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Sustained Reduction of Aldosterone in Response to the Angiotensin Receptor Blocker Valsartan in Patients With Chronic Heart Failure

Results From the Valsartan Heart Failure Trial

Jay N. Cohn, MD; Inder S. Anand, MD; Roberto Latini, MD; Serge Masson, PhD; Yann-Tong Chiang, PhD; Robert Glazer, MD; for the Valsartan Heart Failure Trial Investigators



Background—Aldosterone has been implicated in the progression of heart failure. The Valsartan Heart Failure Trial (Val-HeFT) provided the first opportunity to examine the long-term effects of an angiotensin receptor blocker on plasma aldosterone levels in patients with NYHA class II through IV heart failure.

Methods and Results—Plasma aldosterone was measured by radioimmunoassay in core laboratories at baseline and during follow-up in patients assigned to valsartan at a target dose of 160 mg twice daily or placebo. In the placebo group, aldosterone (baseline, 150 ± 160 pg/mL, mean \pm SD; $n=2025$) increased at 4, 12, and 24 months. In the valsartan group, aldosterone (baseline, 137 ± 124 pg/mL, mean \pm SD; $n=2023$) decreased at 4 months and remained suppressed for up to 2 years. At end point (last measurement in each patient), mean aldosterone increased by 17.8 ± 3.0 pg/mL (SEM) (11.9%) in the placebo group and decreased by 23.8 ± 3.0 pg/mL (SEM) (−17.4%) in the valsartan group ($P < 0.00001$). The effect of valsartan was similar in all subgroups, including those receiving neither ACE inhibitors (ACE-I) nor β -blockers (BB) at baseline and those receiving concomitant ACE-I or BB. In contrast, outcome effects varied in the 4 subgroups, with a statistically significant reduction in the combined mortality/morbidity end point in those receiving neither neurohormonal inhibitor and an adverse trend in those treated with both drugs.

Conclusions—Valsartan added to background therapy for heart failure produces sustained reduction in plasma aldosterone, consistent with the observed significant reduction in the combined mortality/morbidity end point. A similar reduction in all subgroups based on ACE-I or BB therapy, despite differing clinical outcomes in these subgroups, suggests that aldosterone plasma levels may not be a critical marker of the progression of heart failure. (*Circulation*. 2003;108:1306-1309.)

Key Words: heart failure ■ angiotensin ■ trials

Despite the remarkable success of ACE inhibitors (ACE-I) in reducing the mortality and morbidity from heart failure (HF), the addition of the aldosterone inhibitor spironolactone was shown to cause an additional 30% decrease in mortality in the Randomized Aldactone Evaluation Study (RALES).¹ Although ACE-I might be expected to reduce aldosterone levels by reducing the stimulating effect of angiotensin II on aldosterone production, recent studies have demonstrated that neither angiotensin II nor aldosterone plasma levels are suppressed chronically by clinically prescribed doses of ACE-I.^{2,3} Aldosterone has been implicated as a contributor to structural remodeling of the left ventricle,^{4–6} and the beneficial effects of spironolactone on mortality have

been attributed to inhibition of the collagen-generating influence of aldosterone.^{7,8}

Aldosterone secretion is stimulated by several factors in addition to angiotensin II, and these alternate mechanisms may be important determinants of aldosterone production and its levels in the plasma and tissues in patients with HF. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot trial, plasma aldosterone levels were monitored before and after randomized assignment of patients with HF to placebo or the angiotensin receptor blocker (ARB) candesartan.⁹ An initial fall in aldosterone level in response to the ARB was no longer observed by 43 weeks despite continued therapy with the ARB. These

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data provided additional physiological rationale for the use of a direct aldosterone receptor blocker.

The Valsartan Heart Failure Trial (Val-HeFT) evaluated the efficacy of a high dose of the ARB valsartan in patients with moderate to severe HF followed up for an average of 23 months.¹⁰ In this large trial, several plasma neurohormones including aldosterone were measured at baseline and during follow-up. In this contribution, we report the long-term effects of valsartan on plasma aldosterone concentration.

Methods

Study Design and Patients

Val-HeFT was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial. A total of 5010 patients with stable, symptomatic HF, who were undergoing prescribed HF therapy and had left ventricular ejection fraction <40% and left ventricular diameter in diastole adjusted for body surface area (LVlDd/BSA) of ≥ 2.9 cm/m², were enrolled in the study. Results of the main trial have been presented previously in detail.¹⁰

Aldosterone Measurement

Blood samples were collected for measurement of aldosterone before randomization and 4, 12, and 24 months thereafter. Plasma aldosterone was measured with a radioimmunoassay (Milan: DiaSorin, Italy; Minneapolis: Sorin Biomedica) in 2 core laboratories. Values in healthy subjects in our laboratories averaged 67 ± 40 pg/mL (SD). Several Val-HeFT centers did not participate in the neurohormonal studies.

Statistical Analysis

Between-treatment differences of change from baseline in aldosterone concentrations were analyzed by ANCOVA, controlling for baseline value, treatment by baseline interaction, and use of ACE-I or β -blockers (BBs) at baseline and pooled center (or geographic region) as appropriate to the patient subgroup analyzed. To examine the effect of treatment on plasma aldosterone measurements over the 24-month study period, the following analyses were performed. First, the changes from baseline to study end point (ie, last postbaseline observation carried forward) in all patients ($n=3636$) and in 13 different subgroups were studied. Changes at end point were pooled for this analysis, irrespective of the time at which they occurred. Second, changes from baseline to months 4, 12, and 24 in all patients who had paired data at baseline and these time points were examined. The number of patients represented at 4, 12, and 24 months decreased progressively ($n=3467$, 3000, and 1458, respectively).

Least-squares mean and SEM are presented for the ANCOVA. For analysis of treatment effect in subgroups, the placebo-corrected least-squares mean change from baseline to end point and its 95% CI are presented. To assess possible influence of concomitant therapies with ACE-I or BB on the effect of valsartan on aldosterone, the changes from baseline to end point were compared for each of the 4 subgroups (ACE-I no, BB no; ACE-I no, BB yes; ACE-I yes, BB no; and ACE-I yes, BB yes) using ANCOVA. All tests for aldosterone were made at a 2-sided 5% significance level.

Results

Baseline

Aldosterone levels were available in 4048 of 5010 patients at baseline. Mean (\pm SD) baseline aldosterone was 144 (\pm 143) pg/mL ($n=4048$, median 104 pg/mL). Baseline aldosterone was statistically significantly higher in the placebo group (150 ± 160 pg/mL, $n=2025$) than in the valsartan group (137 ± 124 pg/mL, $n=2023$), $P<0.01$.

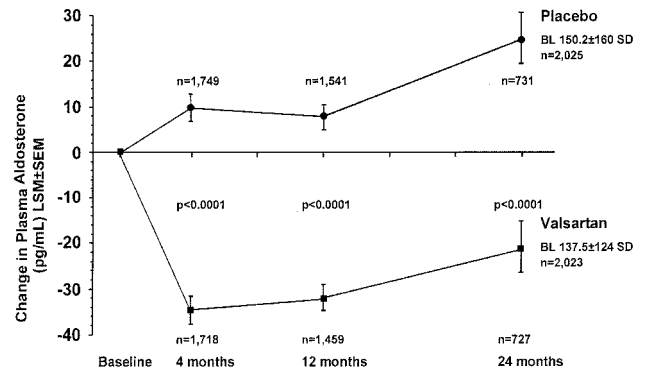


Figure 1. Effect of valsartan on the change in plasma aldosterone from baseline to 4, 12, and 24 months in patients randomized to placebo or valsartan.

Effect of Valsartan on Plasma Aldosterone in All Patients

Plasma aldosterone levels increased over time in the placebo group by 9.9, 7.7, and 25.1 pg/mL at 4, 12, and 24 months. In contrast, aldosterone was significantly reduced in the valsartan group by -34.6 , -31.9 , and -20.8 pg/mL at 4, 12, and 24 months. The differences in aldosterone levels between the 2 groups were highly statistically significant at each time point (Figure 1). At end point (ie, last postbaseline observation carried forward), aldosterone increased by 17.8 ± 3.0 pg/mL SEM (11.9%) in the placebo group and decreased by -23.8 ± 3.0 pg/mL SEM (-17.4%) in the valsartan group ($P<0.00001$). Thus, the mean reduction in aldosterone in the valsartan group compared with the placebo group was 29.3%.

Effect of Valsartan on Plasma Aldosterone in Subgroups

The placebo-corrected decrease in plasma aldosterone was highly significant at all time points and at end point in subgroups of patients based on age, gender, NYHA class, ACE-I or BB use, and baseline ejection fraction, LVlDd/BSA, and aldosterone levels (Figure 2). In the small group of black patients, the placebo-corrected decrease in plasma aldosterone was significant at 4 and 12 months but not at 24 months or end point (Figure 2).

Changes in aldosterone were also analyzed in the 4 subgroups of patients receiving background therapy with various combinations of ACE-I and BB. In all of these groups, a significant and comparable decrease in aldosterone was observed with valsartan at end point despite the small size of some subgroups (Figure 3).

Discussion

Val-HeFT was a multinational trial in 5010 patients with moderate-to-severe HF receiving prescribed HF treatment who were randomized to receive valsartan or placebo therapy. As previously reported, valsartan significantly reduced the risk for the combined end point of mortality and morbidity by 13.2% and risk for first hospitalizations for HF by 27.5% but did not have an effect on mortality.¹⁰ Measurement of plasma neurohormones at baseline and during follow-up has provided the largest database ever collected on neurohormone levels and their response to treatment in HF. The present report demonstrates that

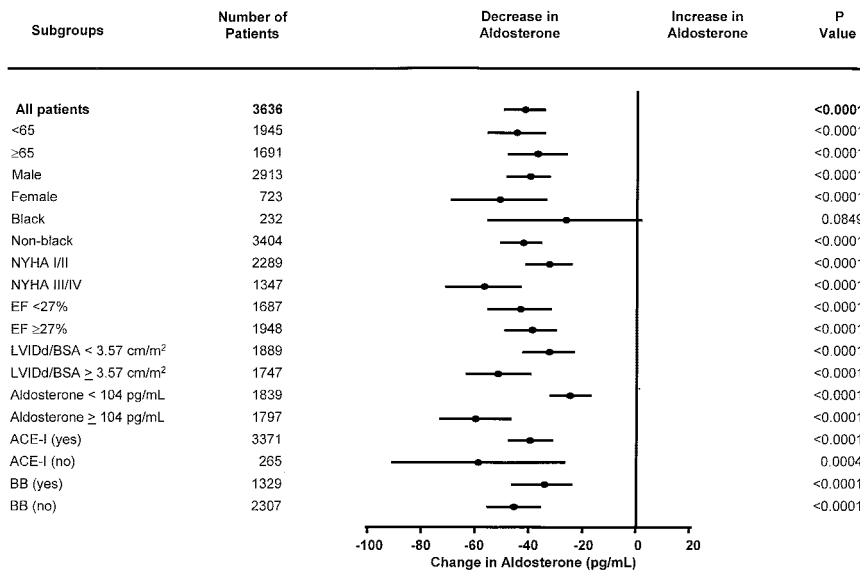


Figure 2. Placebo-corrected change in plasma aldosterone from baseline to end point (last observation carried forward) in subgroups of patients. Point estimates and 95% CIs are shown.

whereas plasma aldosterone increased progressively in the placebo group, in the valsartan group aldosterone fell significantly, and the reduction was sustained throughout the 2-year follow-up period with no evidence of aldosterone escape.

A sustained suppression of plasma aldosterone levels in HF has not previously been reported with any drug treatment. Although short-term therapy with ACE-I lowers circulating levels of aldosterone, up to 20% of patients with HF have elevated plasma aldosterone despite long-term ACE-I administration.^{3,11–13} Different ACE-I genotypes may be involved in this aldosterone escape,¹⁴ but the exact mechanisms underlying incomplete aldosterone suppression with ACE-I have not been adequately investigated. One likelihood is that circulating angiotensin II levels recover during chronic ACE-I therapy.^{15–17} The effects of ARBs on aldosterone are even less clear. In RESOLVD, high dose of the ARB candesartan (16 mg daily) or a combination of candesartan and enalapril suppressed plasma aldosterone levels at 17 weeks, but the effect did not persist at 43 weeks of treatment.⁹ In addition to angiotensin II, aldosterone production is under the control of other factors such as potassium and corticotropins, and these may assume greater importance during aldosterone escape.¹⁸

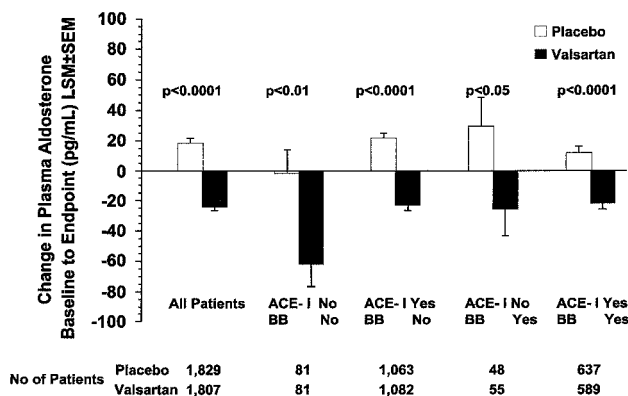


Figure 3. Effect of valsartan on plasma aldosterone at end point in subgroups of patients undergoing different combinations of concomitant ACE-I and BB therapy.

Although it has long been known that aldosterone is important in edema formation,¹⁹ its role in the progression of HF remains unclear. The remarkable result of the RALES trial, which showed a 30% reduction in mortality with the addition of spironolactone in patients with class III and IV HF receiving ACE-I, has renewed interest in the possible pathogenetic role of aldosterone in HF. The recently completed Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) has confirmed in a post-myocardial infarction population the efficacy of an aldosterone inhibitor, in this case eplerenone, in reducing mortality in patients receiving ACE-I or BB.²⁰ Several potential mechanisms have been suggested to explain a beneficial effect of spironolactone. Production of aldosterone is activated in the failing human ventricle.²¹ Aldosterone has been shown to promote cardiac fibrosis in various experimental models^{22,23} and to promote adverse ventricular remodeling in humans.^{4,5} Furthermore, aldosterone antagonism has been reported to reduce perivascular and interstitial fibrosis and to improve myocardial compliance.²⁴ Although no direct measurement of ventricular remodeling was made in RALES, indirect evidence for an improvement in left ventricular remodeling comes from a substudy of collagen formation. In that substudy, patients randomized to spironolactone exhibited a significant reduction of procollagen I and III, markers of ongoing collagen formation and possible independent predictors of mortality.⁷ Tsutamoto et al⁵ demonstrated an improvement in left ventricular volume and ejection fraction in patients with HF treated with spironolactone. Spironolactone may also be effective because it may oppose the effects of aldosterone on sodium retention, loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, baroreceptor function, vascular damage, and arterial compliance.¹

In Val-HeFT, a favorable effect of valsartan on the combined morbidity-mortality end point was accompanied by a sustained regression of left ventricular remodeling as assessed by left ventricular ejection fraction and LVIDd.¹⁰ Although this favorable cardiac structural effect was attributed to inhibition of the direct adverse effects of angiotensin, a possible role for aldosterone inhibition now

cannot be excluded as a contributor to both the clinical and myocardial structural benefit of the drug.

However, another observation in Val-HeFT is discordant with the plasma aldosterone data. In the 1226 patients in the trial receiving background therapy with an ACE-I and a BB, no benefit of valsartan on remodeling was observed,²⁵ and there was an adverse trend on the combined mortality/morbidity end point and a statistically significant adverse mortality effect in the valsartan arm.¹⁰ Despite the absence of clinical benefit of valsartan in this group, a striking, sustained reduction of aldosterone was demonstrated. Because the annual mortality rate was only 6% in the placebo arm of this subgroup, the apparent adverse effect could be explained by a play of chance. Nonetheless, this discordance among clinical outcome, left ventricular remodeling change, and plasma aldosterone levels challenges the simple view that elevated plasma levels of aldosterone contribute to left ventricular structural remodeling and their inhibition reduces mortality by a favorable effect on left ventricular structure.

Several factors complicate the mechanistic interpretation of these plasma aldosterone data. Aldosterone production and tissue levels, particularly in the myocardium, may not correlate with plasma levels. Furthermore, the relationship between plasma aldosterone levels and mineralocorticoid receptor activity has not been clearly established. Although the levels of circulating neurohormones are generally thought to be linearly related to receptor activity, one cannot assume that the 29.3% reduction in mean plasma aldosterone induced by valsartan therapy was associated with a comparable reduction in receptor activity. Indeed, mean plasma aldosterone levels during valsartan therapy were still above the mean levels for healthy subjects, and thus receptor activity might still be enhanced. Furthermore, corticoids may replace aldosterone as a receptor agonist in heart failure²⁶ and as the target for spironolactone and eplerenone therapy. Even if aldosterone were directly contributing to structural remodeling and poor outcome in heart failure, other contributing hormonal and molecular factors might cloud a simple relationship between suppression of circulating aldosterone and a favorable effect on progression of heart failure. Consequently, the fall in plasma aldosterone induced by valsartan does not necessarily imply that addition of a specific aldosterone receptor antagonist would be any less effective.

In summary, contrary to previous limited observations, angiotensin receptor blockade with valsartan in HF produced a sustained reduction in plasma aldosterone levels. Inconsistency in subgroups between the fall in aldosterone, the regression of left ventricular remodeling, and clinical outcome raises questions about a simple, direct relationship between elevated plasma aldosterone and the progression of HF.

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