Effects of Valsartan on Circulating Brain Natriuretic Peptide and Norepinephrine in Symptomatic Chronic Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT)

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Background—Brain natriuretic peptide (BNP) and norepinephrine (NE) are strongly related to severity of and are independent predictors of outcome in heart failure. The long-term effects of angiotensin receptor blockers on BNP and NE in heart failure patients are not known.

Methods and Results—Both BNP and NE were measured in 4284 patients randomized to valsartan or placebo in the Valsartan Heart Failure Trial (Val-HeFT) at baseline and 4, 12, and 24 months after randomization. The effects of valsartan were tested by ANCOVA, controlling for baseline values and concomitant ACE inhibitors and/or β-blockers. BNP and NE concentrations were similar at baseline in the 2 groups and were decreased by valsartan starting at 4 months and up to 24 months. BNP increased over time in the placebo group. At the end point, least-squares mean (±SEM) BNP increased from baseline by 23 ± 5 pg/mL in the placebo group (n=1979) but decreased by 21 ± 5 pg/mL (n=1940) in the valsartan group (P<0.0001). NE increased by 41 ± 6 pg/mL (n=1979) and 12 ± 6 pg/mL (n=1941) for placebo and valsartan, respectively (P=0.0003). Concomitant therapy with both ACE inhibitors and β-blockers significantly reduced the effect of valsartan on BNP but not on NE (P for interaction=0.0223 and 0.2289, respectively).

Conclusions—In Val-HeFT, the largest neurohormone study in patients with symptomatic chronic heart failure, BNP and NE rose over time in the placebo group. Valsartan caused sustained reduction in BNP and attenuated the increase in NE over the course of the study. These neurohormone effects of valsartan are consistent with the clinical benefits reported in Val-HeFT. (Circulation. 2002;106:2454-2458.)

Key Words: heart failure • angiotensin • natriuretic peptides • norepinephrine • trials

Neurohormone activation is characteristic of heart failure (HF), and the magnitude of elevation of circulating levels of norepinephrine (NE), brain natriuretic peptide (BNP), and other neurohormones is directly related to mortality and morbidity.1–4 The influence of therapy on neurohormone levels has been less well studied, in part because, with few exceptions,5–8 hormone assays have usually been conducted in only a subset of the population in trials. The Valsartan Heart Failure Trial (V-HeFT) II demonstrated that enalapril therapy was associated with a reduction in plasma NE levels compared with the isosorbide dinitrate/hydralazine–positive control group.5 In V-HeFT III, felodipine produced a modest reduction in atrial natriuretic peptide levels compared with placebo.9 In the RESOLVD Pilot trial, candesartan combined with enalapril therapy caused a sustained reduction of BNP of ~30 pg/mL over a period of 43 weeks.7 None of those trials, however, had an adequate size to examine the response to therapy in subgroups of the population.

Val-HeFT tested the effect on morbidity and mortality of the angiotensin receptor blocker valsartan versus placebo in addition to standard HF therapy, which may have included an ACE inhibitor (ACEi) and/or a β-blocker (BB) in 5010 patients with symptomatic HF.10,11 Valsartan had no effect on mortality, but it decreased the other primary end point of combined morbidity/mortality by 13.2%; significantly im-

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proved symptoms of HF, left ventricular (LV) function, and LV dilation; and reduced the risk of hospitalization for HF by 27.5%. In Val-HeFT, samples for the measurement of BNP and NE were collected at randomization and serially during the follow-up in all randomized patients in centers that agreed to participate in the blood sampling portion of the study.

In the present article, we report on the effects of valsartan on BNP and NE over the 2-year follow-up in Val-HeFT, in which the unusually large sample studied allowed us to investigate a possible interaction between valsartan and concomitant ACEi and/or BB therapy. The relationship between hormone levels and outcome will be examined in subsequent reports.

Methods

Patients

Val-HeFT was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial. Patients with stable, symptomatic HF (n=5010) who were on prescribed HF therapy and had LV ejection fraction <40% and LV internal diameter in diastole adjusted for body surface area of >2.9 cm²/m² were enrolled from March 1997 to April 1999 at 302 clinical centers in 16 countries. All patients provided written informed consent before enrollment in the study. Study design and protocol have been presented in detail previously.

Blood Sampling and Assays

Blood for neurohormone assays was sampled before the morning dose of study drug at randomization and 4, 12, and 24 months thereafter. Patients were lying supine for 30 minutes before blood collection with an indwelling venous cannula. Blood was centrifuged at 4°C within 10 minutes, and the plasma was divided into aliquots and shipped on dry ice to one of the two core laboratories: the University of Minnesota for the US centers and Mario Negri Institute, Milan, Italy, for the non-US centers. Samples were stored at −70°C until assayed. Different anticoagulants and preservatives were used, as follows: NE, EGTA, glutathione reduced form, BNP, K-EDTA, and aprotinin (500 kallikrein inhibitor units/mL of blood).

Analyses were performed in the two core laboratories with the investigators unaware of the study treatment allocation of the samples; for NE, high-performance liquid chromatography with electrochemical detection; for BNP, immunoradiometric assay, Shionogi (Schering CIS).

Minimum concentrations that could be reliably quantified were 20 and 2 pg/mL for NE and BNP, respectively.

Within-Laboratory Quality Control

BNP and NE were stable when stored at −70°C: 12-month changes were −3% and 6%, respectively. A subset of samples was assayed in duplicate at the beginning of the study. Mean percentage difference (±SD) between assays was 6±6% (mean concentration, 193 pg/mL; range, 4 to 1708 pg/mL; n=200) for BNP and 14±15% (mean concentration, 365 pg/mL; range 67 to 2111 pg/mL; n=181) for NE. In a subgroup of 23 732 samples, a minority of plasma samples was lipemic (2.0%) or hemolyzed (2.0%). No significant differences in neurohormone concentrations were found that could be attributed to hemolysis or to high lipid content, which were therefore not considered reasons for exclusion of the sample from analysis.

Between-Laboratory Quality Control

BNP kits with antibodies from the same batches were purchased for 2 core laboratories. Every 6 months throughout the trial, 8 plasma samples (4 normal volunteers, 4 HF patients) were prepared according to the study protocol and assayed in both core laboratories, and the results were sent to an independent auditor. Overall, 40 quality control samples were assayed over a period of 2 years by the 2 core laboratories. Between-laboratory comparison yielded a correlation of 0.98 (r) for BNP and 0.86 for NE. Within- and between-assay coefficients of variation were 3.9% and 4.7% for BNP and 4.7% and 13.8% for NE, respectively. Mean differences between duplicate assays on different days were 4.2% and 9.5% for BNP (n=200) and NE (n=181), respectively.

Data Analysis

Between-treatment differences of change from baseline (randomization) in BNP and NE concentrations were analyzed by ANCOVA, controlling for baseline value, use of ACEi and/or BB at baseline, and treatment-by-baseline interaction.

To examine treatment effects for different aspects of the study population, BNP and NE measurements over the 24-month study period were analyzed in the following ways: (1) changes from baseline at study end point (BNP, n=3919; NE, n=3920), which include all patients with data at both baseline and end point (ie, last postbaseline observation carried forward); changes at end point were pooled for this analysis, irrespective of the time at which they occurred; (2) changes from baseline at months 4, 12, and 24, including all patients with data at a given time point and at baseline: mean baseline values for these analyses may differ (eg, mean baseline BNP for 4-month observations was 171 pg/mL, compared with 143 pg/mL for 24-month observations). The number of patients represented at each subsequent time point decreases from 4 to 24 months (BNP, n=3740 to 1667; NE, n=3749 to 1656); and (3) repeated-measures ANOVA, selecting patients with all data available up to 2 years, ie, “completers,” which may include an overrepresentation of less severely ill patients.

Least-squares mean and SEM are presented for the ANCOVA. Because of the apparently nonnormal distribution of BNP and NE data, statistical analyses were also done on logarithmically transformed BNP and NE, but untransformed data are presented for ease of reading. To assess a possible influence of concomitant therapies, such as BB and ACEi, on the effect of valsartan on BNP and NE, 2 analyses were done: (1) changes from baseline at study end point between subgroups of patients receiving or not receiving BB or ACEi; ANCOVAs were done within each of the 4 groups [ie, ACEi no (N) BB (N); ACEi(N) BB yes (Y); ACEi(N) BB(N); and ACEi(Y) BB(Y)]; and (2) changes from baseline at study end point on all randomized patients with measurements by ANCOVA controlled for baseline value, combined ACEi/BB usage at baseline (Y/N), treatment-by-baseline interaction, and treatment by combined ACEi/BB usage at baseline.

All tests for BNP and NE were made at a 2-sided 5% significance level.

Results

Baseline

Baseline measurements of both BNP and NE were available in 4284 of the 5010 patients. In these patients, the baseline clinical characteristics were similar to those of the whole population (Table). The all-cause mortality rate of the whole population of the trial was 19.6% (valsartan, 19.7%; placebo, 19.4%; P=0.80), whereas that of patients with BNP and NE available at baseline was 19.3% (valsartan, 19.6%; placebo, 19.1%; P=0.67). The difference was not statistically significant.

Mean (±SD) baseline BNP and NE concentrations were 181±230 and 464±324 pg/mL (medians, 97 and 394 pg/mL), respectively. There was a weak positive correlation between baseline BNP and NE (r²=0.067, n=4284; P<0.001 for test of no correlation). The baseline mean (±SEM) values of BNP and NE in patients randomized to the placebo (178±5 and 472±8 pg/mL) and valsartan (183±5 and 456±6 pg/mL) groups were not found to be different.
Effects of Valsartan on BNP and NE Concentrations Over Time

BNP concentrations rose steadily over time in the placebo group, by 2, 12, and 21 pg/mL at 4, 12, and 24 months, respectively. In contrast, valsartan significantly reduced BNP levels, by 34, 24, and 16 pg/mL at 4, 12, and 24 months, respectively (Figure 1a). At end point, BNP increased by 23 pg/mL in placebo (n=1979) but decreased by 21 pg/mL in valsartan (P<0.0001) compared with baseline. In patients who had data available at all time points up to 24 months (ie, completers), the changes in BNP at 4, 12, and 24 months in the placebo and valsartan groups were 2, 5, and 23 pg/mL and 34, 31, and 20 pg/mL, respectively, with statistically significant differences at all time points (treatment, P<0.0001; repeated-measures ANOVA), which were not affected by time (time×treatment, P=0.5384).

Plasma NE increased in the placebo group by 36, 38, and 35 pg/mL at 4, 12, and 24 months, respectively. Valsartan significantly attenuated this increase (Figure 1b). At end point, NE increased by 41±6 pg/mL in placebo (n=1979) and 12±6 pg/mL in valsartan (n=1940, P=0.0003). In patients who had all data available at all time points up to 24 months, the changes in NE at 4, 12, and 24 months in the placebo and valsartan groups were −2, 5, and 23 pg/mL and −40, −31, and −20 pg/mL, respectively, with statistically significant differences at all time points (treatment, P<0.0001; repeated-measures ANOVA), which were not affected by time (time×treatment, P=0.9955).

The results of these analyses were consistent with those performed on logarithmically transformed BNP and NE concentrations (data not shown).

Effects of Valsartan on BNP and NE Concentrations Over Time by Concomitant ACEi and BB

Changes in BNP and NE from baseline to end point were also analyzed by concomitant baseline therapy with ACEi or BB. The effect of valsartan on BNP and NE in the 4 subgroups showed similar trends despite the small size of some subgroups (Figure 2). A significant valsartan effect on BNP was observed for all 4 subgroups, with the largest reduction in BNP seen in the smallest subgroup, ACEi(N)/BB(Y) (least-squares mean change 62±44, n=58, in valsartan versus 173±49 pg/mL, n=48, in placebo; P=0.0005) (Figure 2a). Valsartan attenuated the increase in NE over time in all 4 subgroups, but significant differences were seen only in the largest subgroup, ACEi(Y)/BB(N) (Figure 2b).

Finally, we compared the group of 1327 patients receiving both ACEi and BB with the remaining 2592 patients on either ACEi or BB alone or none of these drugs. This analysis yielded a statistically significant (P<0.0001) overall effect of valsartan on BNP at end point, as well as significant treatment effects on BNP at end point in both the subgroup on combined ACEi and BB and the subgroup not on combined ACEi and BB. A significant (P=0.0228) interaction between treatment and baseline therapy was also observed (Figure 3a), suggesting that compared with placebo, valsartan decreased
BNP in all patients, but this effect was less pronounced in patients on combined ACEi and BB therapy. Similar analysis for NE showed a statistically significant ($P=0.001$) overall effect of valsartan on NE at end point, in conjunction with a significant treatment effect in patients not on combined ACEi and BB ($n=2595$) and a favorable but not statistically significant treatment difference for valsartan in patients on combined ACEi and BB ($n=1325$). A nonsignificant ($P=0.2289$) interaction between treatment and baseline therapy was observed (Figure 3b), indicating that valsartan attenuated the increase of NE versus placebo overall irrespective of whether patients were on combined concomitant ACEi and BB.

**Discussion**

Val-HeFT randomized 5010 patients with chronic symptomatic HF who were receiving standard prescribed treatment to valsartan or placebo. The results showed that valsartan significantly reduced the risk for the combined end point of mortality and morbidity by 13.2% and for hospitalizations for HF by 27.5%, but not for mortality alone.$^{11}$ In this study, plasma NE and BNP were measured in 4284 patients at baseline and repeatedly during follow-up, making this the largest neurohormone database in an HF trial. This large body of data, therefore, allows us to state with confidence the effects of valsartan on BNP and NE, not only in the whole population but also in subgroups of considerable clinical interest, such as those receiving or those not receiving an ACEi and/or a BB at baseline.

Whereas BNP increased progressively in the placebo group over the 2-year follow-up period (suggesting progressive LV dilation and worsening of HF over time), the NE increased at 4 months and then stabilized to between 35 and 38 pg/mL above baseline. The analysis restricted to the 1555 patients who completed the 24-month study showed a similar profile for BNP, but the NE increase with placebo was more gradual, as expected. This difference between the 2 analyses may be partly a result of different numbers of patients considered at the various time points.

A sustained effect of treatment on a circulating neurohormone over a period of 2 years has never before been reported in HF. Previously, the largest study published was V-HeFT II, in which a significant decrease in circulating NE was reported with enalapril compared with hydralazine and isosorbide.
dinitrate in 743 patients with HF. In that study, the effect of enalapril appeared to wane by 2 years.

Valsartan decreased mean BNP by 34±4 pg/mL at 4 months, and thereafter, BNP rose at the same rate as in the placebo group. Even at 24 months, however, BNP remained below baseline values (mean change±SEM, −16±7 pg/mL). Because BNP has been suggested to be a marker for ventricular remodeling, these findings suggest that valsartan might have reversed ventricular remodeling during the first 4 months. Further analysis of the Val-HeFT echocardiographic data may help to clarify these findings. Unlike its effect on BNP, valsartan attenuated the increase in NE observed in the placebo group by a treatment difference of 24 to 38 pg/mL throughout the study. Similar effects on NE have been observed with ACEI6,14 and may reflect the effects of angiotensin II inhibition at the presynaptic junction.15

The effects of valsartan on BNP and NE were seen in the overall study population. Interestingly, however, the decrease of BNP by valsartan was attenuated in patients with background therapy with both ACEi and BB. Although the mechanisms responsible for these differential effects of valsartan on BNP are not clear, the lack of increase of BNP in placebo in this latter group (Figure 3a) suggests an already effective neurohormone suppression with background therapy. BB therapy generally reduces neurohormone activation in HF, possibly by improving signs and symptoms of HF. In the small ACEI(N)/BB(Y) subgroup (n=106 overall), however, we found a significant increase in BNP in the placebo group at all time points and an increase of >100 pg/mL at end point. Indeed, it has been shown previously that BB can increase plasma BNP.18,19 The mechanisms of such an effect are not clear but may be caused by a BB-induced downregulation of the natriuretic peptide clearance receptor NP-C in the lung.20

In conclusion, it has been shown for the first time that an angiotensin receptor blocker decreases 2 major markers of the severity of HF, BNP, and NE within 4 months and up to at least 24 months. This effect of valsartan on BNP or NE occurs in all subgroups, although to a different extent. Thus, the benefit of valsartan in HF, which was consistent across all variables analyzed with the exception of mortality (ie, combined end point of morbidity and mortality, quality of life, clinical signs, NYHA class, LV ejection fraction, and LV diameter), can now be extended to BNP and NE. The size of the sample analyzed and the number of clinical and instrumental variables collected will enable future analyses to better outline the role of neurohormones in HF.

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for the Val-HeFT Investigators

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