

# Review: B-type natriuretic peptide consistently predicts death and cardiovascular events in heart failure

Doust JA, Pietrzak E, Dobson A, Glasziou PP. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ*. 2005;330:625.

**Clinical impact ratings:** Emergency Med ★★★★★☆ Hospitalists ★★★★★☆☆ Cardiology ★★★★★☆☆

## QUESTION

In patients with heart failure (HF), how well does B-type natriuretic peptide (BNP) or its precursor, N-terminal probrain natriuretic peptide (NT-proBNP), predict mortality and morbidity?

## METHODS

**Data sources:** MEDLINE and EMBASE/Excerpta Medica (January 1994 to March 2004) and reference lists.

**Study selection and assessment:** Studies in any language were selected if they evaluated the prognostic value of BNP in patients with heart failure. Studies were excluded if patients had had recent myocardial infarction or if endpoints were not clearly clinical. Study quality was assessed (i.e., patient selection, completeness of follow-up, and blinding).

**Outcomes:** Death, cardiac death, sudden death, or other cardiovascular events.

## MAIN RESULTS

19 studies assessed the relation between BNP levels and death or cardiovascular events in patients with HF, and 5 studies assessed the same relation in asymptomatic persons. The studies were done in various clinical settings

and used various BNP tests. *Patients with HF:* 4 of 5 studies using continuous measures were pooled using a random-effects model. The relative risk for death per 100 pg/mL of BNP in patients with HF was 35% (95% CI 22% to 49%). The inclusion of the fifth study led to statistically significant heterogeneity. 7 studies used dichotomous measures to assess the relation between BNP and death. Different cutpoint scores were used, and some studies did not adjust for other risk factors. However, a consistently increased risk for death was associated with increased levels of BNP. The largest study showed a hazard ratio for death of 2.10 (CI 1.79 to 2.42) for patients with BNP levels > 97 pg/mL. A similar relation was seen in studies assessing the relation between BNP levels and cardiovascular events (3 used continuous measures; 7 used dichotomous measures). *Asymptomatic patients:* 5 studies showed a relation between increased BNP levels and increased risk for death. The 2 largest studies used low cutpoint scores: For  $\geq 17.9$  pg/mL, the hazard ratio for death was 2.2 (CI 1.2 to 3.8); for > 20.0 pg/mL in men and > 23.3 pg/mL in women, the hazard ratio for death was 1.6

(CI 1.1 to 2.4). 3 studies showed a relation between increased BNP levels and increased risk for cardiovascular events. In the largest study, the hazard ratio for cardiovascular events was 1.8 (CI 1.1 to 2.9) for a cutpoint BNP level > 20.0 pg/mL in men and > 23.3 pg/mL in women. 35 multivariable models included BNP or NT-proBNP to predict survival, cardiac death, readmission, or cardiac events. BNP or NT-proBNP had the smallest *P* value in 23 of these models and was the only predictor that reached statistical significance in 9 models.

## CONCLUSION

In patients with heart failure, higher levels of B-type natriuretic peptide or its precursor, N-terminal probrain natriuretic peptide, are consistently associated with increased risk for death or cardiovascular events.

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## COMMENTARY

BNP is a neurohormone secreted mainly by the ventricles of the heart in response to wall stretching, ventricular dilatation, and/or increased ventricular pressure. Previous studies have shown that elevated plasma levels of BNP may be useful in the diagnosis of HF, especially in patients with acute dyspnea (1). In such a setting, BNP levels < 100 pg/mL have a 90% predictive value for the absence of HF, and levels > 500 pg/mL have a 90% predictive value for the presence of HF. BNP levels between 100 and 500 pg/mL are somewhat less helpful, and other tests may be needed for diagnosis (1). However, these results are not generalizable to stable HF, where a significant proportion (20% to 50%) of symptomatic though well-treated and compensated patients may have levels < 100 pg/mL.

Worse left ventricular (LV) dilatation, greater elevation of LV filling pressure, and more LV remodeling should all lead to higher levels of BNP. Therefore, BNP levels would be expected to be a marker of HF severity.

Doust and colleagues provide a rigorous review and synthesis of the prognostic importance of BNP levels. Using studies of HF, almost all of which were in patients with systolic HF, and studies of asymptomatic populations, they confirmed the consistent association between higher

levels of BNP and increased risk for death and cardiovascular events. Although large studies have identified cutpoints above which the risk is increased, the cutpoint values have varied widely among studies. In addition, for individual patients, a single cutpoint value may be difficult to use because of biological variation in BNP levels, including higher levels in older patients, women, or patients with renal insufficiency and lower levels in obese patients. In patients who have mild-to-moderate elevations in BNP, those who have no or only minimal lowering of BNP in response to HF therapy may also represent a subset with worse prognosis.

Further studies will determine whether more aggressive treatment of patients with persistently elevated levels of BNP is beneficial—that is, whether BNP levels can be used to follow the effects of and titrate therapy for HF.

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## Reference

1. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-7.