.5)** with events grp =3,624.0 (1,888.5, 6,076.3)** D/C mean: NR Cutpoint: >2,061	NT-proBNP, age, gender, LVEF, ischemic heart disease, systolic BP, sodium, creatinine clearance, cTnI, hsCRP	186d** Composite (cardiac death, heart transplantation or HF hospitalization) (63, 152)	Multivariable cox proportional hazard regression	Age, gender, LVEF, ischemic heart disease, systolic BP, sodium, creatinine clearance, cTnI, hsCRP	HR=2.56 (1.360-4.821)
Bruch,[107] 2006	Cohort Patients with chronic HF	n=73 mean age: 55y(10) 77% male	ADM mean: 2,735 (4774) D/C mean: NR Cutpoint: >2,283	NT-proBNP, RFP, E/E ratio, peak early diastolic mitral annular velocity	226d Composite (chronic HF rehospitalization, cardiac death, or urgent cardiac transplantation) (27, 73)	Multivariable cox proportional hazard regression	RFP, E/E ratio, peak early diastolic mitral annular velocity	RR=8.33 (2.65-26.20), chi-square = 14.89
Bruch,[105] 2006	Cohort Patients with stable chronic HF	n=142 mean age: 58y(13) 74% male	ADM mean: 3,466 (8,977) D/C mean: NR Cutpoint: >1,129	NT-proBNP, sodium, eGFR, Hb	383d Composite (cardiac death or urgent cardiac transplantation) (19, 142)	Multivariable cox proportional hazard regression	Sodium, eGFR, Hb	HR=3.79 (1.62-8.89)
	Cohort Patients with stable chronic HF and chronic kidney disease	n=63 mean age: NR % male: NR	ADM mean: 3,466 (8,977) D/C mean: NR Cutpoint: >1,129	NT-proBNP, sodium, eGFR, Hb	383d Composite (cardiac death or urgent cardiac transplantation) (NR, 63)	Multivariable cox proportional hazard regression	Sodium, eGFR, Hb	HR=2.74 (1.04-7.22)

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Grewal,[141] 2008	Cohort HF patients with EF >40%	n=181 mean age: Normal/Mild diastolic grade= 65y(12) Moderate/ severe diastolic grade= 70y(10) 65% male	ADM mean: Normal/Mild diastolic grade= 376 (638) Moderate/severe diastolic grade=1,419 (3,423) D/C mean: NR Cutpoint: >300	NT-proBNP, age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	524d** Composite (CV mortality, HF hospitalization, and MI or stroke) (17, 181)	Multivariable cox proportional hazard regression	Age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	HR=5.8 (1.3-26.4)
			ADM mean: Normal/Mild diastolic grade= 376 (638) Moderate/severe diastolic grade=1,419 (3,423) D/C mean: NR Cutpoint: >600	NT-proBNP, age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	524d** Composite (CV mortality, HF hospitalization, and MI or stroke) (17, 181)	Multivariable cox proportional hazard regression	Age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	HR=8.0 (2.6-24.8)
			ADM mean: Normal/Mild diastolic grade= 376 (638) Moderate/severe diastolic grade=1,419 (3,423) D/C mean: NR Cutpoint: >100	NT-proBNP, age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	524d** Composite (CV mortality, HF hospitalization, and MI or stroke) (17, 181)	Multivariable cox proportional hazard regression	Age, gender, DM, CAD, HT, AF, NYHA class, EF, Candesartan	HR=3.1 (1.2, 8.2)

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bruch,[142] 2008	Cohort Patients with chronic HF	n=341 mean age: 57y(12) 79% male	ADM mean: 2,155 (4,455) D/C mean: NR Cutpoint: ≥1,474	NT-proBNP, eGFR, NYHA class, serum sodium, LVEF	620d Composite (cardiac events = cardiac death or need for assist device or urgent cardiac transplantation) (57, 341)	Multivariable cox proportional hazard regression	eGFR, NYHA class, serum sodium, LVEF	HR=1.56 (1.23–1.98)
	Cohort Chronic HF patients with ischemic CMP	n=205 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: ≥1,474	NT-proBNP, eGFR, NYHA class, serum sodium, LVEF	620d Composite (cardiac events = cardiac death or need for assist device or urgent cardiac transplantation) (37, 205)	Multivariable cox proportional hazard regression	eGFR, NYHA class, serum sodium, LVEF	HR=1.93 (1.24-2.99)
	Cohort Chronic HF patients with chronic kidney disease	n=183 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: ≥1,474	NT-proBNP, eGFR, NYHA class, serum sodium, LVEF	620d Composite (cardiac events = cardiac death or need for assist device or urgent cardiac transplantation) (35, 183)	Multivariable cox proportional hazard regression	eGFR, NYHA class, serum sodium, LVEF	HR=1.48 (1.12-1.97)
Honold,[135] 2008	Cohort Patients with ischemic HF	n=103 mean age: 57y(11) 89% male	ADM mean: 1,188 (1518) D/C mean: NR Cutpoint: NR	NT-proBNP, NYHA-class, Age, Peak VO2, Peak O2 pulse, EqCO2, EqO2, VE/VCO2	668d Composite (CV mortality and HF hospitalization) (14, 103)	Multivariable cox proportional hazard regression	NYHA-class, age, Peak VO2, peak O2 pulse, EqCO2, EqO2, VE/VCO2	HR=NS, p=0.2

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Koç,[133] 2009	Cohort Patients with HF	n=100 mean age: 53.6y(8.9) 88% male	ADM mean: event-free grp =496 (337–731)** with Events grp =5,417 (3,655–8,029)** D/C mean: NR Cutpoint: >1,000	NT-proBNP, Left ventricular mass index, Heart rate, Creatinine, BUN, Sodium, LV E/A ratio, LVEF, SBP, DBP	750d composite (CV mortality and HF hospitalization) (46, 100)	multi-variable logistic regression	Left ventricular mass index, Heart rate, Creatinine, BUN, Sodium, LV E/A ratio, LVEF, SBP, DBP	OR=1.270 (1.072-1.505)
Jankowska,[114] 2010	Cohort Patients with ischemic HF	n=163 mean age: 60y(10) 100% male	ADM mean: 993 (378-3,200)** D/C mean: NR Cutpoint: >500	NT-proBNP, BDI (continuous), DHEAS (continuous), serum TT, LVEF, BMI, chronic HF etiology, eGFR, NYHA class, III–IV, Hb, age, DM	28m Composite (CV hospitalization or CV mortality) (87, 163)	Multivariable cox proportional hazard regression	BDI (continuous), DHEAS (continuous), serum TT, LVEF, BMI, chronic HF etiology, eGFR, NYHA class, III–IV, Hb, Age, DM	HR=1.01 (1.00-1.03), p=0.09
			ADM mean: 993 (378-3,200)** D/C mean: NR Cutpoint: >500	NT-proBNP, BDI (dichotomous), DHEAS (dichotomous), serum TT, LVEF, BMI, chronic HF etiology, eGFR, NYHA class, III–IV, Hb, age, DM	28m Composite (CV hospitalization or CV mortality) (87, 163)	Multivariable cox proportional hazard regression	BDI (dichotomous), DHEAS (dichotomous), serum TT, LVEF, BMI, chronic HF etiology, eGFR, NYHA class, III–IV, Hb, age, DM	HR=1.02 (1.01-1.03), p=0.01
Broch,[174] 2012	RCT Patients with chronic HF of ischemic etiology, in NYHA class II–IV, and with LVEF ≤40% (≤35% if NYHA II)	n=1,452 mean age: 72y(7) 76.6% male	ADM mean: 1,353 (507-2,901) D/C mean: NR Cutpoint: NR	logNT-proBNP, ST2, LVEF, NYHA class, age, BMI, DM, gender, intermittent claudication, heart rate, eGFR, ratio of Apo lipoprotein (Apo) B to ApoA-1, C-reactive protein	2.6y** Composite (CV death, non-fatal MI or stroke) (NR)	Multivariable cox proportional hazard regression	ST2, LVEF, NYHA class, age, BMI, DM, gender, intermittent claudication, heart rate, eGFR, ratio of Apo lipoprotein (Apo) B to ApoA-1, C-reactive protein	HR=1.59 (1.42-1.79)

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cleland,[122] 2009 CORONA	Case series Secondary analysis of RCT data Chronic HF patients, ≥60y, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3,664 mean age: T1=70.8y(6.7) T2= 72.7y(7) T3=74.5y(7.2) 67.6% male	ADM mean: T1=47(26-78)** pmol/L T2=173(133-220)** pmol/L T3=486(367-776)** pmol/L D/C mean: NR Cutpoint: per log unit	logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	32m** Coronary events (741, 3,664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	HR=1.469 (NR)
				logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	32m** CV mortality/non-fatal MI/non-fatal stroke (883, 3,664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	HR=1.587 (NR)
				logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	32m** Atherothrombotic end point (284, 3,664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatine, BMI, heart rate, gender, triglycerides	HR=1.238 (NR)
Wedel,[131] 2009 CORONA	Case series Secondary analysis of RCT data Chronic HF patients, ≥60y, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3,342 mean age: 72.5y(7.1) 75% male	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, NYHA, heart rate	32m** CV mortality/non-fatal MI/non-fatal stroke (883, 3,342)	Multivariable cox proportional hazard regression	NYHA, heart rate	HR=1.59 (1.49-1.71)
				log NT-proBNP, NYHA, heart rate	32m** Atherothrombotic endpoint (284, 3,342)	Multivariable cox proportional hazard regression	NYHA, heart rate	HR=1.24 (1.10-1.40)

Table J-38. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Bajraktari,[172] 2011	Cohort Outpatients with chronic systolic HF, and LVEF≤45%	n=107 mean age: 68y(12) 75% male	ADM mean: 1,257 (553 – 3,212)** D/C mean: NR Cutpoint: ≥2.47 on log scale	logNT-proBNP, age, gender, T-IVT, mean E/Em ratio, LVEF	37m Composite (cardiac mortality + HF hospitalization) (55, 107)	Multivariable logistic regression	Age, gender, T-IVT, mean E/Em ratio, LVEF	OR=4.162 (1.289-13.44)

Abbreviations: ACE = angiotensin converting enzyme; AF = atrial fibrillation; ADM = admission; BB = betablockers; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CMP = cardiomyopathy; cTnI = cardiac troponin I; CV = cardiovascular; d = day(s); D/C = discharge; DHEAS = dehydroepiandrosterone sulfate; DM = diabetes mellitus; E/Em = E wave deceleration time, Em; EF = ejection fraction; eGFR = estimated glomerular filtration rate; grp = group; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; hsCRP = high-sensitivity c-reactive protein; HT = hypertension; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; m = month(s); MI = myocardial infarction; n=number; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pmol/L = picomol per liter; pg/mL = picogram per milliliter; RCT = randomized controlled trial; RFP = restrictive filling pattern; RR = relative risk; SD = standard deviation; T-IVT = total isovolumic time; TT = total testosterone; VO2 = oxygen ventilation; vs. = versus; y = year(s)

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Zielinski,[124] 2009	Cohort Patients with HF	n=658 mean age: 49.1y(11.6) % male: 88	ADM mean: 2,703** D/C mean: NR Cutpoint: NR	NT-proBNP, hsCRP, HFSS, age, sex, NYHA, arterial BP, Na	167d Composite (all-cause mortality or urgent heart transplantation) (161, 658)	Multivariable cox proportional hazard regression	hsCRP, HFSS, age, sex, NYHA, arterial BP, Na	HR=1.056 (1.032-1.079), p<0.01, c-index = 0.653
Franke,[177] 2011	Cohort Patients with stable chronic HF	n=504 mean age: 58y(48.8–67.7)** % male: 79.8	ADM mean: NR D/C mean: NR Cutpoint: NR	lnNT-proBNP at 6m, lnNT-proBNP at baseline, age, gender, systolic BP, NYHA class, BMI, CRT, EF	12m Composite (death, heart transplantation or HF hospitalization) (50, 504)	Multivariable cox proportional hazard regression	lnNT-proBNP at baseline, age, gender, systolic BP, NYHA class, BMI, CRT, EF	HR=2.434 (1.385-4.280)
				lnNT-proBNP at baseline, LnNT-proBNP at 6m, age, gender, systolic BP, NYHA class, BMI, CRT, EF	12m Composite (death, heart transplantation or HF hospitalization) (50, 504)	Multivariable cox proportional hazard regression	LnNT-proBNP at 6m, age, gender, systolic BP, NYHA class, BMI, CRT, EF	HR=0.445 (0.445-1.461), p=0.478
MacGowan[160] 2010	Cohort Patients with advanced HF	n=91 mean age: 49y(40-58)** % male: 68	ADM mean: 2,473 (1,445-5,278)** D/C mean: NR Cutpoint: >2,473	NT-proBNP, cardiac index, bilirubin	359d** Composite (all-cause mortality, worsening of HF) (34, 91)	Multivariable cox proportional hazard regression	Cardiac index, bilirubin	HR=NR, p=0.036, EXP (B) = 1.001
Berger,[117] 2010	RCT HF Patients, NYHA II/IV, cardiothoracic ratio>0.5, LVEF<40%	n=278 mean age: urgent care=71y(13) Nurse MC=73y(11) Intensive BM=70y(12) % male: 67.6	ADM mean: Urgent care=2,469 (355–15,603)** Nurse MC=2,216 (355–18,487)** Intensive BM=2,216 (355–9,649)** D/C mean: NR Cutpoint: NR	NT-proBNP, LVSD, diabetes, COPD, age	12m First HF hospitalization and mortality (141,278)	Multivariable cox proportional hazard regression	LVSD, diabetes, COPD, age	HR=NR

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pascual-Figal,[145] 2008	Cohort Outpatients with destabilized HF	n=71 mean age: 61y(14) % male: 80	ADM mean: 7,421(6,751) D/C mean: NR Cutpoint: NR	NT-proBNP (baseline), age, sex, LVEF, NYHA class, clinical score, % reduction in NT-proBNP	12m Composite (all-cause mortality and HF hospitalization) (40, 72)	Multivariable cox proportional hazard regression	Age, sex, LVEF, NYHA class, clinical score, % reduction in NT-proBNP	HR=1.000 (1.000-1.000), p=0.530
				% reduction in NT-proBNP, NT-proBNP (baseline), age, sex, LVEF, NYHA class, clinical score	12m Composite (all-cause mortality and HF hospitalization) (40, 72)	Multivariable cox proportional hazard regression	NT-proBNP (baseline), age, sex, LVEF, NYHA class, clinical score	HR=0.982 (0.972–0.992), p=0.001
Song,[161] 2010	Cohort Patients with HF	n=210 mean age: 61y(11) % male: 70	ADM mean: 733 (504) D/C mean: NR Cutpoint: >581	NT-proBNP, age, gender, etiology of HF, BMI, NYHA class, LVEF, and total comorbidity score	397d** Composite (all-cause mortality, HF hospitalization, ED visits) (58, 210)	Multivariable cox proportional hazard regression	Age, gender, etiology of HF, BMI, NYHA class, LVEF, and total comorbidity score	HR=2.02 (1.08-3.78)
Gardner,[97] 2003	Cohort Patients with advanced HF referred to the CTU (LVEF ≤35%, NYHA II-IV)	n=142 mean age: 50.4y(10.5) % male: 82.4	ADM mean: 1,490 (511-3,887)** D/C mean: NR Cutpoint: >1,490	NT-proBNP, systolic BP, LVEF, RVEF, PVO2, HFSS, Na	374d** Composite (all-cause mortality or urgent transplant) (24, 142)	Multivariable cox proportional hazard regression	Systolic BP, LVEF, RVEF, PVO2, HFSS, Na	HR=NR, chi-square=12.68 p=0.01
Gardner,[112] 2005	Cohort Patients with advanced HF	n=97 mean age: 50.9y(10.5) % male: 86.6	ADM mean: 1,548 (604, 4,127)** D/C mean: NR Cutpoint: >1548	NT-proBNP, RA pressure, PASP, PA wedge pressure, cardiac index, LVEF	370d** All-cause or urgent transplant (21, 97)	Multivariable cox proportional hazard regression	RA pressure, PASP, PA wedge pressure, cardiac index, LVEF	HR=NR, chi-square=7.8, p=0.0005

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pfister,[148] 2008	Cohort Patients with chronic systolic HF	n=290 mean age: 64y(54 - 72)** % male: 80	ADM mean: 1,001 (355-2,409)** D/C mean: NR Cutpoint: per SD increase	logNT-proBNP, GFR, SHFS	498d** Composite (all-cause mortality, HF hospitalizations, and urgent cardiac transplantation) (65, 290)	Multivariable cox proportional hazard regression	GFR, SHFS	HR=1.9 (1.5, 2.4) per SD increase
				logNT-proBNP, GFR, CHARM score	498d** Composite (all-cause mortality, HF hospitalizations, and urgent cardiac transplantation) (65, 290)	Multivariable cox proportional hazard regression	GFR, CHARM score	HR=1.7 (1.3, 2.3) per SD increase
Moertl,[146] 2008	Cohort Ambulatory HF patients	n=166 mean age: 70y(12) % male: 65	ADM mean: NR D/C mean: 3,946 (4,478) Cutpoint: NR	logNT-proBNP (discharge), GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (63, 166)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 11.5, p<0.001
			ADM mean: NR D/C mean: 3,946 (4,478) Cutpoint: NR	logNT-proBNP at 3m, GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (63, 166)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 41.5, p<0.0001
			ADM mean: NR D/C mean: 3,946 (4,478) Cutpoint: NR	NT-proBNP % change, GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (63, 166)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 7.5, p<0.01

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Moertl,[146] 2008 (cont'd)	Cohort Ambulatory HF Patients with low NT-proBNP	n=83 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: <1751	logNT-proBNP at 3m, GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (11, 83)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 5.2, p<0.05
	Cohort Ambulatory HF Patients with high NT-proBNP	n=83 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: >1,751	logNT-proBNP at 3m, GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (29, 83)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 6.6, p<0.01
			ADM mean: NR D/C mean: NR Cutpoint: >1,751	NT-proBNP % change, GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	18m Composite (all-cause mortality and HF hospitalization) (29, 83)	Multivariable cox proportional hazard regression	GFR, NYHA, age, heart rate, orthopnea, Na, nocturnal dyspnea	HR=NR, chi-square = 25.9, p<0.0001
Gardner,[111] 2005	Cohort Patients with advanced chronic HF, LVEF≤35%, NYHA functional class II to IV	n=182 mean age: 50.6y(10.5) % male: 79.1	ADM mean: 1,505 (517-4,015)** D/C mean: NR Cutpoint: >1,505	NT-proBNP, PVO2, Na, creatinine, HFSS, heart rate, BP, LVEF, Hb, anemia, hematocrit	554d** All-cause death or urgent transplantation (34, 182)	Multivariable cox proportional hazard regression	PVO2, Na, creatinine, HFSS, heart rate, BP, LVEF, hemoglobin, anemia, hematocrit	HR=NR, chi-square=21.8, p<0.001

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Petretta,[158] 2007	Cohort Chronic HF Patients without cachexia referred to institution	n=82 mean age: 61y(13) % male: 74	ADM mean: 844 (220.2 – 2,755.5)** D/C mean: NR Cutpoint: >844	NT-proBNP, NYHA, heart rate, log IGF-I/GH ratio, creatinine, Hb	18.4m Composite (cardiac death, sudden death, HF hospitalization) (33, 82)	Multivariable cox proportional hazard regression	NYHA, heart rate, log IGF-I/GH ratio, creatinine, Hb	HR=4.50 (2.22-9.15)
			ADM mean: 844 (220.2 – 2,755.5)** D/C mean: NR Cutpoint: per log unit	logNT-proBNP, NYHA, heart rate, log IGF-I/GH ratio, creatinine, Hb	18.4m Composite (cardiac death, sudden death, HF hospitalization) (33, 82)	Multivariable cox proportional hazard regression	NYHA, heart rate, log IGF-I/GH ratio, creatinine, Hb	HR=1.02 (1.01 - 1.03) per unit increase
Dini,[143] 2008	Cohort Patients with LV systolic HF, EF ≤45% with moderate to severe MR	n=142 mean age: 71y(11) % male: 78	ADM mean:3,283 (585) D/C mean: NR Cutpoint: ≥3,283	NT-proBNP, RV fractional area change <32%, LVEF, age >70*, NYHA, AF, gender, E/Em, eGFR	20m** All-cause mortality or HF hospitalization (85, 142)	Multivariable cox proportional hazard regression	RV fractional area change <32%, LVEF, age >70*, NYHA, AF, gender, E/Em, eGFR	HR=2.16 (1.27-3.67)
Gardner,[149] 2007 Gardner, 2003	Cohort Patients with advanced HF referred to the CTU (LVEF ≤35%, NYHA II-IV)	n=182 mean age: 51.3y(10.5) % male: 80.2	ADM mean: 1,506 (517-4,014)** D/C mean: NR Cutpoint: >1,506	NT-proBNP, systolic BP, LVEF (%), PVO2, Na, Urea, MDRD-1	642d** Composite (all-cause mortality or urgent transplant) (44, 182)	Multivariable cox proportional hazard regression	Systolic BP, LVEF (%), PVO2, Na, Urea, MDRD-1	HR=2.7 (1.1-6.4)
Gardner,[98] 2005	Cohort Patients with advanced HF referred to the CTU (LVEF ≤35%, NYHA II-IV)	n=150 mean age: 50.4y(10.2) % male: 82.7	ADM mean: 1,494 (530-3,930)** D/C mean: NR Cutpoint: >1494	NT-proBNP, Endothelin-1, TN factor-α, andrenomedullin	666d** Composite (all-cause mortality or urgent transplant) (29, 150)	Multivariable cox proportional hazard regression	Endothelin-1, TN factor-α, Andrenomedullin	HR=NR, chi-square=31.23 (p=0.0001)

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
George,[109] 2005	Cohort Patients with advanced HF attending the outpatient HF clinic	n=88 mean age: 72y(12) % male: 72	ADM mean: NR D/C mean: NR Cutpoint: NR	NT-proBNP, Matrix metalloproteinase-2, age, LVEF, chronic renal failure	2y** Mortality/HF readmission (34, 88)	Multivariable cox proportional hazard regression	Matrix metalloproteinase-2, age, LVEF, chronic renal failure	HR=NR, chi-square 5.83 (p=0.01)
Jankowska,[162] 2010	Cohort Systolic chronic HF attending outpatient clinics or admitted electively in two tertiary referral cardiology centers	n=546 mean age: 55y(11) % male: 88	ADM mean: 1,570 (656-3,723)** D/C mean: NR Cutpoint: NR	logNT-proBNP, age, sex, BMI, chronic HF etiology, NYHA class, LVEF, serum Na, serum hs-CRP, eGFR, DM, ACE inhibitors and/or ARBs, aldosterone antagonist, BB, loop diuretic, statin, antiplatelet drug	731d** All-cause mortality or heart transplantation (NR)	Multivariable cox proportional hazard regression	Age, sex, BMI, chronic HF etiology, NYHA class, LVEF, serum Na, serum hs-CRP, eGFR, DM, ACE inhibitors and/or ARBs, aldosterone antagonist, BB, loop diuretic, statin, antiplatelet drug	HR=1.42 (1.19-1.71)
Dini,[127] 2009	Cohort Outpatients with chronic HF, and LVEF≤45%	n=232 mean age: 69y(10) % male: 84	ADM mean: 891 (174) D/C mean: NR Cutpoint: >544	NT-proBNP, age, LVEF, EDT, gender, CAD, myocardial E wave velocity	29m Composite (all-cause mortality and HF hospitalization) (65, 232)	Multivariable cox proportional hazard regression	Age, LVEF, EDT, gender, CAD, myocardial E wave velocity	HR=2.66 (1.24-5.71)

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Kallistratos,[139] 2008	Cohort HF Patients with LV dysfunction	n=149 mean age: 59y(13) % male: 81.9	ADM mean: 1,072 (1,302) D/C mean: NR Cutpoint: per 100 units increase	NT-proBNP, PV02 ≤10 ml/kg/min, PV02 ≤14 ml/kg/min, LVEF %, LVEF, NYHA class, age, gender	30m** Mortality/heart transplant (27, 149)	Multivariable cox proportional hazard regression	PV02 ≤10 mL/kg/min, PV02 ≤14 mL/kg/min, LVEF %, LVEF, NYHA class, age, gender	HR=1.07 (1.04-1.09)
			ADM mean: 1,072 (1,302) D/C mean: NR Cutpoint: >1,460	NT-proBNP, PV02 ≤10 ml/kg/min, PV02 ≤14 ml/kg/min, LVEF %, LVEF, NYHA class, age, gender	30m** Mortality/heart transplant (27, 149)	Multivariable cox proportional hazard regression	PV02 ≤10 mL/kg/min, PV02 ≤14 mL/kg/min, LVEF %, LVEF, NYHA class, age, gender	HR=7.58 (3.45-16.66)
			ADM mean: 1,072 (1,302) D/C mean: NR Cutpoint: >1164	NT-proBNP, PV02 ≤10 ml/kg/min, PV02 ≤14 ml/kg/min, LVEF %, LVEF, NYHA class, age, gender	30m** Mortality/heart transplant (27, 149)	Multivariable cox proportional hazard regression	PV02 ≤10 mL/kg/min, PV02 ≤14 mL/kg/min, LVEF %, LVEF, NYHA class, age, gender	HR=13.61 (5.07-36.55)
			ADM mean: 1,072 (1,302) D/C mean: NR Cutpoint: >760	NT-proBNP, PV02 ≤10 ml/kg/min, PV02 ≤14 ml/kg/min, LVEF %, LVEF, NYHA class, age, gender	30m** Mortality/heart transplant (27, 149)	Multivariable cox proportional hazard regression	PV02 ≤10 mL/kg/min, PV02 ≤14 mL/kg/min, LVEF %, LVEF, NYHA class, age, gender	HR=15.85 (4.63-54.24)
Cleland,[122] 2009 CORONA	Case series Secondary analysis of RCT data Chronic HF patients, ≥60y, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3664 mean age: T1=70.8y(6.7) T2= 72.7y(7) T3=74.5y(7.2) % male: 67.65	ADM mean: T1=47(26-78)** pmol/L T2=173(133-220)** pmol/L T3=486(367-776)** pmol/L D/C mean: NR Cutpoint: per log unit	logNT-proBNP, age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatinine, BMI, heart rate, gender, triglycerides	32m** Mortality or worsening HF (1,376, 3,664)	Multivariable cox proportional hazard regression	Age, AF, diabetes, NYHA, claudication, APO A-I, EF, systolic BP/10, creatinine, BMI, heart rate, gender, triglycerides	HR=1.639 (NR)

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Wedel,[131] 2009 CORONA	Case series Secondary analysis of RCT data Chronic HF patients, ≥60y, with NYHA II-IV, ischemic etiology, and EF<35-40%	n=3,342 mean age: 72.5y(7.1) % male: 75	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, NYHA, heart rate	32m** All-cause mortality/HF hospitalization (1,376, 3,342)	Multivariable cox proportional hazard regression	NYHA, heart rate	HR=1.64 (1.54-1.74)
Epelman,[126] 2009	Cohort Ambulatory patients with stable, chronic systolic HF, LVEF ≤35%, NYHA II to IV	n=113 mean age: T1=56y(12) T2= 57y(14) T3=58y(14) % male: 77	ADM mean: T1=652 (275-2,189)** T2=1,549 (1,549-2,522)** T3=2,004 (689-4,989)** D/C mean: NR Cutpoint: 1,240	NT-proBNP, age, gender, NYHA III/IV, ischemic etiology, heart rate, systolic BP, BMI, aldosterone antagonist, loop diuretic BB, ARB, ACE inhibitor/ARB, LVEF, LVEDVi, LVESVi, diastolic stage, E/septal, RVSD, PASP, MR, eGFR, diabetes type II, HT	34m** Clinical events (all-cause mortality, cardiac transplantation, or HF hospitalization) (33, 113)	Multivariable cox proportional hazard regression	age, gender, NYHA III/IV, ischemic etiology, heart rate, systolic BP, BMI, aldosterone antagonist, loop diuretic BB, ARB, ACE inhibitor/ARB, LVEF, LVEDVi, LVESVi, diastolic stage, E/septal, RVSD, PASP, MR, eGFR, diabetes type II, HT	HR=1.55 (1.01-2.33)
Tang,[164] 2011	Cohort Patients with chronic systolic HF (LVEF40%)	n=136 mean age: 57y(14) % male: 76	ADM mean: 1,158 (483–3,160)** D/C mean: NR Cutpoint: ≥1,158	NT-proBNP, age, gender, ACE, ARB, eGFR, hsCRP, MPO, NYHA, RVSD	37m** Composite (all-cause mortality, heart transplantation or HF hospitalization) (41, 136)	Multivariable cox proportional hazard regression	Age, gender, ACE, ARB, eGFR, hsCRP, MPO, NYHA, RVSD	HR=2.12 (1.08-4.42)

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Charach,[123] 2009	Cohort Outpatients with severe chronic HF treated in medical center	n=284 mean age: 71.2y(11.31) % male: 76	ADM mean: 3,772 (5,715.34)** D/C mean: NR Cutpoint: NR	NT-proBNP, age, gender, weight, hyperlipidemia, smoking, HT, DM, NYHA, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	3.7y Composite (all-cause mortality or time to first hospitalization) (NR)	Multivariable cox proportional hazard regression	Age, gender, weight, hyperlipidemia, smoking, HT, DM, NYHA, ischemic CMP, LVEF, creatinine, oxidized LDL antibody	HR=1.028 (0.995-1.062)
Anand,[179] 2011	Cohort HF Patients with Preserved Ejection	n=3,480 mean age: NR % male: NR	ADM mean: 869(1,746) D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (1,175, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.46 (1.37-1.57) per log unit
			ADM mean: 869(1,746) D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (1,175, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.79 (1.56-2.10)
	Cohort HF Patients with Preserved Ejection, NT-proBNP quartiles, “Q2 vs. Q1”	n=1,638 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (364, 1,638)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.62 (1.31-2.00) per log unit

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Anand,[179] 2011 (cont'd)	Cohort HF Patients with Preserved Ejection, NT-proBNP quartiles, "Q3 vs. Q1"	n=1,645 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (468,1645)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=2.04 (1.66-2.52) per log unit
	Cohort HF Patients with Preserved Ejection, NT-proBNP quartiles, "Q4 vs. Q1"	n=1,639 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (617, 1,639)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=3.05 (2.49-3.79) per log unit
	Cohort HF Patients with Preserved Ejection, "Irbesartan vs. Placebo", below NT-proBNP median	n=1,737 mean age: placebo= 70y(6.5) Irbesartan=70y(6.4) % male: 35%	ADM mean: NR D/C mean: NR Cutpoint: <339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (382, 1,737)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=0.74 (0.60-0.90), p=0.03
	Cohort HF Patients with Preserved Ejection, "Irbesartan vs. Placebo", above NT-proBNP median	n=1,737 mean age: placebo= 74y(7.1) Irbesartan=73y(6.9) % male: 43.5%	ADM mean: NR D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m Composite (all-cause mortality and CV hospitalizations (866, 1,737)	Multivariable cox proportional hazard regression	age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.05 (0.92-1.20), p=0.47

Table J-39. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of all-cause mortality and cardiovascular morbidity in patients with stable heart failure (continued)

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Frankenstein,[153] 2007	Cohort Patients with systolic HF who underwent cardiac transplantation evaluation at HF clinic	n=513 mean age: 54.7y(10.5) % male: 83	ADM mean: 1,387 (587-3,064)** D/C mean: NR Cutpoint: NR	NT-proBNP, NYHA, LVEF, peak VO2, 6MWT, BB, noradrenaline, adrenaline, ANP	91m Composite (all-cause mortality and transplantation) (271, 513)	Multivariable cox proportional hazard regression	NYHA, LVEF, peak VO2, 6MWT, BB, noradrenaline, adrenaline, ANP	HR=NR, p<0.001

Abbreviations: 6MWT = 6 minute walk test; ACE = angiotensin converting enzyme; AF = atrial fibrillation; ADM = admission; ANP = A-type natriuretic peptide; APO A-I = apolipoprotein A1; ARB = angiotensin receptor blockers; BB = betablocker; BDI = Beck Depression Inventory; BM = NT-proBNP-guided, intensive management; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; cTnI = cardiac troponin I; CTU = cardiac transplant unit; CV = cardiovascular; d = day(s); D/C = discharge; DHEAS = dehydroepiandrosterone sulfate; DM = diabetes mellitus; E/Em = E wave deceleration time, Em; ED = emergency department; EDT = E wave deceleration time; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GH = growth hormone; grp = group; Hb = hemoglobin; HF = heart failure; HFSS = Heart Failure Survival Score; HR = hazard ratio; hsCRP = high-sensitivity c-reactive protein; HT = hypertension; IGF-I = insulin-like growth factor-I; LDL = low-density lipoprotein; ln=natural log; LV = left ventricular; LVESVi = left ventricular end-systolic volume index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; LVSD = left ventricular systolic dysfunction; m = month(s); MC = multidisciplinary care; MDRD = Modification of Diet in Renal Disease formula; MI = myocardial infarction; mL/kg/min=milliliters per kilogram per minute; MPO = myeloperoxidase; MR = mitral regurgitation; n=number; Na = sodium; NR = not reported; NS = non-significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; PASP = pulmonary artery systolic pressure; pmol/L = picomol per liter; pg/mL = picograms per milliliter; PVO2 = peak oxygen ventilation; RFP = restrictive filling pattern; RR = relative risk; RV = right ventricular; RVSD = right ventricular systolic dysfunction; SD = standard deviation; SHFS = Seattle Heart Failure Score; T-IVT = total isovolumic time; TN factor-α = tumor necrosis factor-alpha; TT = total testosterone; VO2 = oxygen ventilation; vs. = versus; y = year(s)

Table J-40. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and all-cause morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Raposeiras-Roubin,[166] 2011	Cohort Patients with chronic HF	n=106 mean age: 72y(63-78.5) 67.3% male	ADM mean: 2,669.8 (3274.5) D/C mean: NR Cutpoint: per 100 pg/mL	NT-proBNP, sRAGE, SHFS, HDL, Hb, creatinine, GFR, age, ischemic cause, kidney failure	1.3y** Cardiac events (chronic HF mortality + hospitalization) (29, 106)	Multivariable cox proportional hazard regression	sRAGE, SHFS, HDL, Hb, creatinine, GFR, age, ischemic cause, kidney failure	HR=1.017 (1.008 - 1.026) per 100 pg/mL
Sherwood,[113] 2007	Cohort HF outpatients, EF≤40%	n=204 mean age: 56.8y(12.2) 67.3% male	ADM mean: 1,477(1,810) D/C mean: NR Cutpoint: 1000	NT-proBNP, age, HF etiology, LVEF, BDI score, antidepressant	3y** CV mortality or hospitalizations (120,204)	Multivariable cox proportional hazard regression	Age, HF etiology, LVEF, BDI score, antidepressant	HR=1.28 (1.16-1.42)
Anand,[179] 2011	Cohort HF patients with Preserved Ejection	n=3,480 mean age: NR % male: NR	ADM mean: 869(1,746) D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (561, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.44 (1.31-1.58) per log unit
	Cohort HF patients with Preserved Ejection	n=3,480 mean age: NR % male: NR	ADM mean: 869(1746) D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (561, 3,260)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.77 (1.43-2.20)

Table J-40. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and all-cause morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Anand,[179] 2011 (cont'd)	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, "Q2 vs. Q1"	n=1,638 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (148, 1,638)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=2.3 (1.61-3.30) per log unit
	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, "Q3 vs. Q1"	n=1645 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (200, 1645)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=2.62 (1.84-3.73) per log unit
	Cohort HF patients with Preserved Ejection, NT-proBNP quartiles, "Q4 vs. Q1"	n=1639 mean age: NR % male: NR	ADM mean: NR D/C mean: NR Cutpoint: per log unit	lnNT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (297, 1639)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=3.72 (2.59-5.34) per log unit

Table J-40. Studies evaluating independent predictive value of NT-proBNP for the outcome of composite of cardiovascular mortality and all-cause morbidity in patients with stable heart failure

Author Year	Study Design Population	n Mean Age (SD) % male	BNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Anand,[179] 2011 (cont'd)	Cohort HF patients with Preserved Ejection, "Irbesartan vs. Placebo", above NT-proBNP median	n=1,737 mean age: placebo= 70y(6.5) Irbesartan= 70y(6.4) 35.0% male	ADM mean: NR D/C mean: NR Cutpoint: <339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (154, 1,737)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=0.57 (0.41-0.80), p=0.001
		n=1,737 mean age: placebo= 74y(7.1) Irbesartan= 73y(6.9) 43.5% male	ADM mean: NR D/C mean: NR Cutpoint: >339	NT-proBNP, age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	49.5m HF death or hospitalization (444, 17,37)	Multivariable cox proportional hazard regression	Age, sex, NYHA, ischemic etiology, HT, AF, DM, COPD, BMI, systolic BP, heart rate, Hb level, EF, eGFR, serum albumin, Na, and neutrophil count	HR=1.13 (0.94-1.37), p=0.71

Abbreviations: AF = atrial fibrillation; ADM = admission; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; 95% CI, = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; d = day(s); D/C = discharge; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; Hb = hemoglobin; HDL = high-density lipoprotein; HF = heart failure; HR = hazard ratio; HT = hypertension; LVEF = left ventricular ejection fraction; m = month(s); n=number; Na = sodium; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; SD = standard deviation; SHFS = Seattle Heart Failure Score; sRAGE = soluble receptor for advanced glycogen end products; vs. = versus; y = year(s)

Table J-41. Risk of bias for prognostic surgical studies using the Hayden Criteria assessing BNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Lellouche,[184] 2007	√	√	√	√	√	√	√	√	√	√	X	?	X	X	X	√	√
Glick,[185] 2006	√	√	√	√	√	√	√	√	√	√	√	?	√	X	X	√	√
El Saed,[186] 2009	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	X
Leibowitz,[187] 2008	X	√	√	√	X	√	√	NA	√	NA	√	?	X	X	X	√	√
Pitzalis,[188] 2006	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Koch,[189] 2012	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✘ = High Risk ? = unclear

Table J-42. Surgical studies evaluating independent predictive value of BNP for the outcome of mortality

Author Year	Study Design Population	n Mean Age (SD) %male	BNP, NT-proBNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI)
Koch,[189] 2011	Cohort Patients with refractory HF and chronic kidney disease	n=118 mean age: 73.2(11.4)y %male: 60.2%	ADM mean: 588 (234–1100)** D/C mean: NR Cutpoint: per log unit	logBNP,age, diabetes, serum urea, NYHA (IV vs. III), endogenous creatinine, urea clearance, serum creatinine, ascites	1.11y All-cause mortality (74, 118)	Multivariable cox regression	Age, diabetes, serum urea,NYHA (IV vs. III), endogenous creatinine, urea clearance, serum creatinine, ascites	HR=1.45 (1.09, 1.92) per log unit
Glick,[185] 2006	Cohort Patients with advanced systolic HF (prolonged QRS complex & assigned to undergo CRT)	n=32 mean age: 68.6 (11.6)y, %male: 96.8	ADM mean: NR D/C mean: NR Cutpoint: Δ in BNP <18.3	change in BNP, hsCRP*	17.7m (8.2) Mortality (6, 32)	Cox regression	NR	HR=0.993 (0.986-0.999)
				Coronary Sinus BNP level, hsCRP*,baseline NYHA class, PVB BNP*, LVEF*, QRS duration*	17.7m (8.2) HF reADM (12, 32)	Cox regression	NR	HR=1.001 (1.0-1.002)
El Saed,[186] 2009	Cohort Patients with advanced but stable HF receiving cardiac resynchronization therapy	n=115 mean age: 67y(10.7) %male: 98.3	ADM mean: 559 (761) D/C mean: NA Cutpoint: ≥492	BNP baseline	17.5m (6.5) All-cause mortality (27,115)	Multivariable cox regression and ROC analysis	Age*, sex*, race*,NYHA class*, LVEF*, QRS duration*, ischemic CMP*, HT*, diabetes*, current smoking*, AF history, statins use*, creatinine*	HR=2.89 (1.06-7.88), AUC=0.72
					17.5m (6.5) HF hospitalization (31,115)	Multivariable cox regression and ROC analysis	Age*, sex*, race*,NYHA class*, LVEF*, QRS duration*, ischemic CM*, HT*, diabetes*, current smoking*, AF history, statins use*, creatinine*	HR=4.23 (1.68-10.6), AUC=0.74
Lellouche,[184] 2007	Cohort Consecutive patients with HF	n=164 mean age: 60y (15) %male: 76	ADM mean: 636 (727) D/C mean: NR Cutpoint: per log unit	BNP, age, LVEF, NYHA, QRS duration	6m CV mortality, HF hospitalization, NYHA class (57, 164)	Multivariable cox regression	Age, LVEF, NYHA, QRS duration	HR=NR (1.001, 1.003), p<0.001

Table J-42. Surgical studies evaluating independent predictive value of BNP for the outcome of mortality (continued)

Author Year	Study Design Population	n Mean Age (SD) %male	BNP, NT-proBNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Pitzalis,[188] 2006	Cohort NYHA class III chronic HF of any etiology, who had been taking conventional medical HF therapy for at least 3m and scheduled for CRT	n=50 mean age: 61y (10) % male: 46	ADM mean: 145(134) D/C mean: 148 (171) Cutpoint: 91.5**	Baseline logBNP, age, gender, NYHA, systolic arterial pressure, underlying CMP (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, BB, digitalis, diuretics, aldosterone antagonists	19m (12)* Progression of HF, defined as death, urgent heart transplantation or hospitalization due to increased HF, or symptoms of progression in change in HF medication	Cox multivariable regression analysis	Age, gender, NYHA, systolic arterial pressure, underlying CMP (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, BB, digitalis, diuretics, aldosterone antagonists	HR=2-07 (1.19-3.62)
		n=50 mean age: 61 (10)y %male: 47	ADM mean: 145(134) D/C mean: 148 (171) Cutpoint: 91.5**	log BNP, nlBNP (ADM to one month), age, gender, NYHA, systolic arterial pressure, Underlying cardiomyopathy (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, beta-blockers, digitalis, diuretics, aldosterone antagonists	19m (12)* Progression of HF, defined as death, urgent heart transplantation or hospitalization due to increased HF, or symptoms of progression in change in HF medication	Cox multivariable regression analysis	Age, gender, NYHA, systolic arterial pressure, underlying CMP (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, BB, digitalis, diuretics, aldosterone antagonists	logBNP HR=3.70 (2.05-6.66); nlBNP HR=2.93 91.62-5.30)
		n=50 mean age: 61 (10)y, %male: 48	ADM mean: 145(134) D/C mean: 148 (171) Cutpoint: 91.5**	logBNP (one month after baseline), age, gender, NYHA, systolic arterial pressure, Underlying cardiomyopathy (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, beta-blockers, digitalis, diuretics, aldosterone antagonists	19m (12)* Progression of HF, defined as death, urgent heart transplantation or hospitalization due to increased HF, or symptoms of progression in change in HF medication	Cox multivariable regression analysis	Age, gender, NYHA, systolic arterial pressure, Underlying cardiomyopathy (%) - ischemic, non-ischemic, QRS (ms), LVEF%, LVEDD (cm), VO2 peak, ACE inhibitors, ATI receptor antagonists, BB, digitalis, diuretics, aldosterone antagonists	HR=2.23 (1.26-3.94)

Table J-42. Surgical studies evaluating independent predictive value of BNP for the outcome of mortality (continued)

Author Year	Study Design Population	n Mean Age (SD) %male	BNP, NT-proBNP Levels (pg/mL)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Leibowitz,[1] [87] 2007	Cohort Patients with CHF	n=44 mean age: 77y (11.8) %male: 41	ADM mean: "No events" 167 (194), "with events" 1366 (1420) D/C mean: NR Cutpoint: 165	BNP, revised cardiac risk score, age, LVEF, diabetes, hypertension, NYHA, CAD	6m Composite (death, MI, worsening CHF) (15, 44)	Multivariable cox regression	Revised cardiac risk score, age, LVEF, diabetes, HT, NYHA, CAD	HR=NR, p=0.023 (significant)

Abbreviations: ACE = angiotensin converting enzyme; ADM = admission; AF = atrial fibrillation; ATI = angiotensin I; BB = betablocker; BNP = B-type natriuretic peptide; BP = blood pressure; BUN=blood urea nitrogen; CAD = coronary artery disease; 95% CI, = confidence interval; CMP = cardiomyopathy; CRT = cardiac resynchronization therapy; CRP = C-reactive protein; CV = cardiovascular; CVD = cerebrovascular disease; d = day(s); D/C = discharge; DM = diabetes mellitus; ED = emergency department; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; h = hour(s); Hb = hemoglobin; HF = heart failure; HR = hazard ratio; HT = hypertension; ln=natural log; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; m = month(s); n=number; Na = sodium; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; pg/mL = picograms per milliliter; QRS = quick release system; RR = relative risk; SD = standard deviation; VO2 = oxygen ventilation; vs. = versus; y = year(s)

Table J-43. Risk of bias for prognostic surgical studies using the Hayden Criteria assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Assmus,[190] 2007	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Berger,[191] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	X	X	X	√	√
Cleland,[192] 2008	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	X

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✖ = High Risk ? = unclear

Table J-44. Surgical studies evaluating independent predictive value of NT-proBNP for the outcome of mortality

Author Year	Study Design Population	n Mean Age (SD) %male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Assmus,[190] 2007 Multi-subs: TOPCARE-CHD, crossover trials and ongoing registry	Cohort Patients with chronic ischemic heart disease, MI≥3 months	n=121 mean age: 62(10)y 87% male	ADM mean: 42-55,456*** D/C mean: NR Cutpoint: NR	NT-proBNP baseline (log), age*, systolic BP*, diabetes*, creatinine, NYHA*, MR*, LVEF*, baseline NT-proANP*	577(422) days Mortality (14,121)	multivariate cox regression, stepwise linear regression with a forward entry-stepping algorithm	age, systolic BP, diabetes, creatinine, NYHA, MR, LVEF, baseline NT-proANP	HR=7.2 (2.4-22.2)
Berger,[191] 2009 CARE-HF	RCT Patients with LVEF 35%, a QRS duration 150 ms or QRS ranging from 120 to 149 ms in addition to echocardiographic criteria for dyssynchrony, and NYHA III or IV despite optimized medical therapy.	n=813 (CRT=409,404 Medical therapy) mean age:NR % male: NR	ADM mean: 1,814**(IQR 152-180) D/C mean: Taken at 3 months but levels not reported Cutpoint: 1,814**(IQR 152-180)	log NT-pro-BNP, updated from baseline to 3 months values, CRT, age, sex, baseline clinical (etiology, NYHA functional class, heart rate, supine systolic BP, glomerular filtration rate), ECG (QRS duration), and echocardiographic characteristics (EF, MR area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a BB)	37.6**months (IQR 31.5-42.5) All-cause mortality (228,813)	Cox proportional hazards model	CRT, age, sex, baseline clinical (etiology, NYHA functional class, heart rate, supine systolic BP, glomerular filtration rate), ECG (QRS duration), and echocardiographic characteristics (EF, MR area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a BB)	HR=1.56 (1.34-1.82) P<0.001

Table J-44. Surgical studies evaluating independent predictive value of NT-proBNP for the outcome of mortality (continued)

Author Year	Study Design Population	n Mean Age (SD) %male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Berger,[191] 2009 CARE-HF (cont'd)	RCT Patients with LVEF 35%, a QRS duration 150 ms or QRS ranging from 120 to 149 ms in addition to echocardiographic criteria for dyssynchrony, and NYHA III or IV despite optimized medical therapy.	n=813 (CRT=409,404 Medical therapy) mean age: NR % male: NR	ADM mean: 1814**(IQR 152-180) D/C mean: Taken at 3 months but levels not reported Cutpoint: 1,814**(IQR 152-180)	log NT-pro-BNP, updated from baseline to 3 months values, CRT, age, sex, baseline clinical (etiology, NYHA functional class, heart rate, supine systolic BP, glomerular filtration rate), ECG (QRS duration), and echocardiographic characteristics (EF, MR area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a BB)	37.6**months (IQR31.5-42.5) Pump failure death (91,813)	Cox proportional hazards model	CRT, age, sex, baseline clinical (etiology, NYHA functional class, heart rate, supine systolic BP, glomerular filtration rate), ECG (QRS duration), and echocardiographic characteristics (EF, MR area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a BB)	HR=1.92 (1.58-2.34) P<0.001
					37.6**months (IQR31.5-42.5) Sudden death (79,813)	Cox proportional hazards model	CRT, age, sex, baseline clinical (etiology, NYHA functional class, heart rate, supine systolic BP, glomerular filtration rate), ECG (QRS duration), and echocardiographic characteristics (EF, MR area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a BB)	HR=1.33 (1.11-1.60) P=0.0025

Table J-44. Surgical studies evaluating independent predictive value of NT-proBNP for the outcome of mortality (continued)

Author Year	Study Design Population	n Mean Age (SD) %male	BNP Levels (pg/ml)	Prognostic Markers	Followup Outcomes (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Cleland,[192] 2008 CARE-HF	Case-series Patients with moderate or severe symptoms of HF (LVEF <35%)	n=813 "CRT grp" n=409 mean age: 66.5 (59.5–72.5)y** 74.3% male "Control grp" n=404, mean age: 66.2 (59.0–71.7)y** 72.5% male	ADM mean: "CRT grp" 1,920 (744–4,288)**, "Control grp" 1,806 (719–3,949)** D/C mean: NR Cutpoint: NR	NT-proBNP at 3 months, age*, LVEF*, NYHA, ischemic etiology, beta-blockers*, GFR*, IVMD, SBP*, ESVI*, CRT	37.6 months** All-cause mortality (255, 813)	multivariable cox proportional hazard regression	age, LVEF, NYHA, ischemic etiology, beta-blockers, GFR, IVMD, SBP, ESVI	HR = 1.615 (1.411–1.848)

*median

Abbreviations: ADM = admission; D/C = discharge; BB = betablocker; EF = ejection fraction; GFR = glomerular filtration rate; grp = group; IQR = Interquartile range; LV = left ventricular; MR = mitral regurgitation; NYHA = New York Heart Association; QRS = quick release system; SBP = systolic blood pressure; CRT = cardiac resynchronization therapy;

Table J-45. Risk of bias for prognostic studies using the Hayden Criteria for both stable and decompensated population assessing NT-proBNP

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	1a	1b	1c	2a	2b	3a	3b	3c	3d	3e	4a	4b	4c	5a	5b	6a	7a
Dini,[193] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	X	X	X	√	√
Dini,[194] 2012	√	√	√	√	√	√	√	√	√	√	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✘ = High Risk ? = unclear

Table J-46. Studies evaluating independent predictive value of NT-proBNP in both decompensated and stable population

Author Year	Study Design Population	n Mean Age (SD) %male	BNP, NT-proBNP Levels (pg/ml)	Prognostic Markers	Followup (Outcomes) (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Dini,[194] 2012	Cohort Patients with chronic systolic HF and LVEF ≤45%	n=400 mean age: 69y(12) 78% male	ADM mean: 1,572pg/mL** (725-3,637) D/C mean: NA Cutpoint: NA	log NT-proBNP age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	32** months All-cause mortality	cox proportional hazards	age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	HR=2.04 (1.25-3.36) Wald Z-squared 8.0 p=0.005
	Cohort Patients with stable HF	n=271 mean age: 68y(11) 81% male	ADM mean: 1,113pg/mL** (522-2,275) D/C mean: NA Cutpoint: NA	log NT-proBNP age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	32** months All-cause mortality	cox proportional hazards	age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	NR

Table J-46 Studies Evaluating independent predictive value of NT-proBNP in both decompensated and stable popualtions (continued)

Author Year	Study Design Population	n Mean Age (SD) %male	BNP, NT-proBNP Levels (pg/ml)	Prognostic Markers	Followup (Outcomes) (#events, #risk)	Model	Adjusted/Non-adjusted Covariates	Measure(s) of Risk (95% CI,)
Dini,[194] 2012 (cont'd)	Cohort Patients with decompensated HF	n=129 mean age: 70y(13) 74% male:74	ADM mean: 3,637pg/mL** (2,323-4,149) D/C mean: NA Cutpoint: NA	log NT-proBNP age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	32** months All-cause mortality	cox proportional hazards	age, sex, NYHA class, prior HF hospitalization, absolute and normalized furosemide dose, heart rate, systolic and diastolic BP, AF, diabetes, LV mass index, end-diastolic and end-systolic LV volume indexes, LVEF, mitral E⁄A ratio, E⁄e0, EDT, moderate to severe MR, LA volume index, right atrial pressure, and pulmonary artery systolic pressure.	HR=1.0 (1.00-1.01) p=0.060
Dini,[193] 2008	Cohort Out Patients with chronic HF, and LVEF≤45%	n=31 mean age: 69y(11) 78% male	ADM mean: 1,492 (617 – 3,540)** D/C mean: NR Cutpoint: >1,492	NT-proBNP, age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	22 months Composite (All-cause mortality + HF hospitalization) (111, 313)	multi-variable cox regression	age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	HR=2.94 (1.83, 4.72)
	Cohort Stabilized Out Patients with chronic HF, and LVEF≤45%	n=219 mean age: 69y(11) 80% male	ADM mean: 1,129 (478 – 2,223)** D/C mean: NR Cutpoint: >1,129	NT-proBNP, age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	22 months Composite (All-cause mortality + HF hospitalization) (NR, 219)	multi-variable cox regression	age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	HR=2.84 (1.44, 5.62)
	Cohort Decompensated Out Patients with chronic HF, and LVEF≤45%	n=94 mean age: 69y(11) 73% male	ADM mean: 3,430 (1,810 – 8,124)** D/C mean: NR Cutpoint: >3,430	NT-proBNP, age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	22 months Composite (All-cause mortality + HF hospitalization) (NR, 94)	multi-variable cox regression	age, gender, NYHA class, LVEF, EDT, gender, coronary artery disease, Myocardial E wave velocity	HR=2.06 (1.16, 3.67)

Abbreviations: ADM = admission; AF = AF; BP = blood pressure; EDT = E wave deceleration time; EDT = E wave deceleration time; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; y=years

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Appendix K. Key Question 4 Evidence Set

Table K-1. Studies evaluating incremental value of BNP to predict the outcome of all-cause mortality in decompensated heart failure patients for all time points

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Maisel,[1] 2010 F/U: 90 days	Study design: Cohort Patients with AHF presenting at ED with dyspnea n, Mean Age (SD), % Males: 568, 71.2yrs(13.8), 62.5% Outcomes (#events, #risk): all-cause mortality (65, 568)	ADM mean: NR D/C mean: NR Cutpoint: NR	log BNP, age, sex, BMI, creatinine	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: Age, sex, BMI, creatinine HR=1.3 (0.9 to 1.9) per increase of 1 IQR	NR	NR	NR	NR
Maisel,[1] 2010 F/U: 90 days	Study design: Cohort Patients with AHF presenting at ED with dyspnea n, Mean Age (SD), % Males: 568, 71.2yrs(13.8), 62.5% Outcomes (#events, #risk): All-cause mortality (65, 568)	ADM mean: NR D/C mean: NR Cutpoint: NR	log BNP*, logMR-proADM, troponin, age, sex, BMI, creatinine	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: logMR-proADM, troponin, age, sex, BMI, creatinine HR=0.9 (0.6 to 1.4) (p=NS) per increase of 1 IQR	NR	BNP failed to add any incremental value to base model + MR-proADM (Inc. chi-square=0.01, p=0.906), whereas MR-proADM added to base model + BNP (Inc. chi-square=23.90, p=0.001)	NR	NRI=38.8% and IDI=5.24%, for logBNP and logMR-proADM vs. BNP alone

Table K-1. Studies evaluating Incremental value of BNP to predict the outcome of all-cause mortality in decompensated heart failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Nunez,[2] 2010 F/U: 6m	Study design: Cohort Patients admitted with AHF n, Mean Age (SD), % Males: 1,111, 73yrs(11), 49% Outcomes (#events, #risk): All-cause mortality (181, 1,111)	ADM mean: 237** (97 to 434) D/C mean: NR Cutpoint: NR	log BNP, log CA125	Model: Adjusted (multivariable) Cox regression Adjusted/Non-adjusted covariates: Age, prior ADM for AHF, AHF category, SBP, angiotensin receptor blockers, beta-blockers HR=1.40 (1.08 to 1.79)	C-statistic for base model with covariates only=0.757; base+BNP=0.789 (p=0.005); base+CRP+BNP=0.810 (p=0.001); base+BNP+TnT=0.799 (p=0.002); base+CRP+BNP+TnT= 0.815 (p<0.001)	NR	NR	Absolute IDI index (%) vs. base model alone: BNP + base model=1.51 BNP + CA125 + base model= 3.45 base model + CA125= 2.08. Addition of CA125 to base model + BNP=1.95
Núñez,[3] 2008 F/U: 9m**	Study design: Cohort Patients with AHF n, Mean Age (SD), % Males: 569, 73.8yrs (10.6), 47.6% Outcomes (#events, #risk): All-cause mortality (156, 569)	ADM mean: 311 (425) D/C mean: NR Cutpoint: NR	BNP	Model: Adjusted (multivariate) Cox regression Adjusted/Non-adjusted covariates: Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, beta-blockers, SBP, serum creatinine, hemoglobin HR=1.05 (1.03 to 1.08), per unit Increase in BNP by increments of 100 pg/mL	C-statistic for BNP=0.798 per 100 pg/mL. The Harrell's C statistic was higher in the model that included BNP compared to the same model without this value (0.801 vs. 0.781). This is a global comparison of BNP in the model vs. BNP out of the model.	NR	NR	NR

Table K-1. Studies evaluating Incremental value of BNP to predict the outcome of all-cause mortality in decompensated heart failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Núñez,[3] 2008 F/U: 9m**	Population: Q2=BNP level (85-123) n, mean age (SD), % males: 114, 73yrs(10), 39.5% Outcomes (#events, #risk): All-cause mortality (23, 114)	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP quintiles	Model: Adjusted (multivariate) Cox regression Adjusted/Non-adjusted covariates: Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, beta-blockers, SBP, serum creatinine, hemoglobin HR=2.75(1.17 to 6.46)	C-statistic=0.801 (one value for all cutpoints/quintiles)-adjusted model	NR	NR	NR
Núñez,[3] 2008 F/U: 9m**	Population: Q3=BNP level (123-250) n, Mean Age (SD), % Males: 114, 74(10)yrs, 48% Outcomes (#events, #risk): All-cause mortality (30, 114)	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP quintiles	Model: Adjusted (multivariate) Cox regression Adjusted/Non-adjusted covariates: Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, beta-blockers, SBP, serum creatinine, hemoglobin HR= 2.76 (1.20 to 6.33)	NA	NR	NR	NR

Table K-1. Studies evaluating Incremental value of BNP to predict the outcome of all-cause mortality in decompensated heart failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Núñez,[3] 2008 F/U: 9m**	Population: Q4=BNP level (251-490) n, mean age (SD), % males: 113, 73yrs(12), 50% F/U: 9 mo ** (3 -18 mo) Outcomes (#events, #risk): All-cause mortality (34,113)	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP quintiles	Model: Adjusted (multivariate) Cox regression Adjusted/Non-adjusted covariates: Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, beta-blockers, SBP, serum creatinine, Hemoglobin HR=3.38 (1.49 to 7.68)	NA	NR	NR	NR
Núñez,[3] 2008 F/U: 9m**	Population: Q5=BNP level (495-3240) n, Mean Age (SD), % Males: 113, 77yrs(9), 55.8% Outcomes (#events, #risk): All-cause mortality (62, 113)	ADM mean: NR D/C mean: NR Cutpoint: NR	BNP quintiles	Model: Adjusted (multivariate) Cox regression Adjusted/Non-adjusted covariates: Age, valvular etiology, baseline NYHA functional class, prior ADM for acute HF, beta-blockers, SBP, serum creatinine, hemoglobin HR=5.82(2.62 to 12.97)	NA	NR	NR	NR

Table K-1. Studies evaluating Incremental value of BNP to predict the outcome of all-cause mortality in decompensated heart failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Dunlay,[4] 2009 F/U: 12m	Study design: Cohort HF patients n, Mean Age, % Males: 593, 76.4yrs, 48% Outcomes (#events, #risk): All-cause mortality (122, 593)	ADM mean: 350 (174 to 647)** D/C mean: NR Cutpoint: NR	BNP>350, age, BMI*, creatinine clearance*, NYHA III/IV, serum sodium*, SBP, CRP, TnT	Model: Multivariate logistic regression Adjusted/Non-adjusted covariates: Age, BMI, creatinine clearance, NYHA, serum sodium <135 mmol/L, SBP HR=1.29 (1.03 to 1.62)	c-statistic for base model with covariates only=0.757 base + CRP=0.782 base + BNP=0.789 base + TnT=0.780 base + CRP + BNP=0.810 base + CRP + TnT=0.797 base + BNP + TnT=0.799 base + CRP + BNP + TnT=0.815. c-stat for BNP as sole variable in model=0.698, CRP as sole variable=0.636, TnT as sole variable=0.652	NR	NR	NR

†Likelihood-based measures (i.e., log likelihood ratio, likelihood ratio chi-square, Global chi-square, incremental chi-square)

*Insignificant

**Median Values

Abbreviations: ADM = admission; AHF = acute heart failure; BMI = body mass index; BMod = behavior modification; BNP = B-type natriuretic peptide; BP = blood pressure; CA125 = carbohydrate antigen 125; CHF = congestive heart failure; CRP = C-reactive protein; CP = cutpoint; D/C = discharge; F/U = followup; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; IDI = integrated risk improvement; IQR = interquartile range; LVEF = left ventricular ejection fraction; mmol/L = milli mol per liter; m = months; MR-proADM = midregional proadrenomedullin; NR = not reported; NRI = NS = not significant; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; SBP = systolic blood pressure; SD = TnT = troponin T; vs. = versus; yrs = years

Table K-2. Studies evaluating incremental value of BNP to predict the outcome of cardiovascular mortality in patients with decompensated heart failure for all time points

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Zairis,[5] 2010 F/U: 31d	Study design: Cohort Population: Patients hospitalized with acutely decompensated severe low-output CHF (NYHA class III/IV) n, Mean Age (SD), % Males: 577, 74.2yrs(8.2), 68.3% Outcomes (#events, #risk): Cardiac mortality (102, 577)	ADM mean: 1,110.1 (410.7) D/C mean: NR Cutpoint: NR	BNP, age ≥75y, acute pulmonary edema, LVEF<25%, GFR<30 ml/min, Hx of MI, CHF of ischemic etiology, AF or flutter, Hb (g/dl), Serum cTnI, Serum hs-CRP	Model: Multivariate Cox regression Adjusted/Non-Adjusted Covariates: Age≥75 (years), acute pulmonary edema, LVEF<25%, GFR<30 ml/min, Hx of MI, CHF ischemic etiology, AFor flutter, Hb (g/dl), serum cTnI, serum hs-CRP HR=2.2 (1.5-3.7)	c-statistics: model with all univariate predictors except biomakers: 0.70 model + BNP=0.79 model + cTnI=0.77 model + hs-CRP=0.74 model + BNP + cTnI=0.81 model + BNP + cTnI + hs-CRP=0.82	NR	NR	NR
Nunez,[2] 2010 F/U: 6m	Study design: Cohort Population: Patients admitted with AHF n, Mean Age (SD), % males: 1,111, 73yrs(11), 49% Outcomes (#events, #risk): CV mortality (154, 1,111)	ADM mean: 237** (97 to 434) D/C mean: NR Cutpoint: NR	log BNP, log CA125	Model: Adjusted (multivariable) Cox Regression Adjusted/Non-Adjusted Covariates: Age, sex, prior ADM for AHF, AHF category, SBP, angiotensin receptor blockers, beta-blockers HR=1.48 (1.24 to 1.77)	NR	NR	NR	Absolute IDI index (%) vs. base model alone: BNP + base model=1.23 BNP + CA125 + base model=3.65 base model + CA125=2.31. Addition of CA125 to base model + BNP=2.41

Table K-2. Studies evaluating Incremental value of BNP to predict the outcome of Cardiovascular in decompensated Heart Failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination statistics (C-statistics/C-index)	Global Model fit statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of risk reclassification (IDI and NRI)
Nunez,[2] 2010 F/U: 6m	Study design: Cohort Population: Patients admitted with AHF n, Mean Age (SD), % Males: 1,111, 73yrs(11), 49% Outcomes (#events, #risk): HF Mortality (99, 1,111)	ADM mean: 237** (97 to 434) D/C mean: NR Cutpoint: NR	log BNP, log CA125	Model: Adjusted (multivariable) Cox regression Adjusted/Non-Adjusted Covariates: Age, sex, prior ADM for AHF, AHF category, SBP, angiotensin receptor blockers, beta-blockers HR=1.47 (1.19 to 1.81)	NR	NR	NR	Absolute IDI index (%) vs. base model alone: BNP + base model=1.23 BNP + CA125 + base model=3.65 base model + CA125=2.31. Addition of CA125 to base model + BNP=2.41

†Likelihood-based measures i.e., log likelihood ratio, likelihood ratio chi-square, Global chi-square, incremental chi-square

*Insignificant

**Median Values

Abbreviations: ADM = admission; AF = atrial fibrillation; AHF = acute heart failure; BMI = body mass index; BMod = behavior modification; BNP = B-type natriuretic peptide; BP = blood pressure; CA125 = carbohydrate antigen 125; CHF = congestive heart failure; CP = cutpoint; CRP = C-reactive protein; cTnI = cardiac troponin I; CV = cardiovascular; d = days; D/C = discharge; F/U = followup; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; Hs-CRP = Hx = history; IDI = integrated risk improvement; IQR = Interquartile range; LVEF = left ventricular ejection fraction; m = months; MI = myocardial infarction; mmol/L = milli mol per liter; NR = not reported; NS = not significant; NYHA = New York Heart Association; pg/mL = picograms per milliliter; SBP = systolic blood pressure; TnT = troponin T; vs. = versus; yrs = years

Table K-3. Studies evaluating incremental value of NT-proBNP to predict the outcomes of mortality in patients with decompensated heart failure for all time points

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow Statistic)	Measure of Risk Reclassification (IDI and NRI)
Pascual-Figal,[6] 2011 F/U: 739**d	Study design: Cohort Patients admitted with ADHF n, Mean Age (SD), % Males: 107, 72yrs(13),56% Outcomes (#events, #risk): Aall-cause mortality (29, 107)	ADM mean: 3,724 (1,954 – 7,666)** D/C mean: NR CP: NR	NT, sST2, hsTnT, Age*, sex*, BMI*, Hb*, NYHA class*, BUN*, prior MI*, creatinine*, LVEF*	Model: Bootstrapped multivariable Cox regression Adjusted/Non-Adjusted Covariates: sST2, hsTnT, age, sex, BMI, Hb, NYHA class, BUN, prior MI, creatinine HR=1.005 (1.000-1.01) per 100 pg/mL increase	C-index: BMod=0.845 BMod + NT=0.852 (p=0.656 vs. BMod) BMod + NT + hsTnT=0.860 (p=0.559 vs. BMod, p=0.767 for model with NT) BMod + NT + hsTnT + sST2=0.864 (p=0.570 vs. BMod and p=0.383 for model in NT) BMod + multimarker (0-3, score based on optimal cutpoints from ROC)=0.906 (p=0.022 vs. BMod and p=0.023 vs. model with NT, significant)	NA	p-value: BMod=0.558, BMod + NT=0.285 BMod + NT+ hsTnT=0.653 BMod + NT + hsTnT + sST2=0.699 BMod + multimarker (0-3, based on optimal cutpoints from ROC)=0.954	IDI: BMod + NT=(2%, p=0.532 vs. BMod), BMod + NT + hsTnT=(8%, p=0.226 vs. BMod; 6%, p=0.322 model with NT), BMod + NT + hsTnT + sST2=(16%, p=0.025 vs. BMod; 13%, p=0.045 NT model), BMod + multimarker (0-3, based on optimal cutpoints from ROC)=(25%, p=0.004 vs. BMod and 22%, p=0.003 vs. model; NT, significant) NRI: NA

Table K-3. Studies evaluating Incremental value of NT-proBNP to predict the outcomes of mortality in decompensated Heart Failure patients for all time points (continued)

Author, Year, Length of F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination statistics (C-statistics/C-index)	Global Model fit statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of risk reclassification (IDI and NRI)
Harutyunyan,[r] 2012 F/U: 6.8yrs	Study design: Cohort Population: Patients with HF and severe LVSD; n, Mean Age, %Male: 717, 70yrs (NR), 73% Outcomes (#events, #risk): All-cause mortality (458, 717)	Admission mean:NR Discharge Mean: NR; Cutpoint: NR	log2 NT-proBNP, YKL-40, age, sex, and LVEF, Hb, history of HF, IHD, COPD, stroke/TIA, and DM, log2 hs-CRP, eGFR	Model: Multivariate cox regression; age, sex, and LVEF, Hb, history of HF, IHD, COPD, stroke/TIA, and DM, log2 hs-CRP, eGFR, YKL-40 HR=1.28 (1.15, 1.44)	NA	Base Model with YKL-40, chi-square=196, Add NT-proBNP to base model with YKL-40, chi-square=214 (p<0.0001)	NA	NA

†Likelihood-based measures i.e., log likelihood ratio, likelihood ratio chi-square, Global chi-square, incremental chi-square
*Insignificant
**Median Values

Abbreviations: ADHF = acute decompensated heart failure; ADM = admission; AHF = acute heart failure; BMI = body mass index; BMod = behavior modification; BNP=B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; CHFb = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CP = cutpoint; D/C = discharge; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; F/U= followup; GFR = glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; hs-CRP = high-sensitivity c-reactive protein; hsTnT = high-sensitivity cardiac troponin T; IDI = integrated risk improvement; IHD = idiopathic heart disease; IQR = interquartile range; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction; mmol/L = milli mol per Liter; NR = not reported; NRI = net reclassification index; NS = not significant; NT = N-Terminal; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; ROC = receiver operating characteristic; SBP = systolic blood pressure; sST2 = ???; TIA = ???; TnT = troponin T; vs. = versus; YKL = human cartilage glycoprotein-39; yrs = years

Table K-4. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for decompensated heart failure population.

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Zairus,[5] 2010	√	√	√	√	√	√	√	√	√	√	√	X	√	X	X	√	√
Maisel,[1] 2010	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Dunlay,[4] 2009	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
Nunez,[3] 2008	√	√	√	?	?	√	√	NA	?	NA	?	?	√	X	X	√	√
Nunez,[2] 2010	√	√	√	?	?	√	√	√	?	?	√	X	√	?	?	√	√
Pascal-Figuel,[6] 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described
7. a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✘ = High Risk ? = unclear

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistic/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
von Haehling,[8] 2009 F/U: 12 mo	Study design: Cohort Patients with chronic CHF n, mean age, %male: 501, 63yrs(11), 92% Outcomes (#events, #risk): all-cause mortality (70, 501)	ADM mean: 878 (348 – 2,480)** D/C mean: NR Cutpoint: NR	log10NT-proBNP, log10MR-proADM, Age, LVEF, NYHA class, creatinine*	Model: Multivariate Cox regression & ROC analysis Adjusted/Non-adjusted covariates: log10MR-proADM, Age, LVEF, NYHA class, creatinine* HR=1.43 (0.89 - 2.3) per SD increase, AUC = 0.75 (0.71 - 0.79)	paired ROC curves (Hanely & McNeil), At 12- mo, AUC for MR-proADM = 0.72, NT-proBNP=0.75 (p=0.32)	logLikelihood ratio, Add MR-proADM to base Model , p=0.0001, Add NT-proBNP to Base Model p=0.0038, Add NT-proBNP to base model + MR-proADM p=0.13, Add MR-proADM to base model + NT-proBNP p=0.00094	NA	NA
Dini,[9] 2008 F/U: 20 mo	Study design: Cohort Patients with LV systolic HF, EF ≤ 45% with moderate to severe MR n, mean age, %male: 142, 71yrs(11), 78% Outcomes (#events, #risk): all-cause mortality (46, 142)	ADM mean: 3,283 (585) D/C mean: NR Cutpoint: ≥ 3,283	NT-proBNP, TAPSE <16min, LVEF*, Age >70y*, NYHA*, AF*, sex*, E/Em*	Model: Multivariate Cox regression Adjusted/Non-adjusted covariates: TAPSE <16min, LVEF, Age >70, NYHA, AF, sex, E/Em HR = 2.58 (1.24 - 5.37)	NA	Base Model (demographics + clinical data), Add EF to base model, $\chi 2$, p-value <0.0001, Add TAPSE to base model + EF, $\chi 2$, p-value <0.0001, Add NT-proBNP to base model + EF + TPASE , $\chi 2$, p-value <0.0001	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Masson,[10] 2006 Val-Hef F/U: 23 mo	Study design: Cohort Secondary analysis of RCT data Patients with stable symptomatic HF (LVEF <40%) n, mean age, %male: 3,916, NR, 80.2% Outcomes (#events, #risk): all-cause mortality (758, 3,916)	ADM mean: 895 (375-1,985)** D/C mean: NR Cutpoint: >895	NT-proBNP, BNP	Model: multivariable Cox regression and ROC analysis Adjusted/Non-adjusted covariates: Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, SBP, HR, digoxin, diuretics, ACE inhibitors, beta-blockers, creatinine HR = 2.07 (1.76, 2.46), AUC = 0.679 (0.011)	NA	Likelihood ratio, add NT-proBNP to Base Model p<0.0001	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74% T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5yrs(7.2), 50% Outcomes (#events, # risk): all-cause mortality (934, 3,663)	ADM mean: T1= 47(26-78) pmol/L, T2= 173(133-220) pmol/L, T3= 486(367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, AF, diabetes, claudication, CABG, NYHA, ApoA-I, EF, sex, MI, SBP/10*, creatinine, BMI, HR, triglycerides*	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, SBP, EF HR=1.597	NA	Base Model $\chi 2$ = 440.2, Base Model + NT-proBNP=600.4 (Inc. Chi-Square=166.719, p<0.0001)	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74% T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5yrs(7.2), 53% Outcomes (#events, #risk): sudden death (407, 3,664)	ADM mean: T1= 47(26-78) pmol/L T2= 173(133-220) pmol/L T3 = 486 (367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, CABG, AF, diabetes, NYHA*, ApoA-I, EF, creatinine*, BMI*, sex	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, SBP, EF HR=1.688	NA	Base Model = 163.4, Base Model + NT-proBNP=246.0 (Inc. Chi-Square=90.097, p<0.0001)	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Schou,[12] 2007 F/U: 30 mo**	Study design: Cohort Systolic HF patients, LVEF ≤45%, all n, mean age, %male: 345, 75 & 69yrs** (Anemia, y/n), 68.1% Outcomes (#events, #risk): all-cause mortality (70, 345)	ADM mean: 2,889 & 1,022** (Anemia, y/n) D/C mean: NR Cutpoint: ≥ 1,381	NT-proBNP, age*, eGFR*, BMI*, LVEF, NYHA	Model: Multivariate cox regression Adjusted/Non-adjusted covariates: age*, eGFR*, BMI*, LVEF, NYHA HR=3.01 (1.84-5.41)	NA	Add NT-proBNP to Base Model (demographics + LVEF + NYHA) significantly improved the model fit (-2 log-likelihood = 695, p<0.001)	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Christensen[13] 2012 F/U: 30 mo**	Study design: Cohort Patients with CHF n, mean age, %male: 194, 69yrs (10), 72% Outcomes (#events, #risk): all-cause mortality (43, 194)	ADM mean: NR D/C mean: NR Cutpoint: per 1 SD increase	NT-proBNP, a-Defensins, age, sex, LVEF, NYHA, creatinine clearance	Model: Multi-variable Cox regression Adjusted/Non-adjusted covariates: a-Defensins, age, sex, LVEF, NYHA, creatinine clearance HR=1.79 (1.30, 2.45) per 1 SD increase	C-statistic Base model = 0.649 (0.554–0.743), Base model + NT-proBNP=0.689 p=0.03, Base model + a-Defensins = 0.679 p=0.13, Base model + NT-proBNP + a-Defensins = 0.709 p=0.006	NA	NA	NRI: Base Model =Reference, Base model + NT-proBNP =10.8 (p=0.35) Base model + a-Defensins=16.4 (p= 0.11) Base model + NT-proBNP + a-Defensins = 17.4 (p=0.18) IDI: Base Model =Reference, Base model + NT-proBNP, p= 0.005; Base model + a-Defensins, p= 0.003; Base model + NT-proBNP + a-Defensins , p= 0.03

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Wedel,[14] 2009 CORONA study F/U: 31 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5yrs (7.1), 75% Outcomes (#events, #risk): total mortality (934, 3,324)	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, heart rate, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP	Model: multi-variable Cox regression Adjusted/Non-adjusted covariates: NR Measure(s) of risk:HR=1.60 (1.49-1.71)	demographics and medical history C-statistic: 0.667, lipid variables added C-statistic: 0.684, addition of NT-proBNP C-statistic: 0.719 (P-value for Step 1 vs. 2 and 2 vs. 3 both <0.0001).	demographics and medical history: $\chi 2$ =343, lipid variables added to $\chi 2$ model = 440, add NT-proBNP: $\chi 2$=600	NA	NA

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Bayes-Genis,[15] 2011 F/U: 33 mo**	Study design: Cohort Ambulatory patients with HF n, mean age, %male: 891, 70.2yrs (60.5 - 77.2)**, 71.6% Outcomes (#events, #risk): all-cause mortality (244, 891)	ADM mean:1,376 (527.1 – 3,024)** D/C mean: NR Cutpoint: 1,829	NT-proBNP, ST2, age, sex, Ischemic etiology, LVEF, NYHA, eGFR, BMI, Diabetes mellitus, ACEI or ARB treatment, Beta-blocker, Na, Hb	Model: Multi-variable Cox regression Adjusted/Non-adjusted covariates: ST2, age, sex, Ischemic etiology, LVEF, NYHA, eGFR, BMI, Diabetes mellitus, ACEI or ARB treatment, Beta-blocker, Na, Hb HR=1.241 (1.089, 1.413) on a continuous scale	C-statistic Base model = 0.76 (0.73–0.79), Base model + NT-proBNP=0.77 (0.74–0.80) p=0.04, Base model + ST2 = 0.78 (0.75–0.81) p=0.001, Base model + NT-proBNP + ST2 = 0.79 (0.76–0.81) p<0.001	Add NT-proBNP and ST2 significantly improved global model fit (likelihood ratio p<0.0001)	Hosmer–Lemeshow statistics indicated good calibration for the model with and without the two biomarkers (p >0.18 for all comparisons)	The NRI after the individual inclusion of ST2 in the model with established mortality risk factors and NT-proBNP was 9.90% (95% CI, 4.34 to 15.46 P<0.001), and the IDI was 1.54 (95% CI, 0.29 to 2.78, p=0.015).

Table K-5. Studies evaluating incremental value of NT-proBNP to predict the outcome of all-cause mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Antonio,[16] 2012 F/U: 33 mo**	Study design: Cohort Ambulatory patients with HF n, mean age, %male: 876, 68yrs (12.3), 71.9% Outcomes (#events, #risk): all-cause mortality (244, 891)	ADM mean: 3,212 ± 6,779 , ng/L D/C mean: NR Cutpoint: 1,720	logNT-proBNP, ln(hs-cTnT), age, gender, Ischemic etiology, LVEF, NYHA, eGFR, BMI, Diabetes mellitus, ACEI or ARB treatment, Beta-blocker, Na, Hb	Model: Multi-variable Cox regression Adjusted/Non-adjusted covariates: ln(hs-cTnT), age, sex, Ischemic etiology, LVEF, NYHA, eGFR, BMI, Diabetes mellitus, ACEI or ARB treatment, Beta-blocker, Na, Hb	C-statistic Base model = 0.76 (0.74−0.79), Base model + NT-proBNP=0.77 (0.75−0.79) p=0.017, Base model + hs-cTnT = 0.78 (0.75−0.80) p=0.002, Base model + NT-proBNP + hs-cTnT = 0.78 (0.76−0.81) p=0.004 addition of NT-proBNP and hs-cTnT improved global model fit (likelihood ratio p<0.0001)	addition of NT-proBNP and hs-cTnT improved global model fit (likelihood ratio p<0.0001)	Hosmer–Lemeshow statistics: Base Model = $\chi2$ = 8.6 (p=0.38), Base model + NT-proBNP=$\chi2$ = 9.8 (p=0.28), Base model + hs-cTnT = $\chi2$ = 2.2 (p=0.98), Base model + NT-proBNP + hs-cTnT = $\chi2$ = 12.1 (p= 0.14)	NRI: Base Model =Reference, Base model + NT-proBNP =1.5 (−5.2 to 8.2) (p=0.67), Base model + hs-cTnT = 7.7 (0.7−14.7) (p =0.03), Base model + NT-proBNP + hs-cTnT = 4.2 (−3.0 to 11.3) (p=0.25) IDI: Base Model =Reference, Base model + NT-proBNP =1.4 (0.3−2.4) (p =0.011), Base model + hs-cTnT =2.8 (1.6−4.0) (p <0.001), Base model + NT-proBNP + hs-cTnT =3.1 (1.7−4.5) (p <0.001)

†Likelihood-based measures (i.e., log likelihood ratio, likelihood ratio $\chi2$, Global $\chi2$, incremental $\chi2$)

*Insignificant

**Median values

Abbreviations: ACEI = Angiotensin Coverting Enzyme; ADM = admission; AF = atrial fibrillation; AHF = Acute heart failure; ApoA1 = apolipoprotein A-I; ARB = angiotensin receptor blocker; AUC = area under the curve; BMI = body mass index; BMod = behavior modifcation; BNP=B-Type Natriuretic Peptide; BP = blood pressure; CABG = coronary artery bypass graft; CHF = Congestive heart failure; CP=Cutpoint D/C = discharge; E/Em = E wave deceleration time, Em; ED = emergency department; EF = ejection fraction; eGFR = estimated glomerular filtration rate; F/U = followup; GFR= glomerular filtration rate; Hb = Hemoglobin; HF = Heart failure; HR = Hazard ratio; hs-cTnT = high-sensitivity cardiac troponin T; hsCRP = high-sensitivity c-reactive protein; IDI = integrated risk improvement; IQR = Interquartile range; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; MI = myocardial infarction; mo = months; MR = mitral regurgitation; MR-proADM = midregional proadrenomedullin; Na = sodium; NA = not applicable; NR = not reported; NS = not significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; SBP = systolic blood pressure; SD= standard deviation; TAPSE = tricuspid annular plane systolic excursion; vs. = versus; yrs= years

Table K-6. Studies evaluating incremental value of NT-proBNP to predict the outcome of cardiovascular mortality in patients with stable heart failure

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Jankowska,[17] 2011 F/U: 12 mo	Study design: Cohort Patients with systolic CHF n, mean age, %male: 491, 63 (11), 91% Outcomes (#events, #risk): CV mortality (70, 491)	ADM mean: 875 (347, 2,465)** D/C mean: NR Cutpoint: 2,465	log10NT-proBNP, CT-proET-1 (log), NYHA, LVEF, age*, serum creatinine*	Model: multivariable Cox proportional hazard; Adjusted/Non-adjusted covariates: NR HR=NR	NA	Base model (Demographic and clinical parameters), $\chi 2$ = 73.20, Base model + LVEF : $\chi 2$= 91.02, Base model + LVEF + E/Em ratio: $\chi 2$ =105.54; Base model + LVEF + E/Em ratio + log NT-proBNP: $\chi 2$=119.30 (all p<0.0001).	NA	NA
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35 to 40% n, mean age, %male: T1: 1,221, 70.8yrs (6.7), 74% T2: 1,222, 72.7yrs (7), 76% T3: 1,221, 74.5yrs (7.2), 54% Outcomes (#events, #risk): HF death (230, 3,664)	ADM mean: T1: 47 (26-78) pmol/L T2: 173 (133-220) pmol/L T3: 486 (367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, AF, diabetes, CABG, NYHA, claudication, ApoA-I*, EF, SBP/10, creatinine*, BMI*, h, smoking*	Model: Multivariable Cox regression; Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, SBP, EF HR=1.986	NA	Base Model = 223.0, Base Model + NT-proBNP=295.8 (Inc. Chi-Square=82.637, p<0.0001)	NA	NA

Table K-6. Studies evaluating incremental value of NT-proBNP to predict the outcome of cardiovascular mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Dini,[18] 2010 F/U: 25 mo**	Study design: Cohort Chronic systolic HF outpatients, LVEF ≤45%, all n, mean age, %male: E/Em≤8: 117, 68yrs(12), 88% E/Em=9-13: 121, 69yrs(10), 82% E/Em≥14: 124, 68yrs(13), 75% Outcomes (#events, #risk): cardiac mortality (61,362)	ADM mean: E/Em≤8: 757(321) E/Em=9-13: 1326(278) E/Em≥14: 2,533(748) D/C mean: NA Cutpoint: 1,872	NT-proBNP, prior HF hospitalization, E/Em ratio, LVEF*, prior hospitalization	Model: multivariate Cox regression Adjusted/Non-adjusted covariates: prior HF hospitalization, E/Em ratio, LVEF*, prior hospitalization, age, sex, and CAD HR=NR	NA	Base model (Demographic and clinical parameters), $\chi 2 = 73.20$, Base model + LVEF : $\chi 2 = 91.02$, Base model + LVEF + E/Em ratio: $\chi 2 = 105.54$ Base model + LVEF + E/Em ratio + log NT-proBNP: $\chi 2 = 119.30$ (all $p<0.0001$).	NA	NA

Table K-6. Studies evaluating incremental value of NT-proBNP to predict the outcome of cardiovascular mortality in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Wedel,[14] 2009 F/U: 31 mo	Study design: Case Series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75% Outcomes (#events, #risk): death from HF (230, 3,342)	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA1, s/creatinine, intermittent claudication, heart rate, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP	Model: multi-variable cox regression Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP HR=1.99 (1.71-2.30)	demographics and medical history C-statistic: 0.742, lipid variables added C-statistic: 0.757, the addition of NT-proBNP C-statistic: 0.800 (p value for Step 1 vs. 2 p<0.25 and 2 vs. 3 p=0.0002).	NA	NA	NA

†Likelihood-based measures i.e., log likelihood ratio, likelihood ratio $\chi 2$, Global $\chi 2$, incremental $\chi 2$

*Insignificant

**Median Values

Abbreviations: ACEI = Angiotensin Coverting Enzyme; ADM = admission; AHF = Acute heart failure; ApoA1 = apolipoprotein A-I; ARB = angiotensin receptor blocker; BMI = body mass index; BMod = behavior modifcation; BNP = B-type natriuretic peptide; BP = blood pressure; CHF = Congestive heart failure; CP = cutpoint D/C = discharge; E/Em = E wave deceleration time, Em; ED = emergency department; F/U = followup; GFR= glomerular filtration rate; Hb = hemoglobin; HF = heart failure; HR = hazard ratio; hs-cTnT = high-sensitivity cardiac troponin T; hsCRP = high-sensitivity c-reactive protein; IDI = integrated risk improvement; IQR= interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; mo = months; Na = sodium; NA = not applicable; NR = not reported; NS = not significant; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pg/mL = picograms per milliliter; vs. = versus; yrs= years

Table K-7. Studies evaluating incremental value of NT-proBNP to predict the outcome of morbidity in patients with stable heart failure

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Mikkelsen,[19] 2006 F/U: 12 mo	Study design: Cohort HF patients n, mean age, %male: SHF: 22, 70yrs (58, 78)** , 45.5% HFPSF: 58, 68yrs (53, 77)**, 51.7% Outcomes (#events, #risk): NYHA class stable or increased (47, 78)	ADM mean: SHF=2,285** (595 – 6,395), HFPSF=199** (92-500) D/C mean: NR Cutpoint: NR	log NT-proBNP, age*, sex*, BMI*,FEV1/FVC*, Tei index	Model: multivariable logistic regression Adjusted/Non-adjusted covariates: age, sex, BMI and FEV1/FVC, Tei index OR=0.49 (0.31-0.78), Wald=9.04, p=0.003	NA	log likelihood ratio $\chi 2$ increased from 9.32 to 20.18 (p=0.001) after adding NT-proBNP to the model	NA	NA

Table K-7. Studies evaluating incremental value of NT-proBNP to predict the outcome of morbidity in patients with stable heart failure (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Masson,[10] 2006 Val-Hef F/U: 23 mo	Study design: Cohort Secondary analysis of RCT data Patients with stable symptomatic HF (LVEF <40%) n, mean age, %male: 3,916, NR, 80.2% Outcomes (#events, #risk): HF hospitalization (634, 3,916)	ADM mean: 895 (375 to 1,985)** D/C mean: NR Cutpoint: >895	NT-proBNP, BNP	Model: multivariable Cox regression and ROC analysis Adjusted/Non-adjusted covariates: Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, SBP, HR, digoxin, Diuretics, ACE inhibitors, beta-blockers, creatinine HR=2.66 (2.19, 3.22), AUC=0.685 (0.011)	NA	Likelihood ratio, add NT-proBNP to Base Model p<0.0001	NA	NA

†Likelihood-based measures i.e., log likelihood ratio, likelihood ratio $\chi 2$, Global $\chi 2$, incremental $\chi 2$

*Insignificant

**Median Values

Abbreviations: ACE = Angiotensin Coverting Enzyme; ADM = admission; AF = atrial fibrillation; AHF = Acute heart failure; ApoA1 = apolipoprotein A-I; AUC = area under curve; BMI = body mass index; BMod = behavior modifcation; BNP = B-type natriuretic peptide; BP = Blood pressure; CHF = Congestive heart failure; CP = Cutpoint D/C = discharge mean; F/U = followup; FVC = forced vital capacity; GFR= glomerular filtration rate; HF = Heart failure; HFPSF = heart failure with preserved systolic function; HR = hazard ratio; IDI = integrated risk improvement; IQR= interquartile range; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; NR = not reported; NS = not stated; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; SBP = systolic blood pressure; SHF = systolic heart failure; vs. = versus; yrs= years

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Dini,[20] 2008 F/U: 22 mo**	Study design: Cohort Outpatients with chronic HF, LVEF≤ 45% n, mean Age, %Males: 313, 69yrs (11), 78% Outcomes (#events, #risk): composite (all-cause mortality + HF hospitalization) (111, 313)	Admission mean:1,492 (617 – 3,540)** Discharge: NR Cutpoint: >1,492	NT-proBNP, age, NYHA class, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocity	Model: Adjusted (Multivariate) Cox regression Adjusted/Non-adjusted covariates: age, sex, NYHA class, LVEF, EDT, coronary artery disease, Myocardial E wave velocity HR=2.94 (1.83, 4.72)	NA	Base model (demographic & clinical variable)=52.7, Base model (clinical variables + LVEF, Em)=78.6, Base model (demographic & clinical variables + LVEF, Em) + NT-proBNP=97.7 (p<0.0001)	NR	NR
Masson,[10] 2006 Val-Hef F/U: 23 mo	Study design: Cohort Secondary analysis of RCT data Patients with stable symptomatic HF (LVEF <40%) n, mean age, %male: 3,916, NR, 80.2% Outcomes (#events, #risk): composite (mortality and morbidity) (1,194, 3,916)	ADM mean: 895 (375-1985)** D/C mean: NR Cutpoint: >895	NT-proBNP, BNP	Model: multivariable cox regression and ROC analysis Adjusted/Non-adjusted covariates: Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, SBP, HR, digoxin, Diuretics, ACE inhibitors, beta-blockers, creatinine HR=2.20 (1.92, 2.51), AUC=0.688 (0.009)	NA	Likelihood ratio, add NT-proBNP to Base Model p<0.0001	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs (6.7), 74% T2: 1,222, 72.7yrs (7.0), 76% T3: 1,221, 74.5yrs (7.2), 50% Composite (CV mortality or nonfatal MI or nonfatal stroke), (883, 3664)	ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, AF, diabetes, claudication, CABG, NYHA, ApoA-I, EF, sex, MI, SBP/10, creatinine*, BMI*, HR*, triglycerides*	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EF HR=1.587		Base model = 314.9, Base model + NT-proBNP=477.1 (Inc. Chi-square=155.445, p<0.0001)		

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74% T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 52% Composite (Atherothrombotic end point (fatal or nonfatal myocardial infarction, or fatal or nonfatal nonhemorrhagic stroke), (284, 3,664)	ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, hsCRP, age, AF, diabetes, claudication, ApoA-I*, MI,	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EF HR=1.238	NA	Base model = 85.981, Base model + NT-proBNP=97.7 (Inc. Chi-square=11.719, p=0.0006)	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74% T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 51% Composite: Coronary events (sudden death , fatal or nonfatal myocardial infarction, coronary revascularization, ventricular defibrillation by an implantable device, resuscitation from cardiac arrest, or hospitalization for unstable angina), (741, 3,664)	ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age*, AF, diabetes, claudication, NYHA, Apo A-I, EF, MI, SBP/10, creatinine*, BMI*, HR*, angina pectoris	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EF HR=1.469	NA	Base model = 182.3, Base model + NT-proBNP=291.0 (Inc. Chi-Square=95.579, p<0.0001)	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Cleland,[11] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74% T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 55% death or worsening HF (1,376, 3,664)	ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, AF, diabetes, NYHA, claudication, ApoA-I, EF, SBP/10*, creatinine*, BMI*, HR, sex, triglycerides*	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EF HR=1.639	NA	Base model = 463.0, Base model + NT-proBNP=700.8 (Inc. Chi-Square=259.612, p<0.0001)	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Wedel,[14] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, 60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75 Outcomes (#events, #risk): Composite (Atherothrombotic endpoint (fatal or nonfatal myocardial infarction, or fatal or nonfatal nonhemorrhagic stroke), (284, 3,342)	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP	Model: multi-variable cox regression Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP HR=1.24 (1.10-1.40)	NA	χ2 for base model + (ALAT,CK,TSH,Apo-1,Apo-B,TG-s) = 74, base model +(ALAT,CK,TSH,Apo-1,Apo-B,TG-s) + NT-proBNP= 97.7 (p=0.0001)	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Wedel,[14] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75% Outcomes (#events, #risk): all-cause mortality/ HF hospitalization (1,376, 3,342)	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP	Model: multivariable Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP HR=1.64-1.74)	demographics and medical history C-statistic: 0.653, lipid variables added C-statistic: 0.666, the addition of NT-proBNP C-statistic: 0.701 (P-value for Step 1 vs. 2 p=0.0.002 and 2 vs. 3 p=0.0001).	Demographic and clinical parameters ($\chi2$= 12.26), LVEF added to the above: $\chi2$= 31.14, the addition of E/Em ratio: $\chi2$=43.64 addition of log transformed NT-proBNP: $\chi2$=49.88 (all P <0.0001)	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Wedel,[14] 2009 CORONA F/U: 24 mo	Study design: Case series Secondary analysis of RCT data Chronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75% Outcomes (#events, #risk): CV mortality/nonfatal MI/nonfatal stroke (883, 3,342)	ADM mean: 166 (70-358)** pmol/L D/C mean: NR Cutpoint: per log unit	log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP	Model: multi-variable cox regression Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP HR=1.59 (1.49-1.71)	NA	χ2 for base model + (ALAT,CK,TSH,ApoA-1,Apo-B,TG-s) = 315, base model +(ALAT,CK,TSH,Apo-1,Apo-B,TG-s) + NT-proBNP= 477 (p=0.0001)	NA	NA
Dini,[21] 2009 F/U: 29 mo	Study design: Cohort Outpatients with chronic HF, and LVEF≤ 45% n, mean age, %male: 232, 69yrs(10), 84% Composite (all-cause mortality + HF hospitalization) (65, 232)	ADM mean: 891 (174) D/C mean: NR Cutpoint: >544	NT-proBNP, age, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocity	Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocity HR=2.66 (1.24, 5.71)	NA	Base model (Demographics & clinical data + EF + EDT + EM) + NT-proBNP = Inc χ2 = p<0.0001	NA	NA

Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued)

Author Year Mean Length F/U	Study Description	Peptide Levels (pg/mL)	Prognostic Markers	Model Descriptions Measure(s) of Risk (95%CI)	Discrimination Statistics (C-statistics/C-index)	Global Model Fit Statistics†	Calibration Statistics (Hosmer-Lemeshow statistic)	Measure of Risk Reclassification (IDI and NRI)
Bajraktari,[22] 2011 F/U: 37 mo	Study design: Cohort Outpatients with chronic systolic HF, and LVEF≤ 45% n, mean age, %male: 107, 68yrs(12), 75% Outcomes (#events, #risk): Composite (cardiac mortality + HF hospitalization) (55, 107)	ADM mean: 1,257 (553 – 3,212)** D/C mean: NR Cutpoint: ≥2.47 on log scale	logNT-proBNP, age, sex, T-IVT, mean E/Em ratio, LVEF	Model: Multivariate logistic regression Adjusted/Non-adjusted covariates: age, sex, T-IVT, mean E/Em ratio, LVEF OR=4.162 (1.289, 13.44)	NA	Base model (age, sex, T-IVT, mean E/Em ratio, LVEF) Chi-square = 35.9 , Base model + NT-proBNP, $\chi 2$ = 38.0 (p<0.0001)	NA	NA

†Likelihood-based measures i.e., log likelihood ratio, likelihood ratio $\chi 2$, Global $\chi 2$, incremental $\chi 2$

*Insignificant

**Median Values

Abbreviations: ADM = admission; AHF = Acute heart failure; ApoA1 = apolipoprotein A-I; BMI = body mass index; BMod = behavior modifcation; BNP = B-type natriuretic peptide; BP = Blood pressure; CHF= Congestive heart failure; CP= Cutpoint; D/C= discharge; EDT = Ethylenediaminetetraacetic acid; F/U= followup; GFR = Glomerular filtration rate; HF = Heart failure; HR = Hazard ratio; IDI = integrated risk improvement; IQR= Interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = Not reported; NS = Not stated; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; vs. = Versus; $\chi 2$ = chi square; Yrs = years

Table K-9. Risk of bias for studies using the Hayden criteria assessing BNP and NT-proBNP for stable heart failure population

	Study Participation			Study Attrition		Prognostic Factors					Outcome Measurement			Confounding		Analysis	Study Design
Author, Year	**1a**	**1b**	**1c**	**2a**	**2b**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**5a**	**5b**	**6a**	**7a**
Mikkelsen,[19] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Schou,[12] 2007	√	√	√	√	√	√	√	√	√	√	√	√	√	√	X	√	√
Masson,[10] 2006	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Dini,[18] 2010	√	√	√	?	X	√	√	√	√	√	√	X	√	X	X	√	√
Dini,[21] 2009	√	√	√	√	√	√	√	√	√	√	√	?	X	X	X	√	√
Dini,[20] 2008	√	√	√	√	√	√	√	NA	√	NA	√	√	X	X	X	√	√
Dini,[9] 2008	√	√	√	?	?	√	√	√	?	?	√	√	√	X	X	√	√
Bajraktari,[22] 2011	√	√	√	?	√	√	√	√	√	√	√	?	X	X	X	√	√
Cleland,[11] 2009 Corona	√	√	√	√	√	√	√	√	√	√	√	?	√	√	√	√	√
Wedel,[14] 2009	√	√	√	√	√	√	√	NA	√	NA	√	?	√	√	√	√	√
Jankowska,[17] 2011	√	√	√	√	√	√	√	√	√	√	√	X	√	√	√	√	√
von Haehling,[8] 2010	√	√	√	X	√	√	√	√	√	√	√	X	√	√	√	√	√
Bayes Genis,[15] 2012	?	?	?	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Antonio,[16] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	√	√	√	√
Christensen,[13] 2012	√	√	√	?	?	√	√	√	?	?	√	√	√	√	√	√	√
Harutyunyan,[7] 2012	√	√	√	√	√	√	√	√	?	?	√	√	√	X	X	√	√

1. a) source population clearly defined, b) study population described c) study population represents source population, or population of interest
2. a) completeness of follow-up described, b) completeness of follow-up adequate
3. a) BNP/NT-proBNP factors defined, b) BNP/NT-proBNP factors measured appropriately, c) Other factors measured appropriately, d) For BNP/NT-proBNP, the extent of and reasons for indeterminate test results or missing data reported, e) for other prognostic factors, the extent of and reasons for indeterminate test results or missing data reported
4. a) outcome defined, b) outcome measured appropriately, c) a composite outcome was avoided
5. a) confounders measured, b) confounders accounted for
6. a) analysis described; 7 a) The study was designed to test the prognostic value of BNP/NT-proBNP

✔ = Low Risk ✖ = High Risk ? = unclear

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Appendix L. Key Question 5 Evidence Set

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Chisalita,[1] 2011	Cohort General population age 66-81	n=851 Mean age: 73y(3.5) % male: 48.7	Admission mean: 276.7 (558.1) Discharge mean: NR Cutpoint: >100	NT-proBNP, IGF-1; serum creatinine, Age, sex, BMI, DM, ischemic heart disease, NYHA class III	8y Cardiovascular mortality (134, 851)	Multivariable cox proportional hazard regression	IGF-1; serum creatinine, Age, sex, BMI, DM, ischemic heart disease, NYHA class III	HR=1.0 (1.0 to 1.001)
Daniels,[2] 2008	Cohort General population	n=957 Mean age: 77y (30 - 79)** % male: 39	Admission mean: low grp=112 high grp=970 Discharge mean: NR Cutpoint: 450	NT-proBNP, baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y All-cause mortality (220, 957)	Multivariable cox proportional hazard regression	baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.67 (1.21 to 2.29) per 1 unit log increase (Model without TnT)
				NT-proBNP, TnT, baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y All-cause mortality (220, 957)	Multivariable cox proportional hazard regression	baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.53 (1.10 to 2.12) per 1 unit log increase (Model with TnT)
				NT-proBNP, TnT, baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y Cardiovascular mortality (92, 957)	Multivariable cox proportional hazard regression	baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.93 (1.17 to 3.19) per 1 unit log increase (Model without TnT)
				NT-proBNP, TnT, baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y Cardiovascular mortality (92, 957)	Multivariable cox proportional hazard regression	baseline CHD, age, sex systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.84 (1.10 to 3.08) per 1 unit log increase (Model with TnT)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Daniels,[2] 2008 (cont'd)	(repeated data) Cohort General population without CHD	n=806 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: 450	NT-proBNP, baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y All-cause mortality (157, 806)	Multivariable cox proportional hazard regression	baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.74 (1.19 to 2.55) per 1 unit log increase (Model without TnT)
				NT-proBNP, TnT, baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y All-cause mortality (157, 806)	Multivariable cox proportional hazard regression	baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.54 (1.04 to 2.29) per 1 unit log increase (Model with TnT)
				NT-proBNP, TnT, baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y CVD mortality (52, 806)	Multivariable cox proportional hazard regression	baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.85 (0.94 to 3.64) per 1 unit log increase (Model without TnT)
				NT-proBNP, TnT, baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	6.8y CVD mortality (52, 806)	Multivariable cox proportional hazard regression	baseline CHD, age, sex, systolic BP, BMI, heart rate, physical activity, total cholesterol, and creatinine clearance	HR=1.83 (0.90 to 3.72) per 1 unit log increase (Model with TnT)
Olsen,[3] 2007	Cohort Community population, recruited from age 30y, 40y, 50y, or 60y	n=2,656 Mean age: NR % male: 50.3	Admission mean: Men=32(13 to 74)** Women=66(37 to 113)** Discharge mean: NR Cutpoint: >32 for men, >66 for women	NT-proBNP, DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	9.4y Composite (CV mortality, MI, stroke) (219, 2656)	Multivariable cox proportional hazard regression	DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	HR=1.64 (1.42 to 1.90) per SD increase (Adjusted for Traditional risk factors only)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Olsen,[3] 2007 (cont'd)	Cohort Community population, recruited from age 30y, 40y, 50y, or 60y	n=2,656 Mean age: NR % male: 50.3	Admission mean: Men=32(13 to 74)** Women=66(37 to 113)** Discharge mean: NR Cutpoint: >32 for men, >66 for women	NT-proBNP, DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	9.4y Composite (CV mortality, MI, stroke) (219, 2656)	Multivariable cox proportional hazard regression	DM, stroke, MI, Age, Sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	HR=1.56 (1.33 to 1.83) per SD increase (Adjusted for Traditional risk factors plus bio-markers (LVEF, RWT, UACR, hsCRP))
				NT-proBNP, DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	9.4y CV mortality (136, 2656)	Multivariable cox proportional hazard regression	DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	HR=1.99 (1.65 to 2.40) per SD increase (Adjusted for Traditional risk factors only)
				NT-proBNP, DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	9.4y CV mortality (136, 2656)	Multivariable cox proportional hazard regression	DM, stroke, MI, Age, sex, Smoking, systolic BP, heart rate, serum LDL, plasma glucose	HR=1.93 (1.56 to 2.39) per SD increase (Adjusted for Traditional risk factors plus bio-markers (LVEF, RWT, UACR, hsCRP)
Patton,[4] 2001	Cohort General population, age >65 y	n=5,447 Mean age: NR % male: 41.4	Admission mean: No SCD=117 (60 - 236)** SCD=198 (79 - 472)** Discharge mean: NR Cutpoint: NR	NT-proBNP, LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (289, 5447)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.3 (1.1-1.5) per SD increase (Adjusted for traditional risk factors + LVEF)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Patton,[4] 2001 (cont'd)	Cohort General population, age >65 y, Quintile of NT-proBNP Q2 vs. Q1	n=2,179 Mean age: Q1=70.5y(NR) Q2=71.2y(NR) % male: Q1=47.4, Q2=39.5	Admission mean: Q1=NR (5 - 50.81)** Q2=NR (50.82 - 91.78)** Discharge mean: NR Cutpoint: >50.81	NT-proBNP (Q2 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.0 (0.6-1.5) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population, age >65 y, Quintile of NT-proBNP Q3 vs. Q1	n=2,176 Mean age: Q1=70.5y(NR) Q3=72.3y(NR) % male: Q1=47.4, Q3=38.4	Admission mean: Q1=NR (5 - 50.81)** Q3=NR (91.79 to 156.09)** Discharge mean: NR Cutpoint: >91.78	NT-proBNP (Q3 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.1 (0.7-1.8) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population, age >65 y, Quintile of NT-proBNP Q4 vs. Q1	n=2,179 Mean age: Q1=70.5y(NR) Q4=73.7y(NR) % male: Q1=47.4, Q4=34.6	Admission mean: Q1=NR (5 - 50.81)** Q4=NR (156.1 to 298.3)** Discharge mean: NR Cutpoint: >91.78	NT-proBNP (Q4 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.6 (1.0-2.5) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population, age >65 y, Quintile of NT-proBNP Q5 vs. Q1	n=2,177 Mean age: Q1=70.5y(NR) Q5=75.9y(NR) % male: Q1=47.4, Q5=47	Admission mean: Q1=NR (5 - 50.81)** Q5=NR Discharge mean: NR Cutpoint: >290.3	NT-proBNP (Q5 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (196, 2177)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.7 (1.0-2.6) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with no CVD, age >65y	n=4,606 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: NR	NT-proBNP, LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (195, 4606)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.2 (1.0-1.5) per SD increase (Adjusted for traditional risk factors + LVEF)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Patton,[4] 2001 (cont'd)	Cohort General population with no CVD, age >65y, Quintile of NT-proBNP Q2 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >50.81	NT-proBNP (Q2 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=0.9 (0.6-1.6) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with no CVD, age >65y, Quintile of NT-proBNP Q3 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >91.78	NT-proBNP (Q3 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.3 (0.8-2.2) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with no CVD, age >65y, Quintile of NT-proBNP Q4 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >156.09	NT-proBNP (Q4 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.1 (0.7-1.9) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with no CVD, age >65y, Quintile of NT-proBNP Q5 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >290.3	NT-proBNP (Q5 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.7 (1.0, 3.0) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with CVD, age >65y	n=841 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: NR	NT-proBNP, LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (94, 841)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.4 (1.1, 1.8) per SD increase (Adjusted for traditional risk factors + LVEF)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Patton,[4] 2001 (cont'd)	Cohort General population with CVD, age >65y, Quintile of NT-proBNP Q2 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >50.81	NT-proBNP (Q2 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=0.9 (0.3, 3.2) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with CVD, age >65y, Quintile of NT-proBNP Q3 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >91.78	NT-proBNP (Q3 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=0.4 (0.1, 1.7) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with CVD, age >65y, Quintile of NT-proBNP Q4 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >156.09	NT-proBNP (Q4 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=3.1 (1.1, 8.5) per SD increase (Adjusted for traditional risk factors + LVEF)
	Cohort General population with CVD, age >65y, Quintile of NT-proBNP Q5 vs. Q1	n=NR Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: >290.3	NT-proBNP (Q5 vs. Q1), LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	12.5y Sudden cardiac death (NR)	Multivariable cox proportional hazard regression	LVEF, age, sex, race, DM, smoking, systolic BP, serum potassium level, ECG conduction delay, and CVD	HR=1.7 (0.6, 4.6) per SD increase (Adjusted for traditional risk factors + LVEF)
Smith,[5] 2011	Cohort General population without prior MI or stroke at baseline	n=187 Mean age: 57.6y(NR) % male: 41	Admission mean: 61.0 (34.0 to 111.0)** Discharge mean: NR Cutpoint: NR	NT-proBNP, age, sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, Smoking, history of MI	13.8 y heart failure (112, 5187)	Multivariable cox proportional hazard regression	age, sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, smoking, history of MI	HR=1.95 (1.63 to 2.34) per SD increase c-index=0.837, IDI=0.03 (p=0.001) NRI=16% (p=0.003) (conventional risk factors only)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Smith,[5] 2011 (cont'd)	(repeated data) Cohort General population without prior MI or stroke at baseline	(repeated data) n=187 Mean age: 57.6y(NR) % male: 41	(repeated data) Admission mean: 61.0 (34.0 to 111.0)** Discharge mean: NR Cutpoint: NR	NT-proBNP, MR-proADM, MR-proANP, CRP, CystC, Copeptin, Age, Sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, Smoking, history of MI	13.8 y heart failure (112, 5187)	Multivariable cox proportional hazard regression	MR-proADM, MR-proANP, CRP, CystC, Copeptin, Age, Sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, smoking, history of MI	HR=1.63 (1.29 to 2.06) per SD increase (conventional risk factors + other biomarkers)
				NT-ProBNP, age, sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, Smoking, history of MI	13.8 y atrial fibrillation (284, 5187)	Multivariable cox proportional hazard regression	age, sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, smoking, history of MI	HR=1.45 (1.28 to 1.65) per SD increase (conventional risk factors only)
				NT-ProBNP, MR-proADM, lnMR-proANP, CRP, CystC, Copeptin, Age, Sex, systolic BP, diastolic BP, BMI, anti-hypertensive teatment, LDL, HDL, DM, Smoking, history of MI	13.8 y atrial fibrilation (284, 5187)	Multivariable cox proportional hazard regression	MR-proADM, MR-proANP, CRP, CystC, Copeptin, Age, Sex, systolic BP, diastolic BP, BMI, anti-hypertensive treatment, LDL, HDL, DM, smoking, history of MI	HR=NS (conventional risk factors + other biomarkers)
Vaes,[6] 2009	Cohort General population, followed at age 90y	n=274 Mean age: NR % male: 27.7	Admission mean: Male=770.1 (236.35-2017.5)** Female=405.9 (235.7-882.35)** Discharge mean: NR Cutpoint: NR	NT-proBNP (tertiles), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV morbidity (180, 274)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=NR
				NT-proBNP (tertiles), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV morbidity (175, 274)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=NR

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Vaes,[6] 2009 (cont'd)	(repeated data) Cohort General population, followed at age 90y	(repeated data) n=274 Mean age: NR % male: 27.7	(repeated data) Admission mean: Male=770.1 (236.35-2017.5)** Female=405.9 (235.7-882.35)** Discharge mean: NR Cutpoint: NR	NT-proBNP (tertiles), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV mortality (58, 274)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=NR
				NT-proBNP (tertiles), weight, height, renal function, hemoglobin, and CV medication	42.3 months overall mortality (170, 274)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=NR
	Cohort General population, followed at age 90y (NT-proBNP tertiles 3 vs. 1)	n=182 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=1771 Female=675.3	NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV morbidity (NR)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=9.7 (3.6 to 26)
				NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV morbidity (NR)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=1.2 (0.59 to 2.6)
	Cohort General population, followed at age 90y (NT-proBNP tertiles 2 vs. 1)	n=183 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=347.5 Female=284.0	NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV morbidity (NR)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=1.3 (0.67 to 2.4)
				NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV morbidity (NR)	Multivariable logistic regression	weight, height, renal function, hemoglobin, and CV medication	OR=1.4 (0.71 to 2.8)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Vaes,[6] 2009 (cont'd)	Cohort General population, followed at age 90y, with specific cardiac diagnosis	n=111 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=912.8 Female=326.2	NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months overall mortality (64, 111)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=2.5 (1.4 to 4.4)
				NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=2.3 (0.8 to 6.5)
				NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=2.7 (1.3 to 5.5)
	Cohort General population, followed at age 90y, with specific cardiac diagnosis	n=111 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=2348 Female=876.3	NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months overall mortality (65, 111)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=2.8 (1.5 to 5.2)
				NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=4.1 (1.5 to 11.0)
				NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=1.9 (0.8 to 4.5)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Vaes,[6] 2009 (cont'd)	Cohort General population, followed at age 90y, with non-specific cardiac diagnosis	n=71 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=211.1 Female=209.7	NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months overall mortality (34, 71)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=1.1 (0.50 to 2.5)
				NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=4.2 (0.8 to 21.0)
				NT-proBNP (sex-specific tertile 2 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=0.6 (0.2 to 1.6)
	Cohort General population, followed at age 90y, with non-specific cardiac diagnosis	n=71 Mean age: NR % male: NR	Admission mean: NR Discharge mean: NR Cutpoint: Male=460.7 Female=408.4	NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months overall mortality (46, 71)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=3.5 (1.6 to 7.5)
				NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=5.6 (1.0 to 30.0)
				NT-proBNP (sex-specific tertile 3 vs. tertile 1), weight, height, renal function, hemoglobin, and CV medication	42.3 months non-CV mortality (NR)	Multivariable cox proportional hazard regression	weight, height, renal function, hemoglobin, and CV medication	HR=3.4 (1.3 to 8.6)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Zethelius,[7] 2008	Cohort General population, male, followed at age 50y	n=1,135 Mean age: 71y(NR) % male: 100	Admission mean: 232 (397) Discharge mean: NR Cutpoint: NR	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (315, 1,135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=1.58 (1.41 to 1.76) per SD increase c-stat=0.657 (p=0.001)
			Admission mean: 232 (397) Discharge mean: NR Cutpoint: ≥ 386	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (315, 1,135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.53 (1.94 to 3.29)
			Admission mean: 232 (397) Discharge mean: NR Cutpoint: >309	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (315, 1,135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.55 (1.98 to 3.28)
			Admission mean: 232 (397) Discharge mean: NR Cutpoint: NR	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (136, 1,135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.03 (1.72 to 2.39) per SD increase c-stat=0.749 (p=0.001)
			Admission mean: 232 (397) Discharge mean: NR Cutpoint: ≥ 386	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (136, 1,135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=3.77 (2.60 to 5.46)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Zethelius,[7] 2008 (cont'd)	(repeated data) Cohort General population, male, followed at age 50y	(repeated data) n=1,135 Mean age: 71y(NR) % male: 100	Admission mean: 232 (397) Discharge mean: NR Cutpoint: >309	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (136, 1135)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=4.10 (2.86 to 5.88)
	Cohort General population without CVD at baseline, male, followed at age 50y	n=661 Mean age: 71y(NR) % male: 100	Admission mean: 145 (213) Discharge mean: NR Cutpoint: NR	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (149, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=1.46 (1.18 to 1.80) per SD increase c-stat=0.653 (p=0.32)
			Admission mean: 145 (213) Discharge mean: NR Cutpoint: ≥ 386	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (149, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.60 (1.56 to 4.31)
			Admission mean: 145 (213) Discharge mean: NR Cutpoint: >309	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y All-cause mortality (149, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.50 (1.60 to 3.89)
			Admission mean: 145 (213) Discharge mean: NR Cutpoint: NR	NT-proBNP, age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (54, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, , total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=2.16 (1.55 to 3.00) per SD increase c-stat=0.722 (p=0.2)

Table L-1. Summary table for prognostic characteristics of studies evaluating BNP/NTpro-BNP as independent predictors of morbidity and mortality in patients with HF, within the community settings (continued)

Author Year	Study Design Population	n Mean Age (SD) % Male	BNP Levels (pg/mL)	Prognostic Markers	Followup* Outcomes (#events, #risk)	Model	Adjusted/ Non-adjusted Covariates	Measure(s) of Risk (95%CI)
Zethelius,[7] 2008 (cont'd)	(repeated data) Cohort General population without CVD at baseline, male, followed at age 50y	(repeated data) n=661 Mean age: 71y(NR) % male: 100	Admission mean: 145 (213) Discharge mean: NR Cutpoint: ≥ 386	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (54, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=4.96 (2.48 to 9.92)
			Admission mean: 145 (213) Discharge mean: NR Cutpoint: >309	NT-proBNP, age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	10y CV Mortality (54, 661)	Multivariable cox proportional hazard regression	age, SBP, antihypertensive treatment, total cholesterol, HDL, lipid-lowering treatment, DM, smoking status, BMI	HR=4.69 (2.53 to 8.72)

*median value

Abbreviations: BMI = body mass index; BNP = B-type natriuretic peptide;BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; HDL = high-density lipoprotein; HR = hazard ratio; NR = not reported; NT-proBNP = N-terminal pro-B-type natriuretic peptide;OR = odds ratio; SBP = systolic blood pressure; y = years

Table L-2. Risk of bias for prognostic studies using the Hayden criteria (n=7)

Author, Year	1a	1b	1c	2a	2b	3a	3b	3c	3d	3e	4a	4b	4c	5a	5b	6a	7a
Smith, [5] 2010	√	√	√	√	√	√	√	√	X	X	√	√	√	√	√	√	√
Vaes,[6] 2009	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√
Daniels,[2] 2008	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Zethelius,[7] 2008	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	?
Olsen,[3] 2007	√	√	√	?	?	√	√	√	?	?	√	√	√	√	√	√	√
Patton,[4] 2011	√	√	√	√	?	√	√	√	√	√	√	X	√	√	√	√	X
Chisalita, [1] 2011	√	√	√	√	√	√	√	NA	√	NA	√	√	√	√	√	√	√

Appendix L Reference List

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