Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure: systematic review of test accuracy studies
Battaglia M, Pewsner D, Juni P, Egger M, Bucher H C, Bachmann L M

CRD summary
This review compared the diagnostic accuracy of enzyme-linked immunosorbent assay (ELISA) and radioimmunosorbent assay in ruling out congestive heart failure (CHF). The authors concluded that both accurately ruled out CHF in primary care and emergency settings, although ELISA performed better. The authors’ conclusions are likely to be reliable, though they are not based on studies directly comparing the two tests.

Authors’ objectives
To compare the diagnostic accuracy of enzyme-linked immunosorbent assay (ELISA) and radioimmunosorbent assay (RIA) in ruling out congestive heart failure (CHF).

Searching
MEDLINE and EMBASE (January 1990 to March 2004), MEDION (December 1971 to March 2004) and the Cochrane Library (Issue 1, 2004) were searched for studies in any language; the search strategy is available from the authors. The reference lists of relevant articles and reviews were also checked, and experts in the field and BNP test manufacturers were contacted.

Study selection
Study designs of evaluations included in the review
Diagnostic accuracy studies were eligible for inclusion.

Specific interventions included in the review
Diagnostic studies of any type of B-type natriuretic peptide (BNP) assay were eligible for inclusion. The tests used in the included studies were ELISA, RIA and the ELISA N-terminal pro-BNP test.

Reference standard test against which the new test was compared
The studies had to compare a BNP test with echocardiography or radionuclide scans to determine ejection fraction, with or without additional clinical criteria, to be included in the review. The included studies used echocardiography alone (with a cut-off ranging from 30 to 50%) or in combination with clinical symptoms, or radionuclide scans alone (with a cut-off ranging from 35 to 40%), as the reference standard.

Participants included in the review
Studies of asymptomatic patients or patients with suspected acute CHF were eligible for inclusion. The prevalence of heart failure in the included studies varied: from 39 to 72% in patients with acute dyspnoea in tertiary care settings, with a similarly high prevalence in patients examined after a myocardial infarction and in patients with an existing diagnosis of CHF (with the exception of one study with low prevalence); from 10 to 30% among out-patients referred by general practitioners; and was less than 10% in screening studies of patients with risk factors for CHF and coronary heart disease.

Outcomes assessed in the review
Studies that presented sufficient data to allow the construction of a 2x2 contingency table were eligible for inclusion. The main outcome of interest was the negative likelihood ratio (LR) as the BNP test is mainly used to rule out CHF.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance. Any discrepancies were resolved by consensus.
Assessment of study quality
The criteria assessed included study design (case-control design or other), type of recruitment (prospective or retrospective, consecutive or other), use of different reference tests, whether reference tests were applied to all participants, and whether interpretation of the test results was done blind. The authors did not state how validity was assessed, or how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data. Any discrepancies were resolved by consensus. The outcome data were extracted to construct 2x2 tables from which the sensitivity, specificity, and the negative LR and 95% confidence interval (CI) were calculated. The value of 0.5 was added to cells with zero values. Where necessary, BNP values were converted from picogram per millilitre to picomole per litre.

Methods of synthesis
How were the studies combined?
Studies using the ELISA test and the RIA test were pooled separately in a random-effects meta-analysis to estimate the pooled negative LR. Summary receiver operating characteristic curves were constructed for both tests separately. Nomograms of the relationship between pre-test and post-test probabilities were given for each test separately.

How were differences between studies investigated?
Heterogeneity was investigated using the I-squared statistic (pronounced heterogeneity was defined as a value of greater than 50%). A random-effects meta-regression was performed to investigate differences between the studies. The variables investigated were type of test, age of the study population, proportion of male participants, presence of typical symptoms of heart failure, type of setting, year of publication, four different quality criterion and type of reference test.

Results of the review
Nineteen diagnostic accuracy studies (n=9,093) describing 22 study populations were included. Ten studies were prospective and the others were retrospective.

No diagnostic case-control studies were identified. Eight of the studies enrolled patients consecutively, interpretation of the test was conducted blind in 11 studies, and reference tests were applied equally to all study participants. No studies were found that directly compared the ELISA and RIA tests.

The negative LR was lower for the ELISA test (0.12, 95% CI: 0.09, 0.16) than for the RIA test (0.23; 95% CI: 0.16, 0.32), and this was a statistically significant difference. For both tests, negative results accurately ruled out a diagnosis of CHF in patients at relatively low risk (the post-test probability after a negative test was 2.9% for ELISA and 5.4% for RIA when a pre-test probability of 20% was assumed). In the meta-regression, the test type had the strongest association with the negative LR. None of the other variables had a statistically significant association with the negative LR when test type was present in the model. Statistical heterogeneity was reduced when test type was included in the regression model, though there was still evidence of heterogeneity (I-squared 45%).

Cost information
The authors stated that the ELISA test cost $55 compared with $11 for the RIA test.

Authors' conclusions
The demand for echocardiography could be reduced by the use of BNP tests to rule out CHF in primary care settings. The advantages of rapid ELISA tests need to be balanced against their higher cost.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. A number of relevant databases were
searched, unpublished data were sought and studies were not excluded on the basis of language, thereby reducing the risk of publication and language bias. The review methodology was well described and included measures to minimise the risk of error and bias. The methodological quality of the studies was assessed and considered in the analysis. Appropriate statistical methods were used to synthesise the data and heterogeneity was investigated, though a moderate amount of heterogeneity seemed to remain unexplained. The authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that BNP tests have the potential to prevent unnecessary patient referral to echocardiography in lower risk patients in primary care and emergency departments, with a negative BNP test used to rule out CHF.

Research: Adequately powered diagnostic accuracy studies that model the probability of CHF given the BNP test result, and take into account the influence of relevant clinical factors, are required. The prediction rules generated then need to be validated in other populations and cost-effectiveness investigated in randomised controlled trials.

**Funding**

Gesellschaft fur das Gemeinnutzige und Gute; Swiss Academy of Medical Science (Kathe Zingg-Schwichtenberg-Foundation).

**Bibliographic details**


**PubMedID**

16717169

**DOI**

10.1001/archinte.166.10.1073

**Original Paper URL**

http://archinte.ama-assn.org

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Biomarkers /blood; Diagnosis, Differential; Enzyme-Linked Immunosorbent Assay; Heart Failure /blood /diagnosis; Humans; Natriuretic Peptide, Brain /blood; Prognosis; Radioimmunoassay; Reproducibility of Results

**AccessionNumber**

12006008228

**Date bibliographic record published**

30/09/2006

**Date abstract record published**

30/09/2006

**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.