CRD summary
This generally well-conducted review concluded that plasma B-type natriuretic peptides were useful in ruling out heart failure and were consistent predictors of mortality and cardiac outcomes in patients with coronary artery disease and heart failure. Their use to monitor treatment response could not be assessed. The reliability of these conclusions is limited by the paucity of good quality studies.

Authors' objectives
To evaluate the use of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) in the diagnosis of heart failure, prediction of cardiac events and monitoring of treatment response in patients diagnosed with heart failure; their use to identify determinants was also reported but was not addressed in this abstract.

Searching
MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and AMED were searched for papers published in English from 1989 to February 2005.

Study selection
Studies with more than 10 participants that evaluating use of plasma BNP or NT-proBNP in adults (18 years or over) and that reported any aspect of health status in those being tested were eligible for inclusion. Trials that evaluated the effectiveness of nesiritide or an unspecified natriuretic peptide were excluded. Outcomes of interest were diagnosis of heart failure, markers for heart failure and cardiac events. Extensive tables of study characteristics were provided.

Where reported, the mean age of participants ranged from 52 to 85.5 years. Most participants were male (range 21% to 100%). Follow-up ranged from 8.3 days to 9.3 years.

Two reviewers independently screened studies; disagreements were resolved by at least one of the local expert team.

Assessment of study quality
Two reviewers independently assessed the quality of diagnostic accuracy studies using QUADAS, randomised controlled trials (RCTs) using the Jadad criteria and non-randomised studies in relation to sampling and blinding; disagreements were resolved by at least one of the local expert team.

Data extraction
Data to construct 2x2 tables were extracted, from which sensitivity, specificity, positive and negative likelihood ratios (LR+/−), and diagnostic odds ratios (DOR), with corresponding 95% confidence intervals (CI), were calculated. Two reviewers independently extracted data; differences were resolved by at least one of the local expert team.

Methods of synthesis
Diagnostic accuracy studies were combined using a random-effects meta-analysis to produce pooled estimates of sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio, with corresponding 95% CI. Heterogeneity was assessed using Cochrane Q and the I² test. Subgroup analyses and meta-regression were used to explore heterogeneity; specific variables to be considered were not reported. Summary receiver operating characteristic (sROC) curves were plotted and the area under the curve calculated. Studies evaluating the prediction of cardiac events and the monitoring of treatment response were combined in narrative syntheses. Differences between studies were discussed in the text and study details and results tabulated.

Results of the review
Diagnosis (14 studies): The quality of the studies was considered good overall. Three studies addressed spectrum bias and three disease progression bias; 14 blinded interpreters of the reference standard and five interpreters of the index test; four used a reference standard likely to correctly diagnose heart failure; one reported uninterpretable results; and
five explained withdrawals.

For patients with symptoms or a diagnosis of heart failure, pooled estimates for BNP using the lowest positive diagnosis cut-off were: sensitivity 94% (95% CI: 92% to 97%); specificity 66% (95% CI: 52% to 79%); positive likelihood ratio 2.92 (95% CI: 2.09 to 4.09); negative likelihood ratio 0.10 (95% CI: 0.05 to 0.22); and diagnostic odds ratio 3.52 (95% CI: 2.55, 4.49). Equivalent results for NT-proBNP were: sensitivity 92% (95% CI: 87%, 97%); specificity 65% (95% CI: 51%, 78%); positive likelihood ratio 2.67 (95% CI: 1.98, 3.59); negative likelihood ratio 0.14 (95% CI: 0.09, 0.23); and diagnostic odds ratio 3.21 (95% CI: 2.57 to 3.86).

Significant heterogeneity was observed for all analyses. The results of subgroup analyses where studies based in emergency departments (14 studies) and primary care (seven studies) settings were pooled separately and reported, and sROC curves were presented.

Prognosis (116 studies in populations of interest): Coronary artery disease risk factors (12 studies); confirmed coronary artery disease (38 studies) or heart failure (58 studies); and screening (8 studies). The studies had a number of methodological flaws: many had small sample sizes, low incidence of outcomes and lack of blinding of outcome assessors.

Results of multiple regression analyses consistently showed positive associations between the level of BNP and NT-proBNP and outcomes (primarily mortality) in patients with coronary artery disease risk factors and established coronary artery disease; the association did not seem stronger for one measure over the other. BNP and NT-proBNP were significant predictors of composite outcomes in patients diagnosed with heart failure: hazard ratios ranged from 1.7 to 3.2 for lower BNP and 2.11 to 5.96 for lower NT-proBNP. There was insufficient evidence to assess the accuracy of BNP and NT-proBNP as screening tools.

Monitoring treatment response (18 studies): Study quality was generally low. Twelve studies were RCTs, nine of which scored 1 or 2 out of a possible 5 on the Jadad scale. The findings were not consistent across studies. There was no support for the use of BNP or NT-proBNP in the monitoring of response to treatment.

Authors’ conclusions
BNP and NT-proBNP showed good diagnostic properties for ruling out heart failure and were consistent independent predictors of mortality and other cardiac outcomes in patients with coronary artery disease risk factors and confirmed coronary heart disease or heart failure. However, there was insufficient evidence to demonstrate changes in BNP and NT-proBNP levels in response to therapies to manage stable chronic heart failure populations.

CRD commentary
The authors addressed a clear review question that was supported by very broad inclusion criteria. Several relevant sources were searched, but publication and language biases could not be ruled out. Each stage of the review was conducted in duplicate, which reduced the potential for error and bias. Study quality was assessed using appropriate criteria, the results were given for each criterion of each study and study quality was taken in to account during the synthesis. The decision to combine most studies in a narrative synthesis seemed appropriate given the clinical heterogeneity between studies. Where pooled estimates were calculated, heterogeneity was generally present, making the reliability of these pooled results uncertain. The authors made efforts to explore heterogeneity. This was a generally well-conducted review, but the reliability of the conclusions is limited by the poor quality of many of the included studies, particularly in the review of prognosis.

Implications of the review for practice and research
Practice: The authors did not state implications for practice.

Research: The authors recommended large multicentre diagnostic studies that reported multivariate analyses that: explored different cut-offs; used standard diagnostic outcomes; evaluated BNP in diastolic heart failure; compared BNP with other diagnostic tests; and evaluated subsets of patients presenting in the emergency department and in long-term care settings. The authors stated that large prognostic studies should focus on the relative benefits and differences between BNP and NT-proBNP in patients at risk of or diagnosed with heart failure and repeat meta-analysis when more data became available. Large RCTs that evaluated BNP and NT-proBNP in monitoring of chronic heart failure patients...
were required.

**Funding**
Agency for Healthcare Research and Quality

**Bibliographic details**

**PubMedID**
17764210

**Original Paper URL**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Age Factors; Atrial Natriuretic Factor /blood; Female; Heart Failure /diagnosis; Humans; Male; Natriuretic Peptide, Brain /blood; Peptide Fragments /blood; Prognosis; Sex Factors

**AccessionNumber**
12009103757

**Date bibliographic record published**
29/04/2009

**Date abstract record published**
19/08/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.