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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. Many studies have tried to determine which factors increase mortality and morbidity in patients with heart failure across a variety of clinical settings. Factors that have been 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] In most countries, it is not currently standard clinical practice to measure these peptides to determine prognosis in patients with heart failure. Our aim in this study 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, such as left ventricular ejection fraction, New York Heart Association class, serum sodium concentrations, age, history of diabetes mellitus, peak oxygen uptake (VO_2), or a scoring system used to estimate the risk of death in patients awaiting heart transplantation, the heart failure survival score.[4]

Methods

We searched Medline and Embase from January 1994 to March 2004 for all studies of the prognostic value of BNP in patients with heart failure, including all stages of heart failure, all clinical settings, and all lengths of follow-up, with no restriction on the language of publication. We also included studies that had estimated the relation between BNP values and prognosis in "asymptomatic" patients. We excluded all studies conducted 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. The search strategy included 17 MeSH or text word terms for the condition "heart failure" and five MeSH terms for the diagnostic test "natriuretic peptides." The full strategy (see bmj.com) retrieved 861 citations. We subsequently checked the reference lists of primary studies and review articles identified by the search for further relevant studies.

Two reviewers (JAD, EP) checked the lists of abstracts and then the full papers for eligible studies and extracted data independently. Where they disagreed on inclusion or exclusion of a

The full search strategy is on bmj.com

Table 1 B-type natriuretic peptide (continuous measures) to predict survival

Study	Population (NYHA class)	Diagnosis of heart failure	Mean age	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Hazard ratio (95% CI)
							Blinded	Objective			
Tsutamoto et al, 1999[7]	Patients with heart failure undergoing cardiac catheterisation (I and II)	Left ventricular ejection fraction <45% by ventriculography	59	290 (24)	1.4	Yes	Not reported	Yes	Adjusted Cox regression	Per 100 pg/ml	1.5 (1.3 to 1.8)
Wijeysundera et al, 2003[8]	Patients enrolled in PRAISE-2 trial and surviving to 6 months (III and IV)	Left ventricular ejection fraction <30%	58	181 (53)	1.9	Subset of trial	Not reported	Yes	Unadjusted Cox regression	Per 100 pg/ml	1.5 (1.2 to 1.8)
Bettencourt et al, 2000[9]	Patients with mild to moderate heart failure referred to heart failure clinic (I-III)	Clinical assessment	67	139 (39)	1.5	Yes	Not reported	Yes	Adjusted Cox regression	Per 100 pg/ml	1.01 (1.00 to 1.02)*
Tsutamoto et al, 2001[10]	Patients with symptomatic heart failure seen in internal medicine clinic (II-IV)	Left ventricular ejection fraction <45% by ventriculography	60	96 (29)	3	Yes	Not reported	Yes	Adjusted Cox regression	Per 100 pg/ml	1.2 (1.1 to 1.3)
Tsutamoto et al, 1997[11]	Patients admitted with heart failure (II-IV)	Left ventricular ejection fraction <45% by ventriculography	60	85 (25)	2	Not stated	Not reported	Yes	Adjusted Cox regression	Per 100 pg/ml	1.3 (1.1 to 1.5)
Imamura et al, 2001[12]	Patients enrolled in a study of I-123-MIBG (II-IV)	Left ventricular ejection fraction <40% by radionuclide angiography or echocardiography	63	171 (11)	2.2	Subset of trial	Not reported	Yes	Unadjusted Cox regression	Per 100 pg/ml	1.6 (1.2 to2.2)

The Shionogi test was used to measure BNP in all studies except that by Wijeysundera et al, for which the test was not reported.
The outcome was death in all studies except that by Imamura et al, where it was cardiac death.
Follow-up was complete in all studies.
*Confidence interval calculated by authors from published P value.
NYMA=New York Heart Association.

study or data extraction, the differences were resolved by consensus or by discussion with a third reviewer. Where possible, data were extracted from multivariable regression models of prognosis.

Table 2 B-type natriuretic peptide (dichotomous measures) to predict survival

Study	Population (NYHA class)	Diagnosis of heart failure	Mean age	BNP test	Outcome	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Relative measure of survival (95% CI)
									Blinded	Objective			
Anand et al, 2003[13]	Patients enrolled in Val-HeFT trial (I-IV)	Left ventricular ejection fraction <40% and/or left ventricular internal diastolic diameter/body surface area ≥2.9 cm/m^2	Not reported	Shionogi	Death	4305 (832)	2-3	Subset of trial	Not reported	Yes	Adjusted Cox regression	>97 pg/ml	Hazard ratio 2.1 (1.8 to 2.4)
Richards et al, 2001[14]	Patients with LV dysfunction enrolled in a trial of carvedilol (I-III)	Left ventricular ejection fraction <45% on ventriculography	Not reported	NT-proBNP	Death	297 (35)	1.5	Subset of trial	Not reported	Yes	Unadjusted relative risk	NT-proBNP >550 pg/ml	Relative risk 4.7 (2.0 to 10.9)
Vrtovec et al, 2002[15]	Patients referred to heart failure clinic (III-IV)	Not reported	67	Biosite	Death	241 (46)	0.5	Yes	Not reported	Yes	Adjusted Cox regression	>1000 pg/ml (relative to >400pg/ml)	Hazard ratio 2.0 (1.2 to 3.4)
Gardner et al, 2003[16]	Patients referred for consideration of transplantation II-IV)	Left ventricular ejection fraction ≤35%	50	NT-proBNP (Roche)	Death	142 (20)	Median 1.0	Yes	Not reported	Yes	Unadjusted odds ratio	>1490 pg/ml	Odds ratio 5.0 (1.6 to 15.9)
Harrison et al, 2002[17]	Patients presenting with dyspnoea to emergency department (N/A)	Excluded trauma, unstable angina or myocardial infarction	65	Biosite	Cardiac death	325 (23)	0.5	No	Yes	Yes	Unadjusted relative risk	>230 pg/ml	Relative risk 37.9 (5.7 to 755.8)
Vrtovec et al, 2002[15]	Patients referred to heart failure clinic (III-IV)	Not reported	67	Biosite	Cardiac death	241 (42)	0.5	Yes	Not reported	Yes	Adjusted Cox regression	>1000 pg/ml (relative to >400 pg/ml)	Hazard ratio 1.8 (1.0 to 3.1)
Yu et al, 1999[18]	Patients admitted for heart failure (II-IV)	Left ventricular ejection fraction ≤50%	61	Peninsula	Cardiac death	91 (19)	1	Yes	Not reported	Yes	Unadjusted relative risk	>165 pg/ml	Relative risk 3.4 (1.4 to 8.4)

Follow-up was complete in all studies except for that by Yu et al, where five patients were lost to follow up.

Table 3 Change in B-type natriuretic peptide to predict survival

Study	Population (NYHA class)	Diagnosis of heart failur	Mean age	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Relative measure of survival (95% CI)
							Blinded	Objective			
Anand et al, 2003[13]	Patients enrolled in Val-HeFT trial (I-IV)	Left ventricular ejection fraction <40% and/or left ventricular internal diastolic diameter/ body surface area ≥2.9 cm/m^2	Not reported	3740 (592)	2-3	Subset of trial	Not reported	Yes	Adjusted Cox regression	Quarter changes after 4 months (relative to greatest change –45%)*	–45 to –13%: relative risk 1.3 (1.0 to 1.7) –13 to +30%: relative risk 1.4 (1.0 to 1.7) +30%: relative risk 1.9 (1.5 to 2.4)
Wijeysundera et al, 2003[8]	Patients enrolled in PRAISE-2 trial and surviving to 6 months (III and IV)	Left ventricular ejection fraction <30%	58	121 (26)	1.9	Subset of trial	Not reported	Yes	Adjusted Cox regression	Decrease at 6 months	Hazard ratio 0.99 (0.98 to 0.99)
Matsui et al, 2002[19]	Patients admitted for dilated cardiomyopathy and surviving 6 months (II-IV)	Left ventricular ejection fraction <45%	55	74 (12)	2	Yes	Not reported	Yes	Unadjusted relative risk	>170 pg/ml after 6 months of treatment	Relative risk 11.8 (2.8 to 49.6)
Maeda et al, 2000[20]	Patients admitted for heart failure and surviving to 3 month (III-IV)s	Left ventricular ejection fraction <45%	64	102 (26)	2.2	Yes	Yes	Not reported	Unadjusted relative risk	>240 pg/ml after 3 months of treatment	Relative risk 4.4 (2.0 to 9.5)

The Shionogi test was used to measure BNP in all studies except that by Wijeysundera et al, for which the test was not reported.
The outcome was death in all studies except that by Maeda et al, where it was cardiac death.
Follow-up was complete in all studies.
*The response to treatment has been divided into four quarters. Each group has been compared with the quarter that had the greatest reduction in BNP after treatment—that is, patients with a reduction in their BNP value of more than 45%.

We assessed the quality of the included studies by determining how patients were selected for the study (in particular, whether the study was a prospective and consecutive cohort of patients), 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. Such models measure 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,

Table 4 B-type natriuretic peptide (continuous measures) to predict cardiovascular events

Study	Population (NYHA class)	Diagnosis of heart failure	Mean age in eyars	Outcome	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Hazard ratio (95% CI)
								Blinded	Objective			
Imamura et al, 2001[12]	Patients enrolled in a study of I-123-MIBG (II-IV)	Left ventricular ejection fraction <40% by radionuclide angiography or echocardiography	63	Death or hospitalisation	171 (27)	2.2	Subset of trial	Not reported	Yes	Unadjusted Cox regression	Per 100 pg/ml	1.8 (1.5 to 2.0)
Koglin et al, 2001[21]	Patients referred to HF clinic (I-IV)	Not reported	51	Death or deterioration	78 (25)	Median 1.1	Not reported	Not reported	No	Unadjusted Cox regression	Per 100 pg/ml	1.5 (1.2 to 1.8)
Tamura, 2001[22]	Patients older than 65 admitted for first episode of HF (I-IV)	Clinical assessment	78	Cardiac death or worsening heart failure or myocardial infarction	48 (12)	0.9	Yes	Not reported	Not reported	Adjusted Cox regression	Per $\log_{10}$ BNP	2.7 (1.2 to 5.8)*

The Shionogi test was used to measure BNP in all studies.
Follow-up was complete in all studies.
*Confidence interval calculated by authors from published P value.

Table 5 B-type natriuretic peptide (dichotomous measures) to predict cardiovascular events

Study	Population (NYHA class)	Diagnosis of heart failure	Mean age	BNP test	Outcome	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Relative measure of risk of cardiovascular event (95% CI)
									Blinded	Objective			
Anand et al, 2003[13]	Patients enrolled in Val-HeFT trial (I-IV)	Left ventricular ejection fraction <40% and/or left ventricular internal diastolic diameter/body surface area ≥2.9 cm/m2	Not reported	Shionogi	Death or hospitalisation	4305 (1309)	2-3	Subset of trial	Not reported	Yes	Adjusted Cox regression	>97 pg/ml	Hazard ratio 2.2 (2.0 to 2.5)
Harrison et al, 2002[17]	Patients presenting with dyspnoea to emergency department (N/A)	Excluded trauma, unstable angina, or myocardial infarction	65	Biosite	Cardiac death hospitalisation	325 (86)	0.5	No	Yes	Yes	Unadjusted relative risk	>230 pg/ml	Relative risk 4.5 (2.9 to 6.9)
Harrison et al, 2002[17]	Patients presenting with dyspnoea to emergency department (N/A)	Excluded trauma, unstable angina, or myocardial infarction	65	Biosite	Death due to heart failure or hospitalisation	324 (50)	0.5	No	Yes	Yes	Unadjusted relative risk	>230 pg/ml	Relative risk 15.5 (6.2 to 43.7)
Harrison et al, 2002[17]	Patients presenting with dyspnoea to emergency department (N/A)	Excluded trauma, unstable angina, or myocardial infarction	65	Biosite	Death due to heart failure or hospitalisation	324 (50)	0.5	No	Yes	Yes	Unadjusted relative risk	> 480 pg/ml	Relative risk 8.2 (4.7 to 14.3)
Richards et al, 2001[14]	Patients with left ventricular dysfunction enrolled in a trial of carvedilol (not reported)	Left ventricular ejection fraction <45%	Not reported	Christchurch	Worsening heart failure	297 (108)	1.5	Subset of trial	Not reported	Yes	Unadjusted relative risk	N-BNP > 550 pg/ml	Relative risk 1.8 (1.3 to 2.5)
Gardner et al, 2003[16]	Patients with advanced heart failure referred for consideration of transplantation (II-IV)	Left ventricular ejection fraction≤35%	50	NT-proBNP (Roche)	Death or urgent transplantation	142 (24)	Median 1.0	Yes	Not reported	Yes	Unadjusted Cox regression	N-BNP >1490 pg/ml	Odds ratio 6.8 (2.2 to 21.1)
Ishii et al, 2002[23]	Patients admitted for worsening heart failure (mean 3.5)	Not reported	69	Shionogi	Cardiac death or hospitalisation	98 (37)	1.2	Yes	Yes	Yes	Adjusted Cox regression	>440 pg/ml	Relative risk 2.18 (1.22 to 3.90)

Follow-up was complete in all studies.

or relative risk from studies by using comparable measures of BNP using the "meta" command of Stata, version 7.0 (Stata Corporation, Texas USA, 2001). This command also tests for the presence of heterogeneity.

Results

From the 861 citations, we identified 32 studies that assessed if BNP 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.[7–38] 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.[26–30] Fourteen studies used BNP or NT-proBNP to predict the relative risk of death or cardiac death in heart failure patients (six used a continuous measure of BNP,[7–12] six used a dichotomised measure,[13–17] and four used a change in BNP over time[8 13 19 20]). Eleven studies used BNP or NT-proBNP to predict the risk of a cardiovascular event, most commonly death or hospital admission (three used a continuous measure of BNP,[12 21 22] five used a dichotomised measure,[13 14 16 16 17 23] and four used a change in BNP over time[13 14 20 25]). Tables 1-6 show the results 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, but it is difficult to assess from the study reports how completely patients in the studies were followed up and how completely outcomes were ascertained in each study. Three studies reported that some patients in the study were lost to follow-up; the remainder either reported complete follow-up or the calculations imply complete follow-up. 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.[7 8 10 11] We excluded the study by Bettencourt et al because the published report did not provide results to sufficient accuracy to enable us to estimate a plausible hazard ratio. Pooling the other four studies gives 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

Table 6 Change in B-type natriuretic peptide to predict cardiovascular events

Study	Population (NYHA class)	Diagnosis of heart failure	Mean age	BNP test	Outcome	No of participants (events)	Mean follow-up in years	Consecutive cohort	Ascertainment of outcome		Model	Units of BNP	Relative measure of risk of cardiovascular event (95% CI)
									Blinded	Objective			
Anand et al, 2003[13]	Patients enrolled in Val-HeFT trial of valsartan (I-IV)	Left ventricular ejection fraction <40% and/or left ventricular internal diastolic diameter/body surface area ≥2.9 cm/m2	Not reported	Shionogi	Death or hospitalisation	3618 (889)	2 to 3	Subset of trial	Not reported	Yes	Adjusted Cox regression	Quarter changes after 4 months (relative to greatest change=–45%)*	–45 to –13%: relative risk 1.4 (1.2 to 1.7) –13 to 30%: relative risk 1.67 (1.36 to 2.04) 30%: relative risk 2.20 (1.80 to 2.67)
Cheng et al, 2001[24]	Patients admitted for heart failure (III)	Clinical assessment	68	Biosite	Death and 30 day readmission	72 (22)	1 month	No	Not reported	Yes	Unadjusted relative risk	Increase from admission to discharge	Relative risk 3.2 (1.5 to 6.8)
Bettencourt et al, 2002[31]	Patients discharged following admission for decompensated heart failure (II-IV)	Not reported	71	Biosite	Death or admission to hospital for cardiac event	43 (20)	0.5	Yes	Not reported	Yes	Unadjusted Cox regression	Increase from admission to discharge	Hazard ratio 3.3 (1.3 to 8.8)
Maeda et al, 2000[20]	Patients admitted for heart failure and surviving to 3 months (III-IV)	Left ventricular ejection fraction < 45%	64	Shionogi	Cardiac death or admission to hospital	102 (47)	2.2	Yes	Yes	Not reported	Unadjusted relative risk	> 240 pg/ml after 3 months of treatment	Relative risk 3.8 (2.4 to 6.2)

Follow-up was complete in all studies.
*The response to treatment has been divided into four quarters. Each group has been compared with the quarter that had the greatest reduction in BNP after treatment—that is, patients with a reduction in their BNP value of more than 45%.

continuous measure to estimate the relative risk of cardiac death[12] in the pooled estimate (again excluding the study by Bettencourt et al) 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, possibly because of the differences in the cut-offs used and because several of the studies estimated the relative risk of BNP to predict mortality or cardiovascular events unadjusted for other risk factors. They show, however, a consistently increased risk of either death or cardiovascular events with raised concetrations of BNP (tables 2 and 5). The pooled estimate from the studies using a continuous measure was consistent with the results seen of the largest study using a dichotomised measure—that is, a study of a subset of patients (4305 patients) from the valsartan heart failure trial (Val-HeFT) trial.[13] This study showed in patients with BNP concentrations >97 pg/ml a hazard ratio of death of 2.10 (1.79 to 2.42).

Patients whose BNP values fail to fall in response to treatment seem to be at particularly high risk of death or a cardiovascular event (tables 3 and 6). Models that included both initial measurements and measurements after treatment showed that the values after stabilisation on treatment were more significant predictors of death and further events than baseline values.[8 13 19 20 24 25]

Asymptomatic patients

BNP and NT-proBNP also predict mortality and cardiovascular events in asymptomatic patients (tables 7 and 8). 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 in the study by McDonagh et al, or ≥20.0 pg/ml in men and ≥23.3 pg/ml in women in the study by Wang et al).[26 27] We could not assess from the data in the studies in this review 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; these included some models that did not estimate the relative risk or hazard ratio.[31–38] In 23 of the 35 multivariable models, BNP or NT-proBNP had the smallest P value. In nine of the 35 models, BNP or NT-proBNP was the only predictor that reached significance; other prognostic markers contained no information beyond that provided by BNP.[7 16 19 20 22 23 30 31 37] Many clinical features that have been shown to be associated with increased mortality, such as New York Heart Association class, serum creatinine concentration, lower systolic blood pressure, and higher heart rate[1] 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.[8 35] N-proANP also excluded BNP and vice versa in the model developed by Wang et al[26] but did not reach significance in 10 other models that included BNP.

Assessing the relative strength of prognostic markers on a continuous scale is difficult because of differences in the scale of each marker. We therefore estimated standardised hazard ratios (see bmj.com). Although theoretically this allows a better comparison between BNP and left ventricular ejection fraction as predictors, the results were quite inconsistent between studies (table 9). Another way to compare the predictive value of prognostic markers in heart failure is to compare the area under a receiver operating characteristic (ROC) curve for each variable, as this method also removes the scaling of the variable. We found only one study (n = 142) that estimated the predictive ability of factors for all cause mortality in advanced heart failure by using

Table 7 B-type natriuretic peptide to predict survival in asymptomatic patients

Study	Population	Excluded patients with heart failure	Mean age	BNP test	No of participants (events)	Mean follow-up in years	Population cohort	Follow up complete	Ascertainment of outcome: Blinded	Ascertainment of outcome: Objective	BNP measurement	Hazard ratio (95% CI)
Wang et al, 2004[25]	Framingham offspring study 1995-8	Yes	59	Shionogi	3346 (119)	5.2	Yes	Yes	Yes	Yes	Per 1 standard deviation of log_{10} BNP	1.3 (1.1 to 1.5)
Wang et al, 2004[25]	Framingham offspring study 1995-8	Yes	59	Shionogi	3346 (119)	5.2	Yes	Yes	Yes	Yes	>80th percentile*	1.6 (1.1 to 2.4)
McDonagh et al, 2001[26]	Random sample of Glasgow population aged 25-74 who participated in MONICA risk factor survey, 1992-93	No	50	Peninsula	1252 (80)	4	Subset of total 1640 patients	Yes	Not reported	Yes	≥17.9 pg/ml	2.2 (1.2 to 3.8)
Groenning et al, 2004[27]	People aged 50 to 90 recruited from four general practices in Copenhagen	No	Median 67	NT-proBNP (in-house)	672 (32)	Median 2.2	Yes	NR	Yes	Yes	NT-proBNP Per log_{10} pmol/l	5.7 (1.4 to 23.2)†
Wallen et al, 1997[28]	People aged 85 in Gothenburg, study	Total=No	85	Shionogi	541 (214)	5	Yes	Not reported	Not reported	Yes	Per log_{10} pmol/l	1.3 (1.1 to 1.5)
Wallen et al, 1997[28]	People aged 85 in Gothenburg, study	Subset of patients in whom a diagnosis of heart failure was excluded=yes	85	Shionogi	209 (not reported)	5	Yes	Not reported	Not reported	Yes	Per log_{10} pmol/	1.4 (1.0 to 1.8)
Ueda et al, 2003[29]	People aged > 80 who participated in community health screening programmes in Tokyo	Yes	86	Shionogi	111 (21)	2	No	Yes	No	Yes	Per 100 pg/ml	2.0 (1.4 to 2.6)

The outcome in all studies was death.
The model used in all studies was adjusted Cox regression.
*20.0 pg/ml in men; 23.3 pg/ml in women.
†Confidence interval calculated by authors from published P value.

ROC curves.[16] 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.

The strength of prognostic variables in models may also be confounded by decisions on treatment. For example, 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[7 13 27 30 32 36 38] BNP may also add to the prognostic information of left ventricular ejection fractions. In the cohort of participants in the 1992 multinational

Table 8 B-type natriuretic peptide to predict cardiovascular events in asymptomatic patients

Study	Population	Excluded patients with heart failure	Mean age	Outcome	No of participants (events)	Mean follow-up in years	Population cohort	Ascertainment of outcome: Blinded	Ascertainment of outcome: Objective	BNP measurement	Hazard ratio (95% CI)
Wang et al, 2004[25]	Framingham offspring study without heart failure	Yes	59	First major cardiovascular event	3036 (79)	5.2	Yes	Yes	Yes	Per 1 standard deviation of log_{10} BNP	1.3 (1.0 to 1.6)
Wang et al, 2004[25]	Framingham offspring study without heart failure	Yes	59	First major cardiovascular event	3036 (79)	5.2	Yes	Yes	Yes	>80th percentile*	1.8 (1.1 to 2.9)
Groenning, 2004[27]	People aged 50-90, recruited from four general practices in Copenhagen	No	Median 67	Admission with heart failure	672 (20)	Median 2.2	Invited to attend	Yes	Yes	NT-pro-BNP per log_{10} pmol/l	13.8 (1.7 to 114.8)†
Groenning, 2004[27]	People aged 50-90, recruited from four general practices in Copenhagen	No	Median 67	Other cardiac admissions	672 (57)	Median 2.2	Invited to attend	Yes	Yes	NT-pro-BNP per log_{10} pmol/l	3.7 (1.3 to 10.6)†
Ueda et al, 2003[29]	People aged >80 who participated in community health screening programmes in Tokyo (excluding patients with heart failure or heart disease)	Yes	86	Cardiac admission	111 (8)	2	Yes	No	Yes	per 100 pg/ml	2.6 (1.4 to 4.4)

Follow-up was complete in all studies except for that by Groenning et al, for which it was not reported.
The model used in all studies was adjusted Cox regression.
All studies used the Shionogi test to measure BNP except that by Groenning et al, which used NT-proBNP (in house).
*20.0 pg/ml in men; 23.3 pg/ml in women.
†Confidence interval calculated by authors from published P value.

Table 9 Standardised hazard ratios for B type natriuretic peptide and left ventricular ejection fraction

Study	N	Inclusion criteria	Measurement of BNP*	Hazard ratio for BNP as continuous variable in multivariable model	Standard deviation of BNP	Standardised hazard ratio of BNP	Hazard ratio for left ventricular ejection fraction as continuous variable in multivariable model	Standard deviation of left ventricular ejection fraction	Standardised hazard ratio of left ventricular ejection fraction
Tsutamoto et al, 1999[7]	290	Patients undergoing cardiac catheterisation, left ventricular ejection fraction <45%	BNP	1.004	230†	2.55	—	8.5	—
Imamura et al, 2001[12]	171	Patients enrolled in study of I-123-meta-iodobenzylguanidine left ventricular ejection fraction <40%	BNP	1.005	188	2.51	0.848	10	5.20
Bettencourt et al, 2000[9]	139	Patients with mild to moderate heart failure determined by clinical assessment	BNP	1.0001	429	1.04	—	13	—
Ueda et al, 2003[29]	111	Patients aged >80 in health screening programme and without heart failure	BNP	1.007	99	1.95	—	Not reported	—
Tsutamoto et al, 2001[10]	96	Patients with heart failure in outpatient clinic, left ventricular ejection fraction <45%	BNP	1.002	317	1.53	0.955	9.6	1.48
Tsutamoto et al, 1997[11]	85	Patients admitted with heart failure, left ventricular ejection fraction <45%	BNP	1.003	286	2.35	—	10.1	—
Koglin et al, 2001[21]	78	Patients referred to heart failure clinic, no left ventricular ejection fraction criteria	BNP	1.004	230†	2.51	—	Not reported	—
Tamura et al, 2001[22]	48	Patients admitted for heart failure determined by clinical assessment	Log BNP	2.656	0.66‡	1.91	0.973	4.4	1.13

*Whether BNP was measured as a normal or log BNP.
†SD not reported in study, taken from Val-HeFT trial (n=3618).[13]
‡SD not reported in study, taken from Berger et al study (n=452).[30]

monitoring of trends and determinants in cardiovascular disease (MONICA) risk factor survey in Glasgow, four year mortality from all causes was determined for patients with and without left ventricular dysfunction (defined as left ventricular ejection fraction $\leq 40\%$ and $>40\%$) and raised and normal concentrations of BNP (defined as ≥ 17.9 pg/ml and <17.9 pg/ml).[27] 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 (table 9).

Comparison of BNP with NT-proBNP

BNP was directly compared with NT-proBNP in only one model. In the multivariable analysis, both log BNP and log NT-proBNP reached significance in univariate analysis, but only log BNP remained significant in the multivariable analysis.[30]

Discussion

BNP 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 systolic function as measured by left ventricular ejection fraction. This is despite the fact that it is recognised that 20-50% of patients with heart failure have preserved systolic function.[39] Currently, no criteria are agreed for how to categorise patients with "diastolic dysfunction." 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. This hypothesis could be tested by a trial of heart failure treatment in patients with discordant results for BNP guided diagnosis compared with standard echocardiographic or clinical diagnosis. This raises further questions. It would not be difficult to enrol patients in a trial of treatment who have a raised BNP measurement but normal left ventricular function. Is it also possible that patients with a low left ventricular ejection fraction but a normal BNP do not 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 by Wang et al and McDonagh et al,[26 27] the relative risk of death and cardiovascular events was doubled at values well below those currently considered diagnostic for heart failure, at 80-100 pg/ml.[17] At what measurement might the benefits of treatment be effective and cost effective?

Monitoring heart failure

The fact that patients with a raised BNP value after treatment, whether in hospital or as outpatients, were at high risk of a further event also implies that BNP may be useful to monitor treatment response and guide decisions on further treatment. Two small trials have proposed that using BNP to guide treatment results in fewer cardiac events than traditional clinical assessment,[40 41] but these results are preliminary and need confirmation in larger clinical trials.

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, 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

Limitations

Despite the abundance of studies, this review has several limitations. In part this is because 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—that is, studies where the variable was considered but did not reach significance—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 from these studies because studies that did not show a significant effect have possibly not been published.

BNP is a powerful prognostic indicator for patients with heart failure at all stages of disease. Both initial values and values after starting treatment are important indicators of disease severity.

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