Papers

How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review

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Abstract

Objective To assess how well B-type natriuretic peptide (BNP) predicts prognosis in patients with heart failure.

Design Systematic review of studies assessing BNP for prognosis in patients with heart failure or asymptomatic patients.

Data sources Electronic searches of Medline and Embase from January 1994 to March 2004 and reference lists of included studies.

Study selection and data extraction We included all studies that estimated the relation between BNP measurement and the risk of death, cardiac death, sudden death, or cardiovascular event in patients with heart failure or asymptomatic patients, including initial values and changes in values in response to treatment. Multivariable models that included both BNP and left ventricular ejection fraction as predictors were used to compare the prognostic value of each variable. Two reviewers independently selected studies and extracted data.

Data synthesis 19 studies used BNP to estimate the relative risk of death or cardiovascular events in heart failure patients and five studies in asymptomatic patients. In heart failure patients, each 100 pg/ml increase was associated with a 35% increase in the relative risk of death. BNP was used in 35 multivariable models of prognosis. In nine of the models, it was the only variable to reach significance—that is, other variables contained no prognostic information beyond that of BNP. Even allowing for the scale of the variables, it seems to be a strong indicator of risk.

Conclusion Although systematic reviews of prognostic studies have inherent difficulties, including the possibility of publication bias, the results of the studies in this review show that BNP is a strong prognostic indicator for both asymptomatic patients and for patients with heart failure at all stages of disease.

Introduction

The clinical assessment of heart failure is notoriously difficult; it is difficult to determine which patients have heart failure and, once the diagnosis is established, to predict which patients are at risk of death or further cardiovascular events. Factors shown to be predictors of mortality are increasing age, a history of diabetes mellitus or renal dysfunction, higher functional disability measures such as New York Heart Association class, lower left ventricular ejection fraction, lower sodium concentrations, lower body mass index, lower blood pressure, the presence of ankle oedema, and lower quality of life scores.[1–4] However, none of these is a strong predictor, and so intense interest has emerged in the predictive value of B-type natriuretic peptide (BNP).

The natriuretic peptides are released by the heart in response to myocardial tension and increased intravascular volume and provide accurate tests for the diagnosis of heart failure compared with echocardiography or expert clinical consensus.[5] Our aim was to review systematically the literature to determine how well BNP or its precursor form, N-terminal pro-brain natriuretic peptide (NT-proBNP), predict mortality and morbidity in patients with heart failure, and to determine if this varied with the clinical setting or severity of heart failure. We also wanted to compare BNP with other traditional prognostic indicators.

Methods

We searched Medline and Embase from January 1994 to March 2004 for all studies of the prognostic value of BNP in patients in all stages of heart failure, all clinical settings, and all lengths of follow-up, and also in "asymptomatic" patients. We excluded studies in patients with recent myocardial infarction because of the likely instability in the relation between BNP concentration and prognosis at this time. We also excluded studies that did not include a clear clinical end point, such as death, hospital admission, or further cardiovascular event. We checked the reference lists of primary studies and review articles identified by the search. See bmj.com for full search strategy.

The full search strategy is on bmj.com

This is the abridged version; the full version is on bmj.com

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Two reviewers checked the abstracts and then the papers for eligible studies and extracted data independently. Disagreements were resolved by consensus or discussion with a third reviewer. Where possible, data were extracted from multivariable regression models of prognosis.

We assessed the quality of the included studies by determining how patients were selected for the study, if follow-up of patients was complete and sufficiently long, and if the ascertainment of the end points was blinded and objective.[6] We assessed the representativeness of each of the included studies by determining the clinical setting, the spectrum of the patients included in each study, the method for diagnosing heart failure, and the age of the patients. We also extracted data on study size and number of outcomes, the method for measuring BNP, the type of statistical model used, and the way in which BNP was modelled in the studies.

The most common form of analysis for prognostic studies is the Cox proportional hazards model which measures the hazard ratio—the relative effect of a predictive factor on an outcome—by assuming that this relation is constant over time. To combine the data from as many studies as possible, we assumed that where the outcome is relatively rare, the relative risk or odds ratio approximates the hazard ratio. For the outcome of death, we planned to combine estimates of the hazard ratio, odds ratio, or relative risk from studies by using comparable measures of BNP. We also tested for heterogeneity.

Results

We retrieved 861 citations, of which 32 assessed if BNP or NT-proBNP predicts death or cardiac events in patients with heart failure or in asymptomatic patients, either via estimating a relative measure of risk such as a hazard ratio, or by measuring the statistical significance of the BNP in a multivariable model of prognosis. We identified 19 studies that assessed the relative risk of death or cardiac events with rises in BNP in patients with heart failure and five studies in asymptomatic patients. Fourteen studies used BNP or NT-proBNP to predict the relative risk of death or cardiac death in heart failure patients. Eleven studies used BNP or NT-proBNP to predict the risk of a cardiovascular event, most commonly death or hospital admission. See bmj.com for tables of each of these groups of studies.

In most studies, the primary outcome of interest was either death or cardiac death. These are reasonably objective end points. It is difficult to assess how completely patients were followed up and how completely outcomes were ascertained. A possibility exists of the selective reporting of outcomes or the biased reporting of only models with significant results.

The studies were conducted in various clinical settings and used various BNP tests. Although BNP and NT-proBNP seem to have skewed distributions, most of the models included BNP as either a continuous variable linearly related to the outcome or used a discrete cut-off point rather than a logarithmic transformation of the variable.

We combined the results of four of the five studies that estimated the relative risk of all cause mortality by using a continuous measure of BNP in a random effects model. This gave an estimate of the relative risk of death per 100 pg/ml of 35% (95% confidence interval 22% to 49%, heterogeneity $\chi = 6.3$, df = 3, $P = 0.096$). Including the one study that used a continuous measure to estimate the relative risk of cardiac death in the pooled estimate gives a similar result of 37% (22% to 54%, heterogeneity $\chi^2 = 10.2$, df = 4, $P = 0.037$).

The studies that used dichotomous measures showed considerable variation in results, but a consistently increased risk of either death or cardiovascular events with raised concentrations of BNP. The pooled estimate from the studies using a continuous measure was consistent with the results seen of the largest study using a dichotomised measure.

Patients whose BNP values fail to fall in response to treatment seem to be at particularly high risk of death or a cardiovascular event, and values after stabilisation on treatment were more significant predictors of death and further events than baseline values.

Asymptomatic patients

BNP and NT-proBNP also predict mortality and cardiovascular events in asymptomatic patients (see bmj.com). Again, the studies used various methods for measuring the relation between BNP and mortality or cardiovascular events. The two largest studies used relatively low cut-off points (≥ 17.9 pg/ml or ≥ 20.0 pg/ml in men and ≥ 23.3 pg/ml in women). We could not assess whether the mortality risk associated with BNP is continuous or there is a threshold effect, but even using these relatively low cut-off levels of BNP, the relative risk of death doubled during the follow up periods of four and five years.

Comparison of BNP with other prognostic markers

Thirty five multivariable models included BNP or NT-proBNP to predict survival, cardiac death, readmission, or cardiac events. In 23, BNP or NT-proBNP had the smallest P value. In nine, BNP or NT-proBNP was the only predictor that reached significance. Many clinical features that have been shown to be associated with increased mortality no longer reached significance in models that included BNP. In two models, BNP or NT-proBNP was not a significant predictor, and in both cases N-terminal pro-atrial natriuretic peptide (N-proANP) reached significance. N-proANP also excluded BNP and vice versa in one model but did not reach significance in 10 other models that included BNP.

We found only one study that estimated the predictive ability of factors for all cause mortality in advanced heart failure by using receiver operating characteristic (ROC) curves. The areas under the ROC curve were 0.738 for NT-proBNP, 0.640 for left ventricular ejection fraction, 0.650 for peak oxygen uptake (VO_2), and 0.654 for the heart failure survival score, indicating that NT-proBNP has the greatest predictive value.

Patients with low left ventricular ejection fractions may be treated more aggressively by clinicians, thereby diluting some of the prognostic value of left ventricular ejection fraction. However, BNP remained a significant predictor of prognosis, even in models in which treatment was included as a variable. BNP may also add to the prognostic information of left ventricular ejection fractions. In one study the risk of mortality for the group with raised BNP alone was 7%; with reduced

left ventricular ejection fractions alone, 8%; and with the two factors combined, 17%, indicating an apparently additive risk.

Comparison of BNP with NT-proBNP

BNP was directly compared with NT-proBNP in only one model. Both log BNP and log NT-proBNP reached significance in univariate analysis, but only log BNP remained significant in the multivariable analysis.

Discussion

B-type natriuretic peptide was a consistently significant prognostic indicator in patients diagnosed with heart failure and in asymptomatic patients in the studies under review. The prognostic information seems to be at least additive with that of left ventricular ejection fraction, and BNP should be used to assess prognosis in patients with heart failure.

Defining heart failure

If BNP predicts prognosis, including in patients not diagnosed with heart failure, it raises important questions concerning the way that heart failure is defined and diagnosed. In most recent trials of treatment and in studies of diagnostic accuracy, the reference standard for the diagnosis of heart failure has been left ventricular ejection fraction. This is despite the fact that 20-50% of patients with heart failure have preserved systolic function.[7] BNP is a strong indicator of cardiac risk and may therefore be a better way of identifying the cohort of patients who would benefit from treatment.

Cut-off values for BNP

The question also arises of what should be considered a "normal" value of BNP. The risk of death and cardiovascular events seems to rise with even small values of BNP. In the studies in asymptomatic patients the relative risk of death and cardiovascular events was doubled at values well below those currently considered diagnostic for heart failure (80-100 pg/ml).[5]

Monitoring heart failure

Because patients with a raised BNP after treatment are at high risk of a further event, it implies that BNP may be useful in monitoring treatment. Two small trials have proposed that using BNP to guide treatment results in fewer cardiac events than traditional clinical assessment,[8 9] but these results are preliminary and need confirmation in larger clinical trials.

Limitations

Systematic reviews of prognostic studies are hampered by the standard of reporting of the original studies. Finding all prognostic studies is difficult as they are not tagged as such in Medline, and finding negative studies is particularly difficult. Many of the studies did not report on features that would ensure objective and unbiased estimates of prognostic indicators. In addition, the true impact on prognosis may be less than estimated because studies that did not show a significant effect have possibly not been published.

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What is already known on this topic

Factors shown to be predictors of mortality in heart failure are increasing age, a history of diabetes mellitus or renal dysfunction, higher New York Heart Association class, lower left ventricular ejection fraction, lower sodium concentrations, lower body mass index, lower blood pressure, the presence of ankle oedema, and lower quality of life scores

The clinical assessment of prognosis in heart failure is difficult, however, and none of the above factors are strong predictors of survival or cardiovascular events

What this study adds

B-type natriuretic peptide is a strong prognostic indicator for patients with heart failure at all stages of disease and seems to be a better predictor of survival than many traditional prognostic indicators, such as New York Heart Association class, serum creatinine concentration, and possibly left ventricular ejection fraction

The relative risk of death increases by about 35% for each 100 pg/ml increase in BNP in patients with heart failure patients

Raised BNP values also predict survival in patients not known to have heart failure, with the risk doubled in patients with a BNP value >20 pg/ml

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Endpiece

The difference

In youth we learn; in old age we understand.

Marie von Ebner-Eschenbach (1830-1916)
in *Aphorisms*

Fred Charatan, retired geriatric physician, Florida