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Role of Brain Natriuretic Peptide in Risk Stratification of Patients With Congestive Heart Failure

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OBJECTIVES Using a prospective study design, we assessed the value of brain natriuretic peptide (BNP) to identify patients with heart failure who have an increased risk of deterioration of their functional status. Furthermore, we examined the relationship between BNP and various clinical characteristics incorporated into an established survival model used for risk stratification.

BACKGROUND Prediction of the clinical course is a crucial part of the decision-making process about the adequate treatment strategy for patients with advanced congestive heart failure (CHF). Although laborious, multivariable indexes have been established for risk stratification, simple plasma BNP measurements may be as useful as prognostic indicators.

METHODS In 78 patients referred to our heart failure clinic, plasma BNP levels were compared with the results of a multivariable prognostic model. To assess the prognostic power of BNP, the clinical course of this cohort was monitored for a median follow-up period of 398 days.

RESULTS At study entry, plasma BNP and the heart failure survival score (HFSS) showed a significant correlation ($r = -0.706$). During follow-up, Kaplan-Meier estimates of freedom from clinical events differed significantly for patients above and below the 75th percentile concentrations of plasma BNP ($p < 0.0001$). Changes in plasma BNP were significantly related to changes in limitations of physical activity, as demonstrated by logistic regression analysis (chi-square statistic = 24.9, $p < 0.0001$). Proportional hazards analysis confirmed BNP as a powerful predictor of functional status deterioration ($p < 0.0001$). This prognostic information was as powerful as that derived from the multivariable HFSS.

CONCLUSIONS Measurement of plasma BNP concentrations might provide a useful and cost-effective screening tool that helps reduce the need and frequency for more expensive cardiac tests. (J Am Coll Cardiol 2001;38:1934–41) © 2001 by the American College of Cardiology

Congestive heart failure (CHF) constitutes one of the major causes of morbidity and mortality in western countries. Although general measures and combination pharmacotherapy adequately control mild and moderate stages of the disease, heart transplantation has been established as an important therapeutic option for patients with refractory heart failure. With an increasing imbalance between patients placed on transplant waiting lists and the limited supply of adequate donor organs, accurate risk stratification that allows comparative prognostic evaluation has become a critical component in the therapeutic approach to patients with advanced forms of CHF. Several algorithms incorporating various hemodynamic variables or symptomatic indexes have been developed in an attempt to assess an individual's prognosis (1–7). However, potentially due to the heterogeneous etiology of different forms of heart failure, most of these single-variable markers were characterized by an often-unsatisfactory discrimination of patients with and without increased heart failure mortality risk (8). Furthermore, as most of these decision strategies depended on invasive testing, they did not prove to be practicable for the management of ambulatory patients. Recently, the clinical approach to risk stratification has been substantially improved by the development of a prospectively validated, clinical index incorporating multiple, independent predictors of mortality (9). This model effectively combined improved sensitivity and specificity, with the advantage of a clinical index based solely on clinical data collected noninvasively. However, the routine prognostic evaluation of ambulatory patients with advanced heart failure remains to be limited by the need for multiple, expensive tests not routinely applicable to a single outpatient visit.

Recently, measurement of plasma brain natriuretic peptide (BNP) levels has been suggested as a cost-effective method of screening for left ventricular (LV) dysfunction (10,11). In the pathophysiology of CHF, BNP participates in adaptive responses to hemodynamic alterations of heart failure. Activation of BNP in patients with LV dysfunction has generated considerable interest in its diagnostic and prognostic properties. Although it is now well established that circulating BNP levels are increased in patients with chronic heart failure in proportion to the severity of the disease (12–14), plasma BNP may be even more useful as a prognostic indicator. Therefore, we hypothesized that single

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CHF = congestive heart failure
HFSS = heart failure survival score
LV = left ventricular
NYHA = New York Heart Association
UNOS = United Network for Organ Sharing
$\dot{V}O_2max$ = maximal oxygen consumption

plasma BNP measurements might represent a clinically useful screening tool to identify patients who need more extensive risk stratification. So far, most of the information on BNP as a prognostic marker is available in patients who have had a myocardial infarction (15–17). Recently, additional evidence was provided by a comparison of BNP levels in survivors and nonsurvivors of CHF (14). However, its value in risk stratification of patients with CHF, independent of the cause of the disease, as well as its prognostic value regarding the clinical course of the disease (deterioration of functional status), has not been studied yet.

The objective of the present study was to assess the prognostic value of plasma BNP measurements in ambulatory patients with CHF. In 78 patients referred to our heart failure outpatient clinic, we first compared plasma BNP measurements with the results of a well-established multivariable prognostic model developed by Aaronson et al. (9). To prospectively validate the prognostic information provided by plasma BNP measurements about survival, without clinical deterioration, we followed this cohort for a median follow-up period of 398 days.

METHODS

Study patients. Our study group consisted of 78 ambulatory patients with chronic CHF, referred to our heart failure outpatient clinic between January 1999 and July 1999. Patients were included after optimization of medical therapy. Of these patients, 89.7% were receiving angiotensin-converting enzyme inhibitors (captopril [n = 28], mean daily dose 59 ± 9 mg; enalapril [n = 18], 15 ± 4 mg; ramipril [n = 22], 7 ± 3 mg) or an angiotensin II antagonist (lorsartan [n = 2], 50 mg). A total of 79.5% of the patients were receiving beta-blockers (carvedilol [n = 30], 39 ± 9 mg; metoprolol [n = 20], 104 ± 14 mg; bisoprolol [n = 12], 7 ± 3 mg). The demographic and initial clinical characteristics of these patients are listed in Table 1. On study entry, a clinical history and physical examination, electrocardiogram, echocardiogram, laboratory results and cardiopulmonary exercise results were obtained in all patients. Thereafter, the patients were seen at least every three months until death, heart transplantation or study termination. The median follow-up period was 398 days (range 248 to 493). During each follow-up visit, changes in the degree of cardiovascular disability were assessed by taking the patient's history (using a standardized questionnaire assessing the maximal walking distance required to produce shortness of breath, number of stairs climbed until shortness of breath, orthopnea [degrees of elevation of the bed at head level, number of pillows] and nocturia [number of events]) and performing a physical examination (changes in pulmonary rales, jugular venous distention, hepatic enlargement or peripheral edema). Although there is a high variability between different individuals, follow-up of this information over time has been shown to provide a subtle measure of changes within the same individual (good intra-individual reproducibility). Changes in the patient's degree of cardiovascular disability over time were categorized as an "improvement," "stabilization" or "deterioration." A patient's death due to a cardiovascular cause was categorized as deterioration. For patients who remained alive and nontransplanted, follow-up was discontinued on June 30, 2000.

Table 1. Characteristics of the Patient Group (n = 78)

Age years	51 ± 9 (24–65)
Male gender	69 (88.5%)
NYHA functional class	
I	10 (12.8%)
II	33 (42.3%)
III	26 (33.3%)
IV	9 (11.5%)
Ischemic cardiomyopathy	24 (30.8%)
Rest heart rate (beats/min)	77 ± 15 (44–110)
Mean blood pressure (mm Hg)	88 ± 13 (62–123)
LV ejection fraction (%)	36 ± 15 (10–59)
Mean PCWP (mm Hg)	15 ± 9 (2–44)
Peak $\dot{V}o_2$ ml/kg (per min)	15 ± 4 (5–25)
Serum sodium (mmol/l)	137 ± 4 (124–147)
IVCD	44 (56.4%)
Medical therapy	
Diuretics	75 (96.2%)
ACE inhibitors, AT-II antagonists	70 (89.7%)
Beta-blockers	62 (79.5%)
Aldosterone antagonists	28 (35.9%)
Digitalis	64 (82.1%)

Data are expressed as the mean value ± SD (range) for continuous variables and as the number % of patients for dichotomous variables.

ACE = angiotensin-converting enzyme; AT = angiotensin; IVCD = intraventricular conduction delay; LV = left ventricular; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; $\dot{V}o_2$ = oxygen consumption.

Measurement of plasma BNP concentrations. Brain natriuretic peptide was measured once, on study entry. Blood samples were collected in ethylenediaminetetraacetic acid after at least 20 min of supine rest, immediately placed on ice and centrifuged within 60 min. The plasma fraction was stored at −70°C until analysis. Plasma BNP concentrations were measured using a specific immunoradiometric assay that detects the biologically active 32–amino acid peptide (Shionoria BNP kit, CIS Bio International, Gifsur-Yvette, France), as described previously (12). This assay uses two monoclonal antibodies against human BNP—one recognizing a carboxy-terminal sequence and the other recognizing the ring structure of human BNP. In our study, the interassay coefficient of variation (n = 18) of the assay was 7% at a mean concentration of 19.7 pg/ml and 5% at 291 pg/ml. Cross-reactivity for atrial natriuretic peptide was specified by the manufacturer as <0.001%.

JACC Vol. 38, No. 7, 2001
December 2001:1934–41

Hemodynamic measurements. The mean blood pressure at rest was estimated as diastolic pressure plus one-third of the pulse pressure measured after at least 20 min of supine rest. The rest heart rate was obtained from a standard 12-lead electrocardiogram. The LV ejection fraction was estimated by echocardiography, using the Simpson's rule (18). Maximal oxygen consumption ($\cdot Vo_2max$) was measured using an incrementally progressive, symptom-limited cardiopulmonary exercise test, as described previously (19).

Risk stratification. For each patient, a prognostic score was derived by using an established, prospectively validated model incorporating multiple, independent predictors of CHF mortality (9). In this model, an individual prognostic score (heart failure survival score [HFSS]) was calculated as the absolute value of the sum of the products of the identified prognostic variables and their computed coefficients. As explanatory variables (model coefficients), this model includes the presence or absence of ischemic cardiomyopathy (−0.6931), rest heart rate (−0.0216), LV ejection fraction (0.0464), mean blood pressure (0.0255), presence or absence of an intraventricular conduction delay ≥120 ms (−0.6083), $\cdot Vo_2max$ (0.0546) and serum sodium (0.0470). The resultant HFSS was used to assign the individual patients to one of three prognostic score risk groups—low risk: HFSS ≥8.10; medium risk: HFSS 7.20 to 8.09; and high risk: HFSS ≤7.20. These prognostic score risk groups have been shown to effectively stratify the risk of death or need for urgent transplantation (one-year event-free survival rates—low risk: 93 ± 2%; medium risk: 72 ± 5%; and high risk: 43 ± 7%).

Statistics. Correlation values were estimated to indicate the relationship between the plasma BNP concentration and HFSS. To determine whether the correlation coefficient is significantly different from zero, the Fisher *r* to *z* transformation was carried out. Analysis of variance was used to compare plasma BNP concentrations between patients in different New York Heart Association (NYHA) functional classes or HFSS risk strata. Post-hoc testing was performed using the Bonferroni/Dunn procedure. A p value <0.05 was considered significant.

Analysis of variance was used to compare plasma BNP concentrations in patients with different clinical outcomes. The ability of the plasma BNP concentration to predict the clinical outcome after 12 months was assessed by logistic regression analysis of polytomographic measurements. The prognostic value of plasma BNP concentrations was tested using a proportional hazards regression model. The Kaplan-Meier method and the log-rank test were used to evaluate differences in freedom from clinical deterioration among patients with high and low plasma BNP concentrations. The ability of plasma BNP concentrations and HFSS to identify patients who will experience clinical deterioration was compared by receiver-operating characteristics analysis.

All data are presented as the mean value ± SEM. Statistical analysis was performed using StatView, version 5.0 (SAS Institute, Cary, North Carolina).

RESULTS

Comparison of plasma BNP with multivariate risk stratification. Plasma BNP concentrations measured at the time of study entry ranged from 5.4 to 686.0 pg/ml (median 105). In 72 patients (92.3%), the plasma BNP concentration was detected above the normal range (>18 pg/ml). Plasma levels of BNP increased significantly according to different NYHA functional classes (class I: 21.6 ± 2.8 pg/ml; class II: 108.6 ± 16.3 pg/ml; class III: 197.1 ± 27.2 pg/ml; class IV: 363.0 ± 67.8 pg/ml; $p < 0.0001$). Plasma BNP levels did not differ between patients with ischemic (150.6 ± 25.7 pg/ml; n = 24) and those with nonischemic cardiomyopathy (158.9 ± 22.2 pg/ml; n = 54).

By use of an established risk-stratification model, a prognostic score—the HFSS—was derived for each patient at the time of BNP measurement. The HFSS ranged from 6.25 to 12.62 (median 8.95). Based on these scores, patients were classified into three different prognostic score risk groups. Ten patients (12.8%) were assigned to the low-risk group; 58 patients (74.4%) to the medium-risk group; and 10 patients (12.8%) to the high-risk group.

As depicted in Figure 1, plasma BNP concentrations and HFSS showed a significant inverse correlation ($r = -0.706$, $p < 0.0001$). A high prognostic HFSS, indicating a low risk of an adverse outcome, was related with low plasma BNP levels, whereas a low HFSS indicated high plasma BNP levels. As shown in Figure 2, this resulted in significant differences in the three different HFSS prognostic risk groups with different mean plasma BNP concentrations (low-risk group: 95.7 ± 11.2 pg/ml; medium-risk group: 244.4 ± 33.4 pg/ml; and high-risk group: 419.9 ± 55.5 pg/ml; $p < 0.0001$).

Prospective validation of the prognostic value of BNP. No patient was lost to follow-up. During follow-up, six patients (7.7%) died of a cardiovascular cause (median 6 months after study entry [range 4 to 11]). Seven patients (9.0%) required urgent United Network for Organ Sharing (UNOS)-1 transplantation (median 9 months after study entry [range 3 to 10]). Six patients (7.7%) underwent UNOS-2 transplantation, without a deterioration of their clinical status before transplantation (median 13 months after study entry [range 6 to 16]). For the Kaplan-Meier analysis, survival data on those patients undergoing UNOS-2 transplantation without previous clinical worsening were censored at the time point of transplantation. Fifty-nine patients remained alive and nontransplanted, 34 of whom (57.6%) did not experience any change in limitation of physical activity (classified as "stabilization"). Thirteen patients (22%) reported improved physical activity (classified as "improvement"). In 12 patients (20.3%), a decrease in physical activity was observed (classified as "deterioration"). As shown in Figure 3, the initial plasma BNP concentration differed between these groups (improvement group: 42.4 ± 8.6 pg/ml; stabilization group: 102.2 ± 16.1 pg/ml; and deterioration group: 256.9 ±

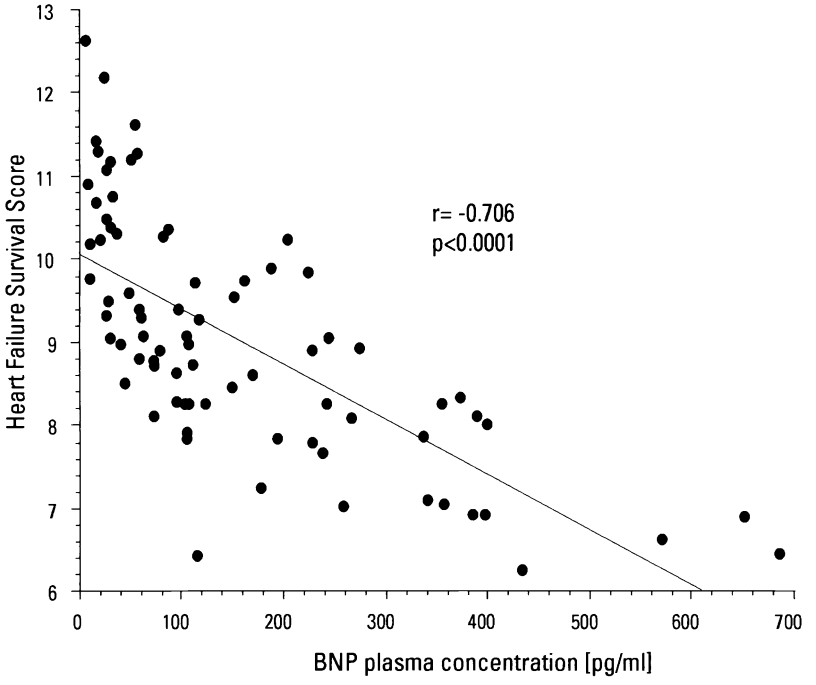

Figure 1. Relationship between brain natriuretic peptide (BNP) plasma concentrations and heart failure survival score (HFSS) in 78 patients. A high HFSS, indicating a low risk of an adverse outcome, was related to low plasma BNP levels, whereas a low HFSS indicated high plasma BNP levels.

28.5 pg/ml; $p < 0.0001$). When examining the overall relationship between changes in cardiovascular disability (as the dependent variable) with plasma BNP levels (as the independent variable), logistic regression analysis showed that changes in plasma BNP were significantly related to changes in limitations of physical activity (likelihood ratio/chi-square statistic = 24.9, $p < 0.0001$). Pairwise comparisons demonstrated that increased plasma BNP levels were strongly associated with a deterioration of physical activity ($p = 0.003$). However, lower plasma BNP levels only showed a modest association with improvement of physical activity ($p = 0.42$).

Kaplan-Meier estimates of freedom from clinical events

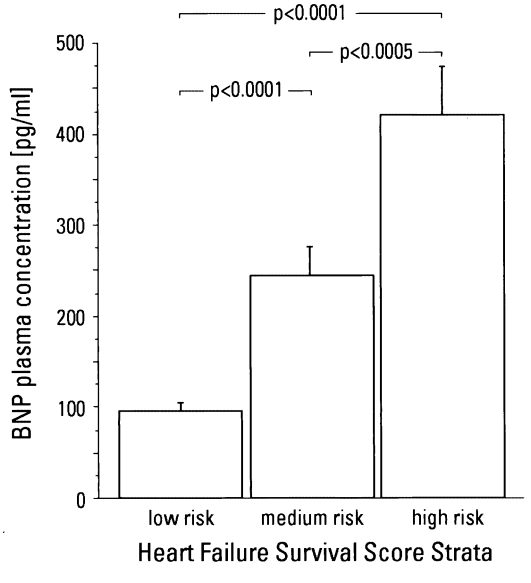

Figure 2. Comparison of brain natriuretic peptide (BNP) plasma concentrations in patients assigned to the three distinct prognostic score risk groups according to their heart failure survival score (HFSS) (low risk: HFSS ≥8.10, n = 58; medium risk: HFSS 7.20 to 8.09, n = 10; and high risk: HFSS ≤7.20, n = 10). Data are presented as the mean value ± SEM.

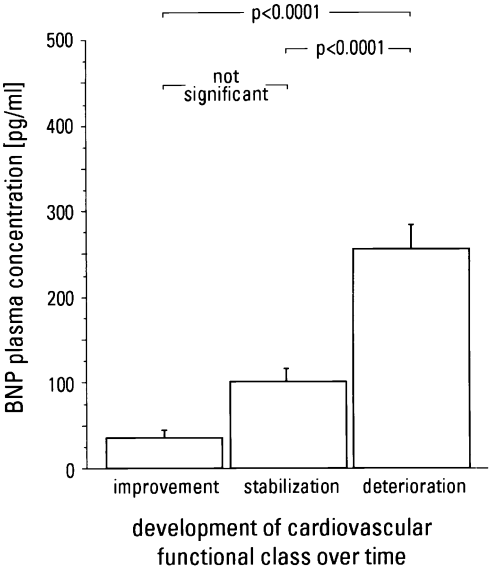

Figure 3. Comparison of brain natriuretic peptide (BNP) plasma concentrations in patients according to their development of cardiovascular function after 12 months (improvement: n = 13; stabilization: n = 34; and deterioration: n = 12). Data are presented as the mean value ± SEM.

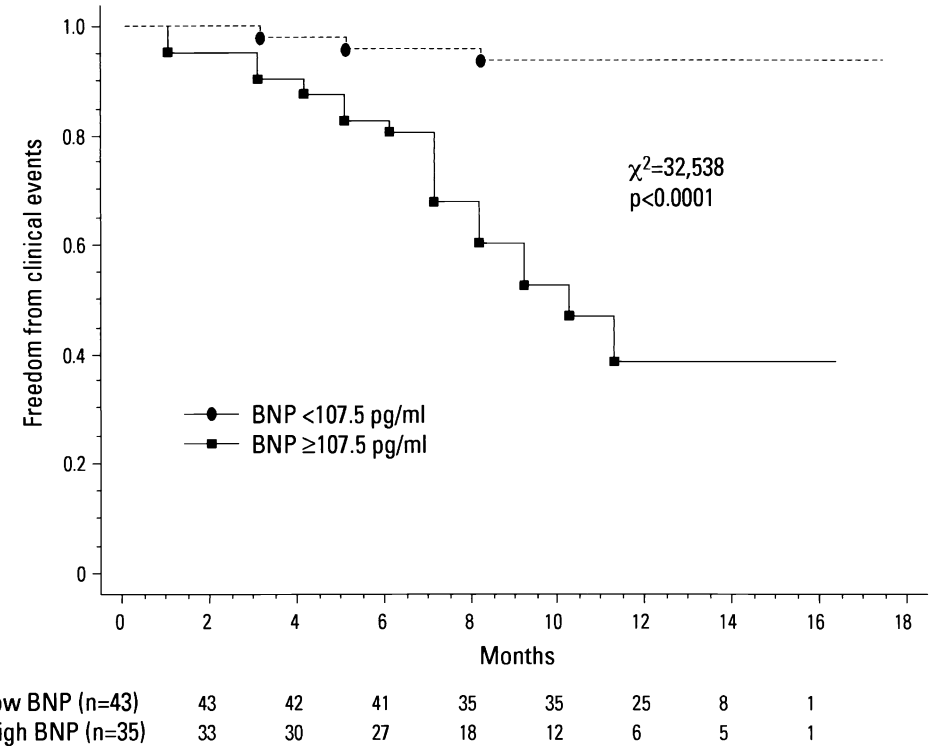

Figure 4. Kaplan-Meier estimates of freedom from clinical deterioration or death in patients stratified into two groups according to the 75th percentile of all plasma brain natriuretic peptide (BNP) concentrations.

were compared for patients classified into two groups according to the 75th percentile concentrations of plasma BNP. Clinical events were defined as progression of a cardiovascular disability (categorized as deterioration) or patient death. As shown in Figure 4, the estimated freedom from clinical events curve for patients with plasma BNP levels below the 75th percentile (BNP <107.5 pg/ml) lies above the estimated function for patients with high plasma BNP levels (≥107.5 pg/ml). These observed differences were statistically significant (log-rank/chi-square statistic = 25.046, $p < 0.0001$).

Univariate proportional hazards analysis showed that BNP was a significant predictor of clinical events (deterioration of physical activity or patient death). The relative hazards ratio for a clinical event associated with an increase in the plasma BNP concentration by 100 pg/ml was calculated at 1.492 (95% confidence interval 1.221 to 1.819). However, as tested with a multivariate regression model, BNP did not add prognostic information independent of HFSS ($p = 0.748$).

The ability of plasma BNP levels and HFSS to identify the risk of a clinical event was assessed by comparison of receiver-operating characteristic curves. As shown in Figure 5, the sensitivity and specificity of plasma BNP were comparable to those of HFSS. With a cut-off value of 107.5 pg/ml (75th percentile), BNP was able to discriminate patients with from those without clinical events, with a sensitivity of 88% and a specificity of 75%.

DISCUSSION

In the present study, we could demonstrate that measurement of plasma BNP provides important prognostic information on patients with CHF, independent of the cause of the disease. Patients with high circulating levels of BNP had a substantially higher probability of deterioration of their functional status or death, as compared with those with only moderately increased levels. The prognostic information provided by this single variable was as powerful as that derived from a commonly used, well-established predictive model incorporating multiple clinical characteristics. Hence, determination of plasma BNP might further improve our current approach to patients with advanced CHF by helping to identify those patients who need more extensive risk stratification, using established multivariable risk-stratification models.

Pathophysiologic rationale for BNP as a potential prognostic marker. Risk stratification of chronic heart failure is confounded by several factors. First, heart failure is a multi-system disease involving not only compromised cardiovascular hemodynamic variables, but also altered regulation of various neurohormonal reflexes and deranged function of other organ systems, such as the kidney or skeletal muscle (20). Second, heart failure mortality is not just caused by mechanical dysfunction of the heart. Furthermore, several trials have suggested that up to 50% of the deaths may be related to an arrhythmic episode, rather than hemodynamic deterioration with terminal pump failure

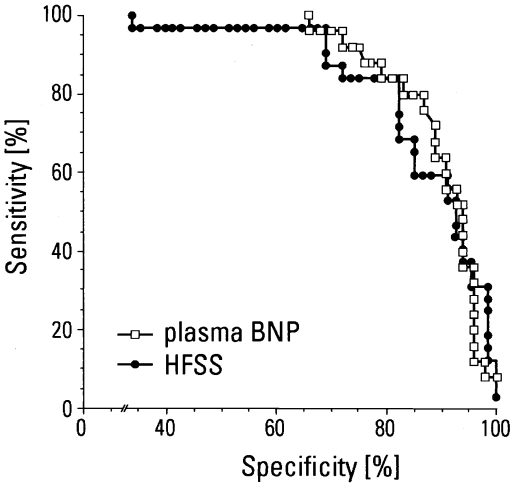

Figure 5. Receiver-operating characteristic curves for plasma brain natriuretic peptide (BNP) concentrations and heart failure survival score (HFSS), to predict the risk of clinical deterioration or patient death.

(21,22). Hence, it does not seem surprising that single hemodynamic markers may help to assess the current severity of the disease; however, they do not provide sufficient information on the patient's future prognosis. In marked contrast, the level of natriuretic peptides has been suggested to not only indicate the severity of the disease, but also reflect the physiologic attempt to compensate for the pathophysiologic sequelae of heart failure and reconstitute circulatory homeostasis (23). Its functional properties might be expected to influence both mechanical dysfunction and arrhythmic instability as the major mechanisms of heart failure mortality. Besides its beneficial effects on systemic vascular resistance and cardiac output, the ability of the cardiac natriuretic peptides to limit the release of catecholamines and renin might reduce the arrhythmogenic potential of these substances. Hence, unlike hemodynamic markers or other neurohormones, measurement of the circulating concentration of a single natriuretic peptide might provide information on multiple constituents of the pathophysiology of CHF, reflecting the complex interplay of several factors contributing to the course of the disease. Unlike vasoconstricting neurohormones, which play a maladaptive, pathogenetic role in the progression of CHF, cardiac natriuretic peptides are believed to participate in adaptive responses thought to limit the pathophysiologic sequelae of heart failure. Infusion of synthetic BNP in patients with chronic heart failure has been shown to decrease pulmonary capillary wedge pressure, diminish systemic vascular resistance and increase cardiac output (24–26). Furthermore, administration of synthetic BNP resulted in a rapid and sustained improvement of the patient's clinical status (26). These studies suggest an important protective role of BNP in delaying the progression of CHF. At first inspection, these beneficial effects appear to be in contrast to the present observation that high circulating BNP levels are predictive of clinical deterioration of the patient's functional status. As one possible explanation, a dissociation of increasing BNP and unchanged levels of its second messenger, cyclic guanosine monophosphate, were reported in nonsurvivors of CHF, indicating a potential relationship between increased BNP levels, impaired BNP activity and mortality in CHF (14). Further studies are needed to elucidate the underlying mechanisms responsible for the progression of chronic heart failure–associated tissue hyporesponsiveness to natriuretic peptides.

Potential role of BNP in risk stratification. In the present study, levels of circulating BNP measured at study entry were used to assess the future course of the disease. This application as a prognostic indicator significantly extends its current use as a diagnostic marker (10,27–29). Established clinical models currently used for risk stratification presuppose assessment of multiple variables (3,9). Some of these variables, such as cardiac output or pulmonary capillary wedge pressure, require invasive testing. Others, such as $\cdot V_{O_2}$max, must be derived by time-consuming, noninvasive testing. Due to the time-consuming and cost-intensive nature of this approach, accurate identification of those patients in need of such extensive risk stratification is mandatory. The results of the present study suggest plasma BNP is a helpful and cost-effective screening tool in the clinical work-up of patients to identify those who require a more extensive prognostic work-up using HFSS or other risk-prediction models, in order to adequately plan future therapeutic strategies, such as placement on a heart transplant waiting list. Hence, BNP assays will not obviate the need for multivariable and prospectively validated risk stratification in those selected patients. However, measurement of BNP could help to reduce the number of patients to be evaluated using these multivariable models, as well as limit the frequency for extended cardiac investigations. In a retrospective analysis in our patient group, optimized sensitivity of BNP to exclude false-negative conclusions was reached using a cut-off value of 94 pg/ml. With exclusion of patients with renal insufficiency or suboptimal medical therapy, this cut-off value proved to be useful in identifying all patients with worsening of their functional cardiovascular status within the follow-up period of 248 to 493 days after BNP measurement. With a specificity of 66% at this cut-off value, this subgroup of patients should undergo further risk stratification to identify potential candidates for placement on a heart transplant waiting list.

Brain natriuretic peptide versus HFSS. The well-established multivariable HFSS might be considered the current reference standard for risk stratification of patients with advanced CHF, to be implemented in most clinical work-up protocols to identify potential candidates for heart transplantation. Although in our study group, the prognostic information of BNP has been shown to be comparable to that of HFSS, to emphasize its prognostic properties, there are some major restrictions to this comparison. Although

the major objective of the study of Aaronson et al. (9) was to develop a model that could select candidates for heart transplantation from an already preselected population of patients with advanced CHF, our goal was to establish a simple variable to be used in a nonselected, ambulatory patient population presenting with clinical signs of heart failure, in order to plan the future therapeutic strategy. Therefore, the characteristics of the present study group differed from those used to derive and validate the original HFSS. This study evaluated a nonselected patient group that was not as severely ill as that evaluated by Aaronson et al. (9), as indicated by a higher mean ejection fraction and a lower mean NHYA functional class. Besides different entry criteria, the patient groups of these two studies also differed with regard to the underlying medical therapy. Although the HFSS was derived from patients recruited before introduction of beta-blockers and aldosterone antagonists to the standard medical therapy of advanced CHF, in our study group, 79.5% of all patients were receiving beta-blockers and 35.9% were receiving spironolactone. It might be speculated that, aside from their proven prognostic benefits, the use of these substances may influence the resultant HFSS by directly modulating the variables of rest heart rate, mean blood pressure, serum sodium and intraventricular conduction delay. Currently, several studies are under way to address the important question of whether HFSS can be revalidated in patients treated with an optimized combination of beta-blockers and aldosterone antagonists.

Conclusions. Methods to detect BNP are inexpensive and widely available. Besides its already-established diagnostic properties, BNP as a neurohormonal prognostic marker could reduce the need and frequency for more expensive cardiac investigations. Of course, factors independent of LV dysfunction also increase BNP concentrations. However, the high negative predictive accuracy of this test still ensures the adequate reliability of BNP levels as a screening tool. Even with additional inducers of BNP expression, independent of LV dysfunction, low BNP levels exclude the need for further risk stratification. High BNP levels necessitate further diagnostic testing and risk stratification.

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REFERENCES

1. Anker SD, Coats AJ. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Circulation 1997;95:538–9.
2. Cohn JN, Rector TS. Prognosis of congestive heart failure and predictors of mortality. Am J Cardiol 1988;62:25A–30A.
3. Haywood GA, Rickenbacher PR, Trindade PT, et al. Analysis of deaths in patients awaiting heart transplantation: impact on patient selection criteria. Heart 1996;75:455–62.
4. Mancini DM, Eisen H, Kussmaul W, Mull R Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86.
5. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe chronic heart failure. Am Heart J 1992;123:421–6.
6. Kelly TL, Cremo R, Nielsen C, Shabetai R. Prediction of outcome in late-stage cardiomyopathy. Am Heart J 1990;119:1111–21.
7. Gradman A, Deedwania P, Cody R, et al., the Captopril-Dignoxin Study Group. Predictors of total mortality and sudden death in mild to moderate heart failure. J Am Coll Cardiol 1989;14:564–70;71–2.
8. Cohn JN. Prognostic factors in heart failure: poverty amidst a wealth of variables. J Am Coll Cardiol 1989;14:571–2.
9. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660–7.
10. Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1349–53.
11. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9–13.
12. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994;90:195–203.
13. Wei CM, Heublein DM, Perrella MA, et al. Natriuretic peptide system in human heart failure. Circulation 1993;88:1004–9.
14. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509–16.
15. Omland T, Aakvaag A, Vik-Mo H. Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. Heart 1996;76:232–7.
16. Darbar D, Davidson NC, Gillespie N, et al. Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction. Am J Cardiol 1996;78:284–7.
17. Richards AM, Doughty R, Nichols MG, et al., the Australia-New Zealand Heart Failure Group. Neurohumoral prediction of benefit from carvedilol in ischemic left ventricular dysfunction. Circulation 1999;99:786–92.
18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
19. Schwaiblmair M, von Scheidt W, Uberfuhr P, Reichart B, Vogelmeier C. Lung function and cardiopulmonary exercise performance after heart transplantation: influence of cardiac allograft vasculopathy. Chest 1999;116:332–9.
20. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577–85.
21. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314:1547–52.
22. Massie BM, Fisher SG, Radford M, et al., the CHF-STAT Investigators. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure (published erratum appears in Circulation 1996;94:2668). Circulation 1996;93:2128–34.
23. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
24. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. Circulation 1996;94:3184–9.
25. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail 1998;4:37–44.

26. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Med 2000;343:246–53.
27. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994;343:440–4.
28. Davidson NC, Naas AA, Hanson JK, Kennedy NS, Coutie WJ, Struthers AD. Comparison of atrial natriuretic peptide B-type natriuretic peptide and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am J Cardiol 1996;77: 828–31.
29. Yamamoto K Burnett JC, Jr., Jougasaki M, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996; 28:988–94.