

## Limited value of brain natriuretic peptide as a prognostic marker in acute heart failure – A meta-analysis

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Brain natriuretic peptide (BNP) is secreted by cardiomyocytes in response to excessive stretching. BNP plasma levels are useful for diagnosis in patients with dyspnea [1] predicting heart failure better than clinical assessment alone [2]. Therefore, determination of BNP when heart failure is suspected has become standard of care [3]. However, for patients with established heart failure who undergo an exacerbation, it is unknown whether BNP determination adds any clinical value. Although studies have shown an association between greater BNP levels and adverse events [4,5], the additive value of its determination on top of known predictors for heart failure prognosis has not been tested.

We performed a systematic review and meta-analysis of all studies in which BNP levels were used for prognosis in patients admitted with decompensated heart failure in order to assess the predictive value of an above median BNP level for all cause mortality, and to determine the discriminative value of elevated BNP levels.

Two trained investigators (A.B., A.A.) independently performed a systematic search for studies using PubMed and The Cochrane Collaboration CENTRAL database from January 1990 to December 2009. Proceedings from the American College of Cardiology, American Heart Association, the European Society of Cardiology and the Heart Failure Society of America annual meeting were also searched for the prior 3 years.

Potentially relevant studies were recovered as complete manuscripts and assessed for compliance to inclusion and exclusion criteria. Cross examination of the reference lists was performed to collect additional relevant studies.

Inclusion criteria were: a) determination of BNP values within the first 24 h of hospitalization, b) subjects admitted with decompensated heart failure, c) studies that had reported all cause mortality, and d) enrolling > 10 subjects.

Studies that employed NT pro-BNP were excluded. When uncertain about published data, the principal investigator was contacted by correspondence at least two times. Eventually, in case of unobtainable data, the study was excluded.

All cause mortality was chosen as the endpoint of interest. A fixed-effect model, computing relative risks (RRs) with 95% confidence

intervals (CI) was used. A weighted symmetric summary receiver-operating characteristic plot, with pertinent area under the curve, was computed using the Moses–Shapiro–Littenberg method. In addition, a funnel plot of treatment effect versus study precision was created for the primary outcome. The risk of small study bias was appraised with the Peters' test. Statistical analysis was performed using the Review Manager 4.2.4 (Plone Foundation, Houston, Texas) and Meta-DiSc (Hospital Universitario Ramón y Cajal, Madrid, Spain).

Overall, the search permitted the retrieval of 1545 citations. Twenty-nine complete articles assessed according to selection criteria and 1516 were excluded because they were not relevant. Afterward, another 24 articles were excluded according to explicit inclusion criteria. Therefore, only 5 studies were finally included in the systematic review (Table 1).

The 5 studies included a total of 49,273 patients. Three studies used a single cut off value, one study used 2 cut off values with tertiles and the other study used 3 cut off values with quartiles. In 4 of the studies patients were followed for at least one year, the fifth study had a median follow up of over 3 years.

No heterogeneity was found for the outcome of interest. No publication biases were found.

All studies showed a RR favoring survival for BNP levels less than median value with a significant 52% lower risk of death ( $P < 0.001$ ) (Fig. 1). However, at a receiving operator curve analysis used to assess the discriminatory value of BNP above median had a sensitivity of <70% and a specificity as low as 50% for all cause mortality (Fig. 2).

Pooled data from 49,273 of patients confirms showed that levels less than median values predicted better survival in patients admitted with ADHF. We aimed to assess whether the discriminatory value of BNP was high enough to justify its routine use in patients with ADHF. Not surprisingly, while associated with worse prognosis in the entire cohort, BNP levels above median had limited sensitivity (meaning that many patients who died did not have BNP above median) and rather limited specificity (meaning that most of the patients with BNP below median did not die). While we agree that this is likely true for many if not all biomarkers [6–8], we believe that the findings of the current study add to common knowledge and do not support the routine use of BNP levels as sole prognostic marker for patients with ADHF. BNP is only one of the many biomarkers and predictors available for patients with heart failure.

As stated in the methods section, studies measuring N-terminal pro-BNP (NT-pro-BNP) were excluded and only BNP was used as a prognostic factor for this review and meta-analysis. Whether NT-pro-BNP levels have any additive value to BNP levels is uncertain and needs further investigation.

As for all systematic reviews and meta-analyses many limitations exist, and the results of this analysis should not be considered conclusive.

In summary, the results of a meta-analysis of 5 studies and 49,273 patients recommend against routine use of BNP values to identify patients with decompensated heart failure at higher risk of death. The value of BNP determination for clinical decision making in patients with ADHF remains uncertain.

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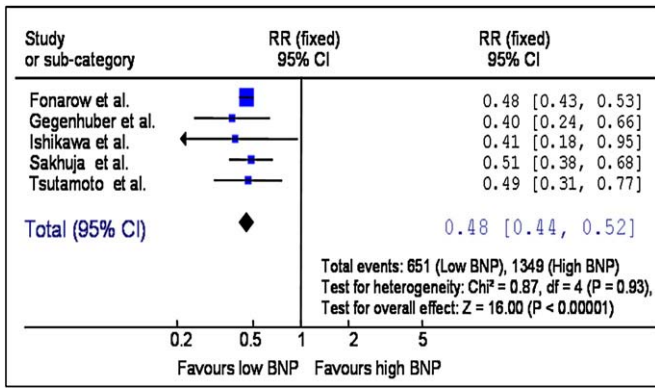


Fig. 1. Forest plots showing individual and pooled risks of death. CI = confidence interval.

Table 1  
 Details of included studies.

Authors	Year	Number of patients	Follow up (days)	BNP groups (mg/dl)	Death (%)
Fonarow GC. et al.	2007	48,629	6	<430	1.9
				430–839	2.8
				840–1729	3.8
				>1729	6
				>1729	6
Gegenhuber A. et al.	2007	137	365	<495	15.2
				495–1250	24.4
				>1250	50
Ishikawa C. et al.	2006	84	2433	<110	15
				>110	36.4
Sakhjuja R. et al.	2007	209	365	<352	35.3
				>352	69.2
				>352	69.2
Tsutamoto T. et al.	2007	214	1197	<93	19.4
				>93	39.6

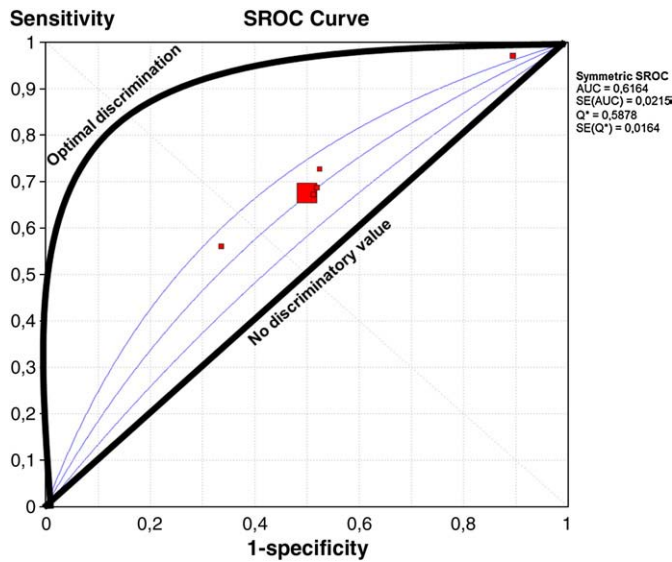


Fig. 2. The receiver-operating characteristic curve provides a graphic display of discriminatory value by plotting 1 – specificity in the horizontal axis and sensitivity in the vertical axis. The pertinent area under the curve (AUC) and Q\* statistic (the point where sensitivity and specificity are maximal), both with standard errors (SE), are also included. SROC = summary receiver-operating characteristic.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [9].

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