Changes in Brain Natriuretic Peptide and Norepinephrine Over Time and Mortality and Morbidity in the Valsartan Heart Failure Trial (Val-HeFT)

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Background—Neurohormones are considered markers of heart failure progression. We examined whether changes in brain natriuretic peptide (BNP) and norepinephrine (NE) over time are associated with corresponding changes in mortality and morbidity in the Valsartan Heart Failure Trial.

Methods and Results—Plasma BNP and NE were measured before randomization and during follow-up in ~4300 patients in the Valsartan Heart Failure Trial. The relation between baseline BNP and NE and all-cause mortality and first morbid event (M&M) was analyzed in subgroups, with values above and below the median, and by quartiles. The change and percent change from baseline to 4 and 12 months in BNP and NE were also analyzed by quartiles for subsequent M&M. Risk ratios for M&M were calculated using a Cox proportional hazard model. Risk ratio of M&M for patients with baseline BNP or NE above the median was significantly higher than that for patients with values below the median. Baseline BNP and NE in quartiles also showed a quartile-dependent increase in M&M. BNP had a stronger association with M&M than NE. Patients with the greatest percent decrease in BNP and NE from baseline to 4 and 12 months had the lowest whereas patients with greatest percent increase in BNP and NE had the highest M&M.

Conclusions—Not only are plasma BNP and NE important predictors of heart failure M&M, but changes in these neurohormones over time are associated with corresponding changes in M&M. These data further reinforce their role as significant surrogate markers in HF and underscore the importance of including their measurement in HF trials. (Circulation. 2003;107:1278-1283.)

Key Words: heart failure ■ trials, clinical ■ natriuretic peptides ■ norepinephrine

The syndrome of heart failure (HF) is characterized by hemodynamic abnormalities,1 impaired exercise capacity,2 neurohormonal activation,3,4 and a relentless progression with high mortality.5 Although the mechanisms are not entirely clear, HF progresses through a process of structural remodeling of the heart, to which neurohormonal activation may make an important contribution.6 Several lines of evidence support the role of neurohormones in the progression of HF. Norepinephrine (NE)7 and angiotensin II8 may be directly toxic to cardiac myocytes; the degree of neurohormonal activation in HF is proportional to disease severity, increases with the progression of HF, and is related to prognosis.9 Furthermore, treatment with drugs such as angiotensin-converting enzyme inhibitors (ACE-I) that decrease HF morbidity and mortality also cause a reduction or attenuation in neurohormones.10,11 However, there is no evidence to show that changes in neurohormonal activation over time, occurring either spontaneously or in response to pharmacological therapy, are associated with proportional changes in subsequent mortality and morbidity. Such a relationship would further support the hypothesis that changes in neurohormone levels could serve as a useful surrogate for outcomes.12

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In the Valsartan Heart Failure Trial (Val-HeFT), which evaluated the efficacy of valsartan in patients with moderate to severe HF, blood was sampled for brain natriuretic peptide (BNP) and NE assay in all patients at baseline and at 4, 12, and 24 months during follow-up. The neurohormonal database in Val-HeFT is the largest ever collected in a HF trial.13 In this study, we examined the relationship between baseline BNP and NE and their changes over time, with subsequent mortality and morbidity.
Methods

Patients
Val-HeFT was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial. Five thousand ten patients with stable, symptomatic HF who were undergoing prescribed HF therapy and had left ventricular (LV) ejection fraction (EF) <40% and LV internal diameter in diastole adjusted for body surface area (LVIDd/BSA) of ≥2.9 cm/m² were enrolled in the study. Results of the main trial have been presented in detail previously.13

Blood Sampling and Hormone Assays
Blood samples were collected for measurement of BNP and NE before randomization and 4, 12, and 24 months thereafter. Plasma was separated, and samples were stored at −70°C until assay. Plasma NE was measured with high-performance liquid chromatography (HPLC) with electrochemical detection and BNP with radio-immunooassay by Shionogi (CIS, Tronzano).14

Data Analysis

Baseline BNP and NE as a Prognostic Marker
Two analyses were made based on baseline subgroups. For BNP and NE, we first analyzed the relation between baseline values above and below the median (97 pg/mL for BNP and 394 pg/mL for NE) with respect to all-cause mortality and first morbid event (defined as death, sudden death with resuscitation, hospitalization for heart failure, or intravenous inotropic or vasodilator therapy for at least 4 hours). An analysis was also done in subgroups of patients defined by baseline BNP and NE quartiles. All analyses were carried out irrespective of the assigned treatment group. For both all-cause mortality and first morbid event, the hazard risk ratio (RR) and its 95% confidence interval (CI) were calculated relative to the subgroup below the median (97 pg/mL for BNP and 394 pg/mL for NE) with respect to all-cause mortality and first morbid event (defined as death, sudden death with resuscitation, hospitalization for heart failure, or intravenous inotropic or vasodilator therapy for at least 4 hours). An analysis was also done in subgroups of patients defined by baseline BNP and NE quartiles. All analyses were carried out irrespective of the assigned treatment group. For both all-cause mortality and first morbid event, the hazard risk ratio (RR) and its 95% confidence interval (CI) were calculated relative to the subgroup below the median in the first analysis and relative to the subgroup in the first quartile for the second analysis. In addition, a global test across all quartiles was performed. For the baseline median subgroup analyses, a Cox proportional hazard model was used with NYHA class, LVEF, baseline ACE-I and β-blocker category, etiology, and age as covariates. For the baseline quartile subgroup analyses, a Cox model without covariates was used. In an additional analysis, the relative predictive value of baseline BNP was compared with that of baseline NE for mortality and morbidity by comparing the estimated relative risks based on standardized BNP (ie, BNP/SD(bnp)) and standardized NE (ie, NE/SD(ne)) in a Cox model including both standardized covariates.

Changes in BNP and NE Over Time and Subsequent Events
For this analysis, change from baseline and the percent change in BNP and NE from baseline to 4 months and 12 months were analyzed by quartiles for subsequent mortality and first morbid

| Table 1. Association Between Baseline BNP and NE in Quartiles and All-Cause Mortality and First Morbid Event (All Randomized Patients) |
|-----------|-----------|-----------|-----------|-----------|
| Groups (1 vs 2) | Group 1 | Group 2 | RR | 95% CI | Cox P |
| Baseline BNP | All-cause mortality | (P for global test of no difference among quartiles <0.00001) | | | |
| Quartile 2 vs 1 | 152/1065 (14.3) | 104/1069 (9.7) | 1.474 | 1.149 to 1.892 | 0.0023 |
| Quartile 3 vs 1 | 226/1090 (20.7) | 104/1069 (9.7) | 2.266 | 1.796 to 2.859 | <0.0001 |
| Quartile 4 vs 1 | 350/1081 (32.4) | 104/1069 (9.7) | 3.952 | 3.175 to 4.920 | <0.0001 |
| First morbid event | (P for global test of no difference among quartiles <0.00001) | | | | |
| Quartile 2 vs 1 | 244/1065 (22.9) | 167/1069 (15.6) | 1.495 | 1.228 to 1.821 | <0.0001 |
| Quartile 3 vs 1 | 372/1090 (34.1) | 167/1069 (15.6) | 2.457 | 2.047 to 2.949 | <0.0001 |
| Quartile 4 vs 1 | 526/1081 (48.7) | 167/1069 (15.6) | 4.086 | 3.432 to 4.864 | <0.0001 |
| Baseline NE | All-cause mortality | (P for global test of no difference among quartiles <0.00001) | | | |
| Quartile 2 vs 1 | 179/1083 (16.5) | 147/1067 (13.8) | 1.259 | 1.012 to 1.566 | 0.0384 |
| Quartile 3 vs 1 | 247/1075 (23.0) | 147/1067 (13.8) | 1.890 | 1.541 to 2.319 | <0.0001 |
| Quartile 4 vs 1 | 260/1076 (24.2) | 147/1067 (13.8) | 2.044 | 1.669 to 2.503 | <0.0001 |
| First morbid event | (P for global test of no difference among quartiles <0.00001) | | | | |
| Quartile 2 vs 1 | 305/1083 (28.2) | 243/1067 (22.8) | 1.310 | 1.107–1.551 | 0.0017 |
| Quartile 3 vs 1 | 352/1075 (32.7) | 243/1067 (22.8) | 1.629 | 1.383–1.919 | <0.0001 |
| Quartile 4 vs 1 | 411/1076 (38.2) | 243/1067 (22.8) | 2.065 | 1.761–2.420 | <0.0001 |

Cox regression without covariate adjustments. Events occurring after permanent treatment discontinuation were not censored.
Morbid events include death, sudden death with resuscitation, therapeutic IV HF therapy for >4 hours, or hospitalization for HF.
event. For mortality and first morbid event, the hazard RR and its 95% CI were calculated for quartiles 2 to 4 compared with quartile 1 using a Cox proportional hazard model with the baseline value as a covariate.

**Results**

The mean±SD for plasma BNP at baseline (n=4305) was 181±230 pg/mL (median, 97 pg/mL) and for plasma NE at baseline (n=4301) was 464±323 pg/mL (median, 394 pg/mL). The mean±SD plasma BNP was 142±167 pg/mL in NYHA class I/II patients compared with 244±296 pg/mL in class III/IV patients. The corresponding values for plasma NE were 425±250 and 522±409 pg/mL, respectively. Baseline values for both BNP and NE were available in 4284 patients.

**Baseline BNP and NE and Events**

The incidence of all-cause mortality and first morbid events was significantly higher for patients with baseline BNP or NE above the median than for those with values below the median. The RRs for these events (mortality and first morbid event) for values above versus below the median were higher for BNP [RR (95% CI), 2.1 (1.79 to 2.42) and 2.2 (1.98 to 2.52), respectively, for mortality and morbidity] than for NE [1.5 (1.28 to 1.71) and 1.4 (1.23 to 1.54), respectively] (Figure 1). BNP exhibited a relatively stronger association with mortality and morbidity than NE (P<0.0001).

Baseline BNP and NE in quartiles also showed a significant quartile-dependent increase in mortality and first morbid event (Table 1, Figure 2). The baseline values for BNP in quartiles were <41, 41 to <97, 97 to <238, and ≥238 pg/mL and for NE were <274, 274 to <394, 394 to <572, and ≥572 pg/mL. Similar findings were observed for BNP and NE values at 4 months and 12 months and subsequent events (data not shown).

**Changes in BNP and NE Over Time and Subsequent Events**

The relationship between change in neurohormone level and outcome can be examined either as absolute change over time or as subgroups by quartiles for BNP and NE.

**Effect of Valsartan on Changes in BNP and NE Over Time and Subsequent Events**

A report on effects of valsartan on BNP and NE in Val-HeFT has been published. Both BNP and NE increased progressively over the duration of the study in the placebo group. Valsartan caused a sustained reduction in BNP and attenuated the increase in NE over the course of the study. The difference in the change from baseline in BNP and NE between the 2 groups was highly significant at each time
point. At last observation, the mean ± SEM BNP increased by \(23 \pm 5\) pg/mL in the placebo group and decreased by \(21 \pm 5\) pg/mL in the valsartan group; NE increased by \(41 \pm 6\) pg/mL and \(12 \pm 6\) pg/mL in placebo and valsartan groups, respectively. This effect of valsartan on BNP and NE might have contributed to the observed 13.2% reduction in morbidity in the overall population of Val-HeFT.

When the association between changes over time in BNP/NE and mortality/morbidity was assessed separately in the 2 randomized groups, a similar relationship was observed. It indicated that the association holds irrespective of treatment groups.

**Discussion**

Baseline NE and BNP are important and independent prognostic markers in patients with HF.\(^3,15\) BNP has also been shown to predict mortality and morbidity in other cardiovascular conditions, such as acute coronary syndromes and acute myocardial infarction.\(^15-17\) The present data represent the largest study to confirm the prognostic importance of both these neurohormones in patients with moderate to severe HF. Furthermore, the findings also demonstrate that BNP is a more sensitive predictor than NE of morbidity and mortality in HF. More importantly, the data provide evidence for the first time that changes in these neurohormones over time are associated with corresponding changes in subsequent mortality and morbidity. Because neurohormone levels increase with the progression of HF and are strikingly correlated with outcomes, these data suggest that BNP and NE levels could serve as guide to the severity of heart failure and the efficacy of its treatment.

Because neurohormones have not been measured sequentially in most earlier HF clinical trials, the association of changes in NH over time with prognosis has not been described previously. In the BEST study, NE was measured at baseline and at several time points during the trial. A preliminary report from that study shows that compared with the group of patients with no change or a small change in NE over time, the groups with a large increase or large decrease in NE had a higher mortality and morbidity,\(^18\) similar to the observations in our patient subgroups. The discrepancy between grouping by change and percent change in levels of BNP and NE is understandable. Circulating hormone levels would be expected to change as a percentage of baseline levels after a change in the hormone secretory rate or sympathetic nerve-firing rate. High initial levels reflecting activation of the systems would be expected to exhibit greater absolute declines than low initial levels, although the percent change in these two groups might be comparable. Indeed, quartiles with the greatest absolute change (rise or fall) exhibited higher baseline levels that render them at higher risk for morbidity and mortality regardless of the change in levels over time (Figure 3). When BNP and NE were related over time to outcome based on quartiles of percent change of neurohormones from baseline, a consistent and progressive increase in outcome risk was observed with increasing percent changes in BNP and NE. Patients with the greatest
percent decrease in BNP or NE at 4 months had the lowest subsequent mortality and first morbid event rates, and patients with the highest percent increase had the highest subsequent increase in event rates. Thus, both baseline and percent change in BNP and NE are important determinants of subsequent mortality and morbidity.

These observational data from Val-HeFT do not allow any conclusions about a possible pathophysiologic link between hormone level and outcome. Norepinephrine has been implicated as a contributor to structural remodeling of the left ventricle, and the inhibition of its cardiac effects by \( \beta \)-blockade has been associated with reversal of ventricular remodeling. Thus, it would be appropriate to suggest the possibility that the relationship between poor outcome and NE levels reflects an adverse effect of sympathetic stimulation rather than merely serving as a marker for more severe disease. It is interesting, however, that the relationship between BNP and outcome is even more powerful and BNP has not been implicated as a contributor to the progression of heart failure. Because BNP is produced in the heart, changes in circulating BNP may be considered a biological marker for changes in LV remodeling. However, there are few data correlating structural changes in the heart with changes in BNP. It is likely that the association of changes in BNP over time with mortality and morbidity noted in our study will correspond with structural and functional changes in the heart. Correlation of the echocardiographic and BNP data with mortality and morbidity in Val-HeFT may help to clarify this relationship. Such an analysis is in progress.

The findings of this study raise important questions regarding the use of BNP and NE as guides to efficacy of HF therapy. In the case of BNP, preliminary data suggest that the use of a BNP-guided approach, targeted to reduce BNP to a predefined level, is associated with a significant reduction in cardiovascular events compared with a clinically guided approach.\(^{19,20}\) These preliminary data would be supported by the findings in Val-HeFT. The evidence for the use of NE-guided approach is less clear, and the data from the PRIME II\(^{21}\) and MOXCON\(^{22}\) trials are troublesome in this regard. Both of these trials were terminated prematurely because of the adverse effects of ibopamine and moxonidine.

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### Table 2. Association Between Percent Change in BNP and NE From Baseline to 4 Months in Quartiles and Subsequent All-Cause Mortality and First Morbid Event, Adjusting for Baseline BNP or NE as a Covariate (All Patients Who Did Not Die or Did Not Have a First Morbid Event Before Month 4)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Group 1, n/N (%)</th>
<th>Group 2, n/N (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>Cox P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in BNP from baseline to 4 months, All-cause mortality</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Quartile 2 vs 1</td>
<td>145/935 (15.5)</td>
<td>127/935 (13.6)</td>
<td>1.303</td>
<td>1.026 to 1.656</td>
<td>0.0302</td>
</tr>
<tr>
<td>Quartile 3 vs 1</td>
<td>141/935 (15.1)</td>
<td>127/935 (13.6)</td>
<td>1.359</td>
<td>1.065 to 1.735</td>
<td>0.0136</td>
</tr>
<tr>
<td>Quartile 4 vs 1</td>
<td>179/935 (19.1)</td>
<td>127/935 (13.6)</td>
<td>1.923</td>
<td>1.522 to 2.429</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Change in NE from baseline to 4 months, All-cause mortality</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quartile 2 vs 1</td>
<td>150/937 (16.0)</td>
<td>135/936 (14.4)</td>
<td>1.228</td>
<td>0.971 to 1.553</td>
<td>0.0861</td>
</tr>
<tr>
<td>Quartile 3 vs 1</td>
<td>147/936 (15.7)</td>
<td>135/936 (14.4)</td>
<td>1.280</td>
<td>1.009 to 1.622</td>
<td>0.0415</td>
</tr>
<tr>
<td>Quartile 4 vs 1</td>
<td>164/937 (17.5)</td>
<td>135/936 (14.4)</td>
<td>1.480</td>
<td>1.171 to 1.870</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

 Cox regression with baseline covariate adjustment. Events occurring after permanent treatment discontinuation were not censored. Morbid events include death, sudden death with resuscitation, therapeutic IV HF therapy for >4 hours, or hospitalization for HF.
on mortality despite significant reductions in plasma NE. Hence, although a physiological change in hormone levels may be a marker for outcome, strategies to reduce neurohormonal levels for mortality and morbidity benefit are at present premature and not justified.

**Conclusions**

Percent changes in BNP and NE over time are associated with corresponding changes in subsequent mortality and morbidity, thus supporting their role as important surrogate markers in HF. These data, therefore, underscore the importance of including the measurement of neurohormones, especially of BNP in all patients, in future HF clinical trials. Because the annual mortality in patients with moderate to severe HF has now been reduced to 7% to 9% with appropriate use of ACE-I and β-blockers, it is likely that future HF trials will not need to rely on markers for the progression of the disease to provide adequate power to demonstrate reduced morbidity. BNP and other surrogate measures such as LV structure and function could be considered sufficiently robust supplement morbidity end points to demonstrate the beneficial effects of a newer therapy in heart failure.

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**References**

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