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Valsartan Benefits Left Ventricular Structure and Function in Heart Failure: Val-HeFT Echocardiographic Study

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OBJECTIVES The objective of the study was to evaluate the effect of an angiotensin receptor blocker on left ventricular (LV) structure and function when added to prescribed heart failure therapy.

BACKGROUND The clinical benefit derived from heart failure therapy is attributed to the regression of LV remodeling.

METHODS At 302 multinational sites, 5,010 patients in New York Heart Association (NYHA) classification II to IV heart failure taking angiotensin-converting enzyme inhibitor (ACEI) and/or beta-blocker (BB) were randomized into valsartan and placebo groups and followed for a mean of 22.4 months. Serial echocardiographic measurements of left ventricular internal diastolic diameter (LVIDd) and ejection fraction (EF) were recorded. Total study reproducibility calculated to 90% power at 5% significance defined detectable differences of 0.09 cm for LVIDd and 0.86% for EF.

RESULTS Baseline LVIDd and EF for valsartan and placebo groups were similar: 3.6 ± 0.5 versus 3.7 ± 0.5 (cm/m^2) and 26.6 ± 7.3 versus 26.9 ± 7.0 (%). Mean group changes from baseline over time were compared. Significant decrease in LVIDd and increase in EF began by four months, reached plateau by one year, and persisted to two years in valsartan compared with placebo patients, irrespective of age, gender, race, etiology, NYHA classification, and co-treatment therapy. Changes at 18 months were −0.12 ± 0.4 versus −0.05 ± 0.4 (cm/m^2), $p < 0.00001$ for LVIDd, and +4.5 ± 8.9 versus +3.2 ± 8.6 (%), $p < 0.00001$ for EF. The exception occurred in patients taking both ACEI and BB as co-treatment, in whom the decrease in LVIDd and increase in EF were no different between valsartan and placebo groups.

CONCLUSIONS The Val-HeFT echocardiographic substudy of 5,010 patients with moderate heart failure demonstrated that valsartan therapy taken with either ACEI or BB reversed LV remodeling. (J Am Coll Cardiol 2002;40:970–5vi) © 2002 by the American College of Cardiology Foundation

Recent clinical trials in patients with heart failure have demonstrated remarkable reductions in mortality and morbidity with the introduction of nitrate and hydralazine, angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers (BBs) (1–4). A common finding has been that the drugs that exert a favorable effect on outcome also result in an increase in ejection fraction (EF) or a reduction in left ventricular (LV) dimension (5–8). This favorable effect on LV chamber size and function has been attributed to regression of structural remodeling (9).

Echocardiography has been performed in some trials as a substudy in a small sample of the overall study population. Although this strategy has made it possible to identify the average effect of the agent under study, the limited sample could only imply a relationship between changes in echocardiographic measurements and outcome, and could not examine the variability of responses in subgroups of the population (10–12).

The objectives of the Valsartan in Heart Failure Trial (Val-HeFT) were to assess the effect of the addition of valsartan (Novartis Pharma AG, Basel, Switzerland), an angiotensin receptor blocker (ARB), on mortality and morbidity, and on secondary end points, including signs and symptoms, quality of life, and neurohormonal and echocardiographic variables in patients already receiving standard therapy, including ACEI and/or BB. The study showed that all-cause mortality was similar for valsartan and placebo patients ($p = 0.801$). However, the valsartan group showed a reduction in combined all-cause mortality and morbidity compared to placebo ($p = 0.009$). Valsartan patients also

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Abbreviations and Acronyms

ACEI	= angiotensin-converting enzyme inhibitor
ANCOVA	= analysis of covariance
ARB	= angiotensin receptor blocker
ANGII	= angiotensin II
BB	= beta-blocker
EF	= ejection fraction
LV	= left ventricular
LVIDd	= left ventricular internal diastolic diameter
LVIDd/BSA	= left ventricular internal diastolic diameter/body surface area
NYHA	= New York Heart Association
RAAS	= renin-angiotensin-aldosterone system
Val-HeFT	= Valsartan in Heart Failure Trial

experienced significant improvements in the symptomatic and quality of life variables (13). The aims of the echocardiographic examination were to evaluate the effect of valsartan on left ventricular internal diastolic diameter (LVIDd) and EF as secondary variables with the entry criteria of >2.9 cm/m^2 and $<40\%$ respectively. With a large recruitment and echocardiography planned for all patients, Val-HeFT provided the advantage of examining the effects of valsartan on ventricular remodeling in the whole population as well as in subgroups, including those based on background drug therapy.

METHODS

In the Val-HeFT echocardiography study, three core laboratories (Los Angeles, Milan, and Stockholm) qualified 291 laboratories based on single and duplicate readings of seven variables: end-systolic and end-diastolic diameters, lengths, and volumes; and EF. The measurements were derived from two-dimensionally directed M-mode recordings from the parasternal short-axis view, and apical four-chamber view using the area-length method. Quality of recording was defined by a scoring system; accuracy of reading, by agreement with core readings; reproducibility, and by agreement between duplicate studies. After randomization, recording quality and reading accuracy of the study end points, LVIDd and EF, were monitored from a random sampling of studies measured at baseline, 4, 12, and 18 months into the trial. The qualifying process brought 95% of the sites to an equivalent level of quality. The monitoring process showed that recording quality and reading accuracy were maintained during the trial. From a retrospective power analysis using the sites' reproducibility and a population of 4,000 patients to 90% power with a significance level of 5%, detectable change between treatment and placebo groups at a single point in time were calculated: the detectable difference for LVIDd was 0.09 cm and for EF, 0.86%. Details have been reported in a method paper (14).

Statistical analyses. Measurements of LVIDd and EF were performed locally at each site and sent to the data center for analysis. LVIDd/BSA values were obtained by adjusting LVIDd by each patient's body surface area (BSA). Analysis of covariance (ANCOVA) was performed to analyze change from baseline in LVIDd/BSA and EF at four, 12, 18, and 24 months, and at end point (last post-randomization observation carried forward). The ANCOVA model applied included effects for treatment group, pooled center, baseline value, baseline use of ACEI and/or BB, and treatment by baseline value interaction. Comparisons between valsartan and placebo were made for all patients and within exploratory subgroups categorized by age, gender, race, and concurrent use of ACEI and BB. Between-treatment comparisons were based on least-squares treatment group means from the ANCOVA, which were adjusted for differences among patients with respect to other effects in the ANCOVA model. All statistical comparisons presented are for a significance level of $p < 0.05$. Between-treatment comparisons of mean change from baseline in blood pressures and heart rates were made at 4, 12, 18, and 24 months, and at end point using ANCOVA.

RESULTS

Baseline characteristics and demographics have already been published, and no clinically relevant differences between the valsartan and placebo groups were found (13,15). Briefly summarized, the study population was predominantly white (90%) and averaged 63 years of age, with a male/female distribution of 4/1. Ninety-eight percent of patients (62% and 36%, respectively) were in New York Heart Association (NYHA) functional class II and III, and ischemia was the etiology of heart failure in 57%. Ninety-three percent of patients were on ACEI therapy and 35% were on BB therapy. The echocardiographic baseline measurements and the distribution of the total population randomized to valsartan and placebo are summarized in Table 1. Baseline LVIDd/BSA and EF were generally equivalent for valsartan and placebo patients, whether considered as a whole or separated into age, gender, race, etiology, NYHA classification, and co-treatment subgroups. This baseline equivalence in EF was also seen between patients taking a BB alone or with an ACEI (+ACEI+BB and +BB−ACEI) and patients not taking a BB (+ACEI−BB and −BB−ACEI) (+ indicates co-treatment; − indicates not a co-treatment) . The overall mean ± SD baseline LVIDd/BSA and EF for valsartan patients were 3.6 ± 0.5 cm/m^2 and 26.6 ± 7.3%, and for placebo patients, 3.7 ± 0.5 cm/m^2 and 26.9 ± 7.0%, respectively.

Figure 1 illustrates the mean changes from baseline in EF and LVIDd/BSA at four, 12, 18, and 24 months, and at end point (last available observation after baseline carried forward) for the two treatment groups. A statistically significant increase in EF ($p = 0.00075$) and decrease in LVIDd/BSA ($p = 0.00002$) were observed with valsartan compared to placebo. With valsartan, EF increased and LVIDd/BSA decreased from baseline values starting at four months and persisting throughout the follow-up period for patients remaining under echocardiographic evaluation. The

Table 1. Baseline LVIDd/BSA and EF*

	LVIDd/BSA (cm/m^2)				EF (%)			
	V	N	P	N	V	N	P	N
All	3.6 ± 0.5	2,511	3.7 ± 0.5	2,499	26.6 ± 7.3	2,509	26.9 ± 7.0	2,499
Age								
<65	3.6 ± 0.5	1,367	3.6 ± 0.5	1,293	26.5 ± 7.3	1,367	26.6 ± 7.3	1,293
≥65	3.7 ± 0.5	1,144	3.7 ± 0.5	1,206	26.7 ± 7.2	1,142	27.2 ± 6.8	1,206
Gender								
M	3.6 ± 0.5	2,007	3.6 ± 0.5	2,000	26.6 ± 7.2	2,006	27.1 ± 7.0	2,000
F	3.9 ± 0.6	504	3.9 ± 0.6	499	26.6 ± 7.6	503	26.0 ± 7.1	499
Race								
White	3.7 ± 0.5	2,255	3.7 ± 0.5	2,271	26.9 ± 7.2	2,253	27.0 ± 7.0	2,271
Black	3.6 ± 0.5	182	3.6 ± 0.5	162	24.3 ± 7.5	182	26.0 ± 7.5	162
Oriental/other	3.8 ± 0.5	74	3.9 ± 0.6	66	22.5 ± 7.3	74	24.2 ± 7.5	66
Etiology								
Ischemic	3.6 ± 0.5	1,446	3.6 ± 0.5	1,419	27.2 ± 7.2	1,444	27.4 ± 6.9	1,419
Non-ischemic	3.7 ± 0.6	1,065	3.7 ± 0.6	1,080	25.8 ± 7.3	1,065	26.2 ± 7.2	1,080
NYHA class								
I–II	3.6 ± 0.5	1,562	3.6 ± 0.5	1,538	27.4 ± 7.0	1,560	27.6 ± 7.0	1,538
III–IV	3.7 ± 0.6	949	3.7 ± 0.5	961	25.2 ± 7.4	949	25.7 ± 7.0	961
Subgroup†								
+ACEI+BB	3.6 ± 0.5	794	3.6 ± 0.5	816	27.2 ± 7.3	794	27.2 ± 7.4	816
+ACEI−BB	3.7 ± 0.5	1,532	3.7 ± 0.5	1,502	26.2 ± 7.3	1,532	26.5 ± 6.9	1,502
+BB−ACEI	3.6 ± 0.5	73	3.6 ± 0.6	67	28.5 ± 7.1	71	28.9 ± 7.0	67
−BB−ACEI	3.7 ± 0.5	112	3.7 ± 0.6	114	27.1 ± 6.4	112	28.6 ± 6.4	114

*The entries are mean ± SD. The varying N between V and P, and between LVIDd/BSA and EF were determined by the data available for the analyses. †Under subgroup, + designates co-treatment, − designates not a co-treatment.

ACEI = angiotensin-converting enzyme inhibitor; BB = beta blocker; EF = ejection fraction; LVIDd/BSA = left ventricular internal diastolic diameter/body surface area; N = number of patients; NYHA = New York Heart Association; P = placebo; V = valsartan.

between-treatment differences in mean change from baseline were statistically significant at all observation periods, with valsartan providing larger increases in EF and larger decreases in LVIDd/BSA than placebo. In the placebo group the increase in EF and decrease in LVIDd progressed continuously for 24 months.

Figure 2 summarizes the mean changes from baseline to end point in EF and LVIDd/BSA for valsartan and placebo

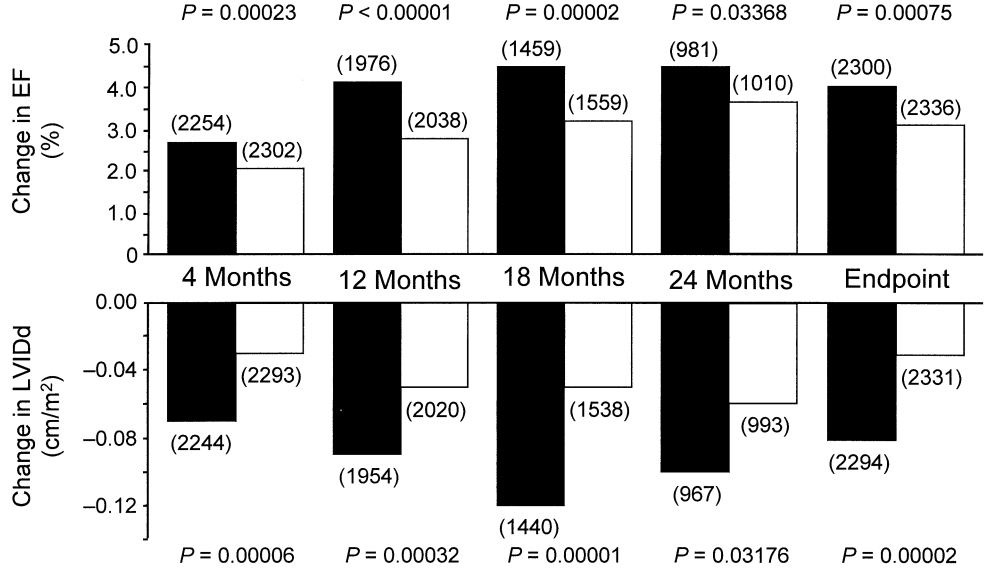

Figure 1. Effects of valsartan on left ventricular internal diastolic diameter/body surface area (LVIDd/BSA) and ejection fraction (EF) compared to placebo: change from baseline to month of observation. The histobars represent mean changes (adjusted for effects for treatment group, pooled center, baseline value, baseline use of angiotensin-converting enzyme inhibitor or beta blocker, and treatment by baseline value interaction by analysis of covariance) between baseline values and those at months 4, 12, 18, 24, and at end point (last observation available carried forward) for valsartan **(black bars)** and placebo **(white bars)**. Baseline values at each observation period are adjusted for the number of patients with available data. Change is expressed in absolute units for EF (%) and LVIDd/BSA (cm/m^2). The p values for the between-treatment comparison are determined from least-squares mean change.

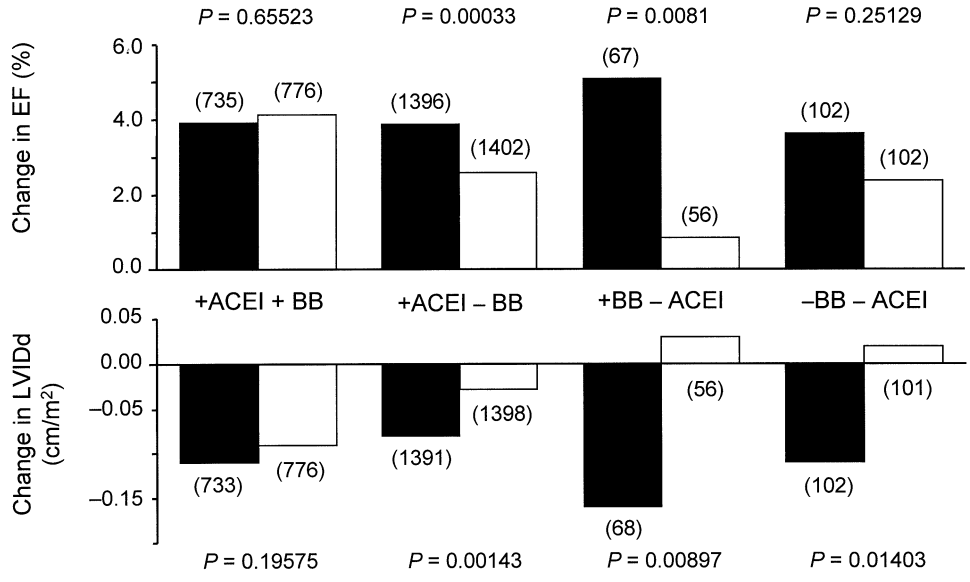

Figure 2. Effects of valsartan on left ventricular internal diastolic diameter/body surface area (LVIDd/BSA) and ejection fraction (EF) compared to placebo by co-treatment group: change from baseline to end point. The histobars represent mean changes (adjusted for effects for treatment group, pooled center, baseline value, baseline use of angiotensin-converting enzyme inhibitor [ACEI] and/or beta-blocker [BB], and treatment-by-baseline value interaction by analysis of covariance) between baseline values and those at end point (last observation available carried forward) for co-treatment subgroups randomized to valsartan **(black bars)** and placebo **(white bars)** groups. Baseline values at each observation period are adjusted for the number of patients with available end point data. Change is expressed in absolute units for EF (%) and LVIDd/BSA (cm/m^2). The p values for the valsartan versus placebo comparison are determined from least-squares mean change. Subgroups are designated by (+) = co-treatment and (−) = not a co-treatment with ACEI and BB.

patients by co-treatment subgroups, +ACEI+BB, +ACEI−BB, +BB−ACEI, and −BB−ACEI with adjustments by ANCOVA. In every group, except those patients taking both ACEI and BB, valsartan produced a rise in EF and a reduction in LVIDd/BSA of significance compared to placebo, with the exception of EF in the relatively small −BB−ACEI group (n = 102) in which the 1.3% unit greater increase in the valsartan group did not reach statistical significance. In the patients taking both co-treatments, valsartan did not produce further improvement in EF and LVIDd/BSA.

Systolic blood pressure was reduced by a greater extent with valsartan than placebo, −5.2 ± 15.8 (mean ± SD) mm Hg versus −1.2 ± 14.8 at four months ($p < 0.0001$), and −5.2 ± 16.0 mm Hg versus −1.3 ± 15.9 at one year ($p < 0.0001$). Valsartan slowed heart rate by 0.3 to 0.8 beats/min more than placebo, with statistically significant differences at month 4 ($p < 0.005$) and 12 ($p < 0.05$).

DISCUSSION

The objective of the Val-HeFT echocardiographic examination was to study the effects of valsartan treatment on LVIDd and EF as secondary outcomes. The results from serial echocardiograms recorded and read locally on 5,010 patients were conclusive: diastolic dimension is reduced and systolic function is improved, both being statistically significant in the group of patients receiving valsartan in addition to their prescribed treatment compared to placebo. Because all of the patients were studied echocardiographically, the relationship between outcomes and LV structure and function was confirmed. In addition, the large volume of studies provided sufficient data to track the relationship between outcomes and LV remodeling in subgroups of patients. The most notable subgroup differences emerged in those treated with different background neurohormonal-inhibiting therapy (13).

In the subgroups treated with either ACEI or BB, or neither, valsartan demonstrated significant baseline-to-end point changes for EF and LVIDd compared to placebo. As previously reported (13), these subgroups exhibited a favorable effect of valsartan on combined morbidity-mortality, and a trend for a benefit on mortality. Valsartan produced similar benefit on remodeling and outcomes in the subgroup not taking ACEI, with or without BB, despite the small population of less than 10% of the total recruitment (Fig. 2). In distinct contrast, in the subgroup treated with both ACEI and BB, valsartan showed no effect on LV remodeling and, as previously reported, showed a trend for an adverse effect on morbidity and mortality.

Background therapy probably played a role in the unusually positive placebo effect on LVIDd and EF. The sustained two-year decrease in LV diameter and increase in LV emptying may reflect a delayed response to co-treatment, particularly to BB, which require several months to achieve maximum change in LV remodeling and function (16). Both the design of the study, which mandated stability of background treatment for only two to four weeks, and the baseline findings, which found patients taking BB and not taking BB to have equivalent EF and LVIDd, corroborate a delayed response to co-treatment in the placebo group.

The mechanism of the favorable effect of valsartan on outcome and LV remodeling must remain conjectural;

however, the results suggest that angiotensin II (ANGII) contributes to the progression of heart failure even in patients treated with ACEI and BB, both of which act to inhibit the renin-angiotensin-aldosterone system (RAAS). Because ANGII is formed by angiotensin-converting enzyme and non–angiotensin-converting enzyme pathways, distal blockade with an ARB provides more complete blockade of the RAAS (17). Although ANGII acts at multiple sites, a plausible mechanism of valsartan action is on ANGII that directly affects the structural abnormalities in the left ventricle by its known mitogenic effect (18–20). As valsartan also lowered systolic blood pressure by an average of 5 mm Hg, afterload reduction cannot be excluded as a factor in the anti-remodeling result. The experience with vasodilators is mixed, with prazosin producing a sustained blood pressure fall without improving EF (21), and felodipine lowering blood pressure and increasing EF from the same LVIDd (22). Nevertheless, ANGII is ubiquitous and any proposed mechanism for ARB reversing remodeling becomes inferential.

Val-HeFT provided convincing evidence that additional inhibition of the RAAS with an ARB in heart failure can improve LV structure and function beyond that affected by prescribed therapy, including ACEI or BB alone. Val-HeFT also demonstrated that given the low annual mortality of 9% in the placebo subgroup taking prescribed treatment, it is unlikely that future trials can target mortality as a primary end point. The link between the echocardiographic results and a benefit on the morbidity-mortality end point strongly supports regression of LV remodeling as a surrogate marker for a favorable prognosis, for future design of clinical trials, and for guiding efficacy of heart failure therapy.

Conclusions. The benefit on outcome in Val-HeFT was accompanied by echocardiographic evidence for regression of LV remodeling. The background therapy subgroup that had an unfavorable outcome had no effect on remodeling. The trial results further illustrate the usefulness of monitoring structural changes in the left ventricle as a guide to long-term efficacy in heart failure treatment.

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