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Effects of Valsartan on Morbidity and Mortality in Patients With Heart Failure Not Receiving Angiotensin-Converting Enzyme Inhibitors

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OBJECTIVES A subgroup analysis of the Valsartan Heart Failure Trial (Val-HeFT) was performed to evaluate the effects of the angiotensin II receptor blocker, valsartan, in the patients with chronic heart failure (HF) not receiving angiotensin-converting enzyme (ACE) inhibitors.

BACKGROUND The ACE inhibitors reduce mortality and morbidity in patients with HF. Nonetheless, nearly 20% of potentially eligible patients may not be prescribed ACE inhibitors.

RESULTS Val-HeFT was an international, randomized, double-blinded trial that compared valsartan with placebo when added to the prescribed treatment of patients with HF. The two primary end points of the study were all-cause mortality and the composite of all-cause mortality and morbidity (sudden death with resuscitation, hospital admission for HF, or administration of intravenous inotropic or vasodilator drugs for ≥4 h without hospital admission). Of the 5,010 patients enrolled in the trial, 366 (7.3%) were not treated with ACE inhibitors at baseline. The effects of valsartan on the primary and secondary end points of the study were assessed in this subgroup of patients.

RESULTS Both all-cause mortality and combined mortality and morbidity for patients not treated with ACE inhibitors were significantly reduced in the valsartan treatment group compared with the placebo group (17.3% vs. 27.1%, $p = 0.017$ and 24.9% vs. 42.5%, $p < 0.001$, respectively). Consistent with the data on clinical events, patients randomized to valsartan showed improvements in physiologic variables, such as ejection fraction, left ventricular internal diameter in diastole, and plasma neurohormone levels. Permanent discontinuation of study treatment because of adverse experiences was comparable between the two groups.

CONCLUSIONS Val-HeFT has provided the first placebo-controlled outcome data demonstrating a favorable effect of an angiotensin receptor blocker on mortality and morbidity in patients with HF not treated with ACE inhibitors. Based on these results, valsartan appears to be an effective therapy in ACE inhibitor-intolerant patients. (J Am Coll Cardiol 2002;40:1414–21)
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Angiotensin-converting enzyme (ACE) inhibitors reduce the mortality and morbidity of patients with chronic heart failure (HF) (1). The mechanisms of the beneficial effect of ACE inhibitors are not fully established, but it is likely that inhibition of angiotensin II production is at least partially responsible (2,3). However, nearly 20% of potentially eligible patients are not prescribed ACE inhibitors, presumably because of actual or perceived intolerance to the drug (4,5).

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Angiotensin receptor blockers (ARBs) produce a more complete blockade of the effects of angiotensin II by a combination of both ACE-dependent and non–ACE-dependent pathways, but they lack some of the effects thought to be important to the benefits of ACE inhibitors, such as inhibition of bradykinin degradation (6). Moreover, patients intolerant to ACE inhibitors appear to tolerate ARBs relatively well (7). However, it is not clear whether the treatment of ACE inhibitor-intolerant patients with ARBs leads to a reduction in morbidity and mortality.

The Valsartan Heart Failure Trial (Val-HeFT) showed that the ARB, valsartan, significantly reduced the combined end point of mortality and morbidity by 13.2% when added to the prescribed therapy of patients with HF (8,9). In this trial, 7% of the patients were not receiving an ACE inhibitor as part of their background therapy (9). Although the reasons for withholding an ACE inhibitor in this group were not established, given the kind of centers involved and the high rate of ACE inhibitor usage in the overall population, it is likely that ACE inhibitor intolerance was the most common reason.

This report evaluates the effects of valsartan in patients not receiving ACE inhibitors on the primary end point of all-cause mortality and the composite end point of all-cause mortality and morbidity, defined as sudden death with

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ARB	= angiotensin receptor blocker
BNP	= brain natriuretic peptide
BSA	= body surface area
HF	= heart failure
LSM	= least squares mean
LVEF	= left ventricular ejection fraction
LVIDD	= left ventricular internal diastolic diameter
MLHFQ	= Minnesota Living with Heart Failure Questionnaire
Val-HeFT	= Valsartan Heart Failure Trial

resuscitation, hospital admission for HF, or administration of intravenous inotropic or vasodilator drugs for ≥4 h without hospital admission. The effects of valsartan were also evaluated in terms of neurohormone levels, left ventricular internal diastolic diameter (LVIDD) adjusted for body surface area (BSA), left ventricular ejection fraction (LVEF), and quality of life.

METHODS

Design and eligibility. Val-HeFT was a randomized, placebo-controlled, double-blinded, parallel-arm trial. A detailed description of the study protocol has been reported elsewhere (8). A total of 5,010 patients were randomized to either valsartan or placebo. The investigation conformed to the principles of the Declaration of Helsinki.

Men and women ≥18 years old with a history and clinical findings of HF for at least three months before screening were eligible. Patients were in New York Heart Association (NYHA) functional classes II to IV, were clinically stable, and were receiving a fixed-dose drug regimen that might include ACE inhibitors, diuretics, digoxin, and beta-blockers for at least two weeks. To be included in the trial, patients had to have documented LVEF <40% and echocardiographically measured LVIDD/BSA >2.9 cm/m^2. Echocardiograms were analyzed locally after each center underwent validation of technical and reader quality by centralized core laboratories that also monitored quality during the study.

The present analysis is focused on the 366 patients (7.3% of the total trial population) who were not treated with ACE inhibitors.

Placebo run-in period and dose titration. Patients were assessed for two to four weeks to confirm their eligibility, stability, and compliance while taking single-blinded placebo twice daily. Valsartan was initiated at 40 mg twice daily and was doubled every two weeks to a target dose of 160 mg twice daily. Criteria for upward titration included standing systolic blood pressure of ≥90 mm Hg, no symptoms of hypotension, and serum creatinine <2.0 mg/dl or no greater than 50% above baseline. Patients were stratified according to their use of beta-blockers as part of their background therapy for chronic HF.

Follow-up. Patients returned for follow-up at two, four, and six months and every three months thereafter. Physical examination, review of symptoms, and adverse events were assessed at each visit; quality-of-life assessment was performed at one, four, and six months and every three months thereafter; hematology, blood chemistry, and urinalysis were performed at 4 and 6 months and every 6 months thereafter; echocardiograms were obtained at 4 and 12 months and every 6 months until the end of the study. Blood samples for brain natriuretic peptide (BNP) and norepinephrine assays were collected at 4, 12, and 24 months and at study end.

Outcome measures. The study was designed with two primary end points: time to death and time to composite end point of first mortality or morbidity, defined as death, sudden death with resuscitation, hospital admission for HF, or administration of intravenous inotropic or vasodilator drugs for ≥4 h without hospital admission. The events considered in the two primary end points were centrally validated by the independent End Points Committee.

Secondary end points included changes in the following from baseline to end point (last available observation after randomization): ejection fraction, left ventricular end-diastolic volume adjusted for BSA, quality-of-life scores, and neurohormonal profile.

Quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) in centers in the U.S., U.K., Australia, and Italy, where the questionnaire has been validated.

A Val-HeFT substudy evaluated exercise capacity by the 6-min walk test after four months of double-blinded treatment. Of the 633 patients included in the substudy, 35 were not receiving ACE inhibitors as background therapy.

Statistical analysis. Inter-treatment comparisons of the primary end points for patients not treated with an ACE inhibitor were made using the log-rank test, and relative risks with 95% confidence intervals were obtained for these comparisons using a Cox regression model with prespecified baseline co-variates, including NYHA class, ejection fraction (above or below the median value), cause of HF (ischemic or nonischemic), age (<65 or ≥65 years old), and beta-blocker use or nonuse. Inter-treatment comparisons for the first occurrence of the secondary mortality/morbidity end points were also made using the log-rank test, and relative risks for these variables were obtained from the Cox regression model described earlier.

Inter-treatment comparisons for BNP, norepinephrine, LVEF, LVIDD, and MLHFQ, as well as for the substudy analysis of 6-min walk test, were made for patients not treated with an ACE inhibitor, by using analysis of covariance (ANCOVA) adjusted for geographic region (U.S. or non-U.S.), baseline values, beta-blocker usage (yes or no), and treatment–baseline interaction. Changes over time from baseline at each analyzed time point were expressed as the least squares mean (LSM) value, based on the corresponding ANCOVA.

Inter-treatment comparisons of sudden deaths and rea-

Table 1. Baseline Characteristics of Patient Receiving or Not Receiving Angiotensin-Converting Enzyme Inhibitors

		Non–ACE Inhibitor Group		
	ACE Inhibitor Group (n = 4,644)	**Total (n = 366)**	**Valsartan (n = 185)**	**Placebo (n = 181)**
Age (yrs)	62.3 ± 11.0*	67.2 ± 10.4	66.6 ± 10.3	67.7 ± 10.4
Age ≥65 yrs (%)	45.6*	63.4	60.0	66.9
Females (%)	19.3*	28.7	24.3	33.1
Whites (%)	90.0*	95.1	95.1	95.0
NYHA class III–IV (%)	37.4*	47.0	41.1	53.0†
Ischemic etiology (%)	56.4*	67.5	69.2	65.7
Duration HF (months)				
Median	36.0	36.0	36.0	36.0
Mean ± SD	50.8 ± 50.6*	56.3 ± 58.0	57.8 ± 61.9	54.8 ± 53.9
Beta-blockers (%)	34.7	38.3	39.5	37.0
SBP (mm Hg)	124 ± 19*	126 ± 18	128 ± 19	125 ± 18
DBP (mm Hg)	76 ± 11	76 ± 10	77 ± 9	75 ± 11†
HR (beats/min)	73 ± 13	73 ± 12	73 ± 12	73 ± 13
S_3 (%)	25.7	27.6	21.6	33.7†
LVEF (%)	26.6 ± 7.2*	28.2 ± 6.7	27.6 ± 6.7	28.7 ± 6.6
LVIDD/BSA (cm/m^2)	3.7 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.7 ± 0.6
MLHFQ score	32.2 ± 22.9 (n = 2,881)	35.2 ± 23.8 (n = 220)	35.0 ± 21.9 (n = 115)	35.3 ± 25.8 (n = 105)
Serum creatinine (μmol/l)	113.43 ± 27.17 (n = 4,637)	115.51 ± 30.35 (n = 366)	113.20 ± 28.24 (n = 185)	117.86 ± 32.28 (n = 181)
Norepinephrine (pg/ml)	462 ± 325 (n = 3,989)	491 ± 295 (n = 312)	480 ± 296 (n = 159)	502 ± 293 (n = 153)
BNP (pg/ml)	179 ± 231 (n = 3,993)	199 ± 219 (n = 312)	205 ± 206 (n = 159)	192 ± 232 (n = 153)
Aldosterone (pg/ml)	132 ± 120* (n = 3,929)	190 ± 197 (n = 311)	163 ± 173 (n = 159)	218 ± 216† (n = 152)
Plasma renin activity (ng/ml per h)	15.1 ± 24.3* (n = 3,978)	4.2 ± 7.3 (n = 313)	4.0 ± 6.9 (n = 159)	4.3 ± 7.7 (n = 154)

*Statistically significant at $p < 0.05$ when comparing ACE inhibitor group versus non–ACE inhibitor group. †Statistically significant at $p < 0.05$ when comparing valsartan versus placebo in non–ACE inhibitor group. Data are presented as the mean value ± SD or percentage of patients.

ACE = angiotensin-converting enzyme; BNP = brain natriuretic peptide; DBP = sitting diastolic blood pressure; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; LVIDD/BSA = left ventricular internal diastolic diameter/body surface area; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; SBP = sitting systolic blood pressure; S_3 = third heart sound.

sons for permanent treatment discontinuation in patients not treated with an ACE inhibitor were made using the chi-square test. Inter-treatment comparisons for patients not treated with an ACE inhibitor were based on the Cochran-Mantel-Haenszel test for the number of hospital admissions, stratified for beta-blocker usage and NYHA class (I/II vs. III/IV), using modified ridit scores. Baseline comparisons of ACE inhibitor versus non–ACE inhibitor treatment and valsartan versus placebo within the non–ACE inhibitor group were made using the chi-square and F tests. A two-sided significance level of 0.05 was used for all non–ACE inhibitor subgroup tests.

RESULTS

Of the 5,010 patients randomized in the Val-HeFT trial, 366 (7.3%) were not receiving an ACE inhibitor at randomization.

Table 1 shows the baseline characteristics of patients receiving and not receiving ACE inhibitors. Patients not prescribed an ACE inhibitor were older and more frequently female and had more severe HF (NYHA class III/IV), a higher rate of ischemic etiology, and higher LVEF and systolic blood pressure at baseline. However, heart rate, S_3 gallop, and LVIDD/BSA were similar in patients receiving and not receiving ACE inhibitors. Patients not receiving an ACE inhibitor had higher levels of circulating aldosterone and lower levels of plasma renin activity than did patients receiving ACE inhibitors, although circulating levels of norepinephrine and BNP were similar.

There were few distinguishable differences in the baseline summary characteristics of patients not treated with an ACE inhibitor who were randomized to valsartan or placebo, except that more patients in the placebo group were in NYHA class III/IV ($p = 0.022$) and had more frequent S_3 gallop ($p = 0.010$), lower baseline diastolic blood pressure ($p = 0.024$), and higher baseline aldosterone levels ($p = 0.006$). The overall mean duration of observation for patients not treated with an ACE inhibitor was 22.68 months (range 0.03 to 36.73).

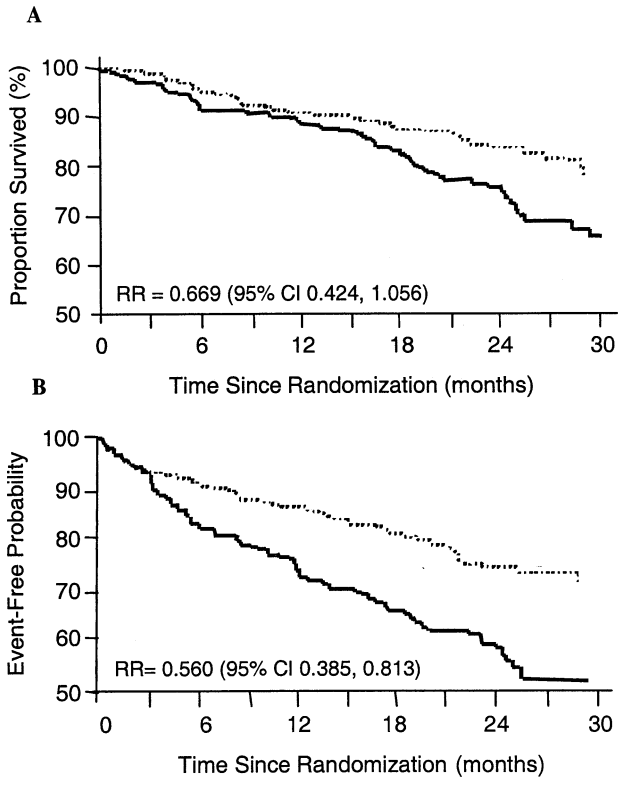

Figure 1. (A) Kaplan-Meier curves for mortality in the valsartan **(dotted line)** and placebo **(solid line)** groups (n = 185 and 181, respectively) without angiotensin-converting enzyme (ACE) inhibitor background therapy (p = 0.017 by log-rank test). **(B)** Kaplan-Meier curves for the combined end point of mortality and morbidity in the valsartan **(dotted line)** and placebo **(solid line)** groups without ACE inhibitor background therapy (p < 0.001 by the log-rank test). Risk ratio (RR) and 95% confidence interval (CI) obtained using Cox regression.

Effects of valsartan on mortality, morbidity, and hospital admission. Both all-cause mortality and the composite end point of mortality and morbidity for patients not treated with an ACE inhibitor were significantly reduced in the valsartan treatment group as compared with the placebo group (Fig. 1, Table 2A). All-cause mortality was 17.3% in the valsartan group and 27.1% in the placebo group (reducing the relative risk by 33%, p = 0.017), and the rates of first hospital admission for HF were 13.0% and 26.5% in the valsartan and placebo groups, respectively (reducing the relative risk by 53%, p = 0.0006). Sudden death was the most frequent type of death in both the valsartan and placebo groups: 16 of 32 deaths and 19 of 49 deaths, respectively. There were very few sudden deaths with resuscitation and use of intravenous inotropic therapy. The favorable effect of valsartan on mortality and the composite end point of morbidity and mortality was observed both in the 140 patients receiving beta-blockers (relative risk reductions of 19% [p = NS] and 42%, respectively) and in the 226 patients not receiving beta-blockers (relative risk reductions of 42% and 44%, respectively).

Valsartan significantly reduced the total number of hospital admissions for HF, both those adjudicated as primary events and those classified by investigators, but had no effect on total hospital admissions for reasons other than HF (Table 2B).

Effects of valsartan on secondary variables and other clinical events. The LVEF increased over time in both treatment groups, but the increase was significantly greater in patients randomized to valsartan than in those randomized to placebo (Fig. 2A). Valsartan also decreased the

Table 2. Clinical Events in Patients Not Treated With Angiotensin-Converting Enzyme Inhibitors: A) Mortality and Morbidity End Points and B) Total Investigator-Assessed Hospital Admissions

A	Valsartan Group (n = 185)	Placebo Group (n = 181)	RR*	95% CI*	p Value†
Primary end points					
All-cause mortality	32 (17.3%)	49 (27.1%)	0.67	0.42–1.06	0.017‡
Mortality/morbidity	46 (24.9%)	77 (42.5%)	0.56	0.39–0.81	< 0.001‡
Secondary mortality/morbidity end points (first occurrence)					
Cardiovascular deaths	29 (15.7%)	40 (22.1%)	0.76	0.46–1.24	0.074
Nonfatal morbid event	24 (13.0%)	49 (27.1%)	0.46	0.28–0.76	< 0.001‡
Sudden death with resuscitation	1 (0.5%)	2 (1.1%)	0.46	0.04–5.25	0.529
Therapy for HF	0	1 (0.6%)	—	—	—
Hospital admission for HF	24 (13.0%)	48 (26.5%)	0.47	0.29–0.78	< 0.001‡
B	**Valsartan**	**Placebo**	**Diff.§**	**% Diff.**	**p Value¶**
Hospitalization cause					
All-cause	199	262	−63	−24.0	0.260
HF	51	117	−66	−56.4	0.010‡
Non–HF	148	145	3	2.1	0.567

*Risk ratio (RR) and 95% confidence interval (CI) obtained using Cox regression, adjusting for New York Heart Association (NYHA) class, left ventricular ejection fraction baseline beta-blocker usage, etiology, and age group. †Based on log-rank tests. ‡Statistically significant at p < 0.05. §Difference (valsartan − placebo); % Diff = 100 × Diff/placebo. ¶Based on the Cochran-Mantel-Haenzel test for the number of hospital admissions stratified by beta-blocker usage and NYHA class, using modified ridit scores.

HF = heart failure.

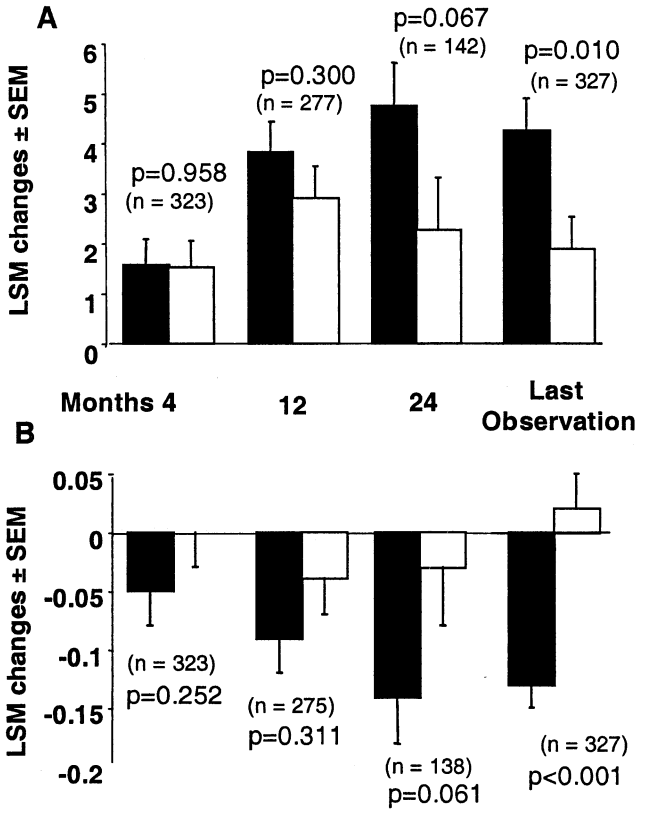

Figure 2. Echocardiographic changes over time. **(A)** Least squares mean (LSM) change (±SEM) from baseline in left ventricular ejection fraction (%). **(B)** LSM change from baseline in left ventricular internal diastolic diameter/body surface area (cm/m^2). The p values refer to the LSM comparison between the valsartan **(solid bars)** and placebo **(open bars)** groups by analysis of co-variance. n = total number of patients in the valsartan and placebo treatment groups.

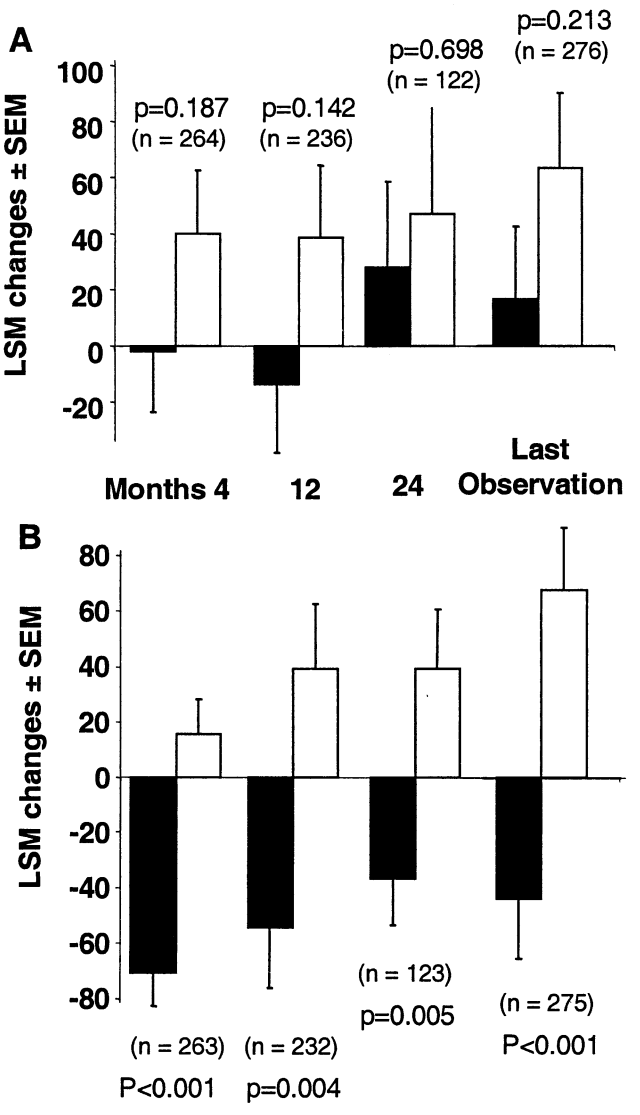

Figure 3. Neurohormonal changes over time: least squares mean (LSM) changes from baseline in the plasma concentrations of norepinephrine **(A)** and BNP **(B)**. The p values refer to the LSM comparison between the valsartan **(solid bars)** and placebo **(open bars)** groups by analysis of co-variance. n = total number of patients in the valsartan and placebo treatment groups.

LVIDD/BSA over time (Fig. 2B). At the last available observation, patients randomized to valsartan had a significantly smaller mean LVIDD/BSA than did patients randomized to placebo.

A favorable effect of valsartan was also observed on plasma BNP and norepinephrine levels (Figs. 3A and 3B). Valsartan tended to attenuate the increase in norepinephrine levels over time and significantly reduced the levels of BNP over time, as compared with the placebo group. The MLHFQ was administered to 57% of patients not prescribed an ACE inhibitor (n = 209). Valsartan improved the MLHFQ score for these patients throughout the course of the trial, although the difference was statistically significant only at one year (Table 3).

The favorable effects of valsartan on clinical and physiologic end points were accompanied by a significant reduction in sitting systolic blood pressure, as compared with placebo (Table 3). This blood pressure-lowering effect was not associated with any reflex increase in heart rate.

With respect to the 35 patients included in the substudy on exercise capacity, there was a statistically significant increase in the walk distance in valsartan-treated patients as compared with those who received placebo (50.3-m increase with valsartan vs. 34.2-m decrease with placebo; LSM treatment difference of 84.4 m; p = 0.022)

Safety profile. Table 4 shows the rate of permanent discontinuation of study treatments. Overall, 82.7% and 75.1% of patients not treated with an ACE inhibitor randomized to valsartan or placebo, respectively, remained on study treatment until the end of the follow-up period. Permanent study treatment discontinuation due to adverse events were comparable between the two groups. The rates of treatment discontinuation due to symptomatic hypotension and renal dysfunction were not different between the two treatment groups, and none of the patients experienced angioedema or cough.

The most common adverse events, regardless of study

Table 3. Changes in Quality of Life (Assessed by the MLHFQ), Sitting SBP, and HR in Patients Not Treated With Angiotensin-Converting Enzyme Inhibitors

	Valsartan	Placebo	p Value
Change in MLHFQ score (LSM ± SEM)			
One year	−4.15 ± 1.78 (n = 86)	1.01 ± 2.11 (n = 73)	0.047*
Two years	−1.07 ± 2.30 (n = 48)	5.62 ± 3.18 (n = 27)	0.078
Last observation	−0.98 ± 1.71 (n = 112)	3.17 ± 1.98 (n = 97)	0.095
SBP (mm Hg) (LSM ± SEM)			
One year	−7.5 ± 1.1 (n = 150)	−0.5 ± 1.2 (n = 133)	< 0.001*
Two years	−8.4 ± 1.8 (n = 97)	0.6 ± 2.0 (n = 76)	0.001*
Last observation	−8.1 ± 1.2 (n = 184)	−3.2 ± 1.2 (n = 180)	0.004*
HR (beats/min) (LSM ± SEM)			
One year	−2.4 ± 0.8 (n = 150)	−0.3 ± 0.8 (n = 133)	0.065
Two years	−2.4 ± 1.0 (n = 97)	−3.6 ± 1.2 (n = 76)	0.430
Last observation	−0.6 ± 0.8 (n = 184)	−0.6 ± 0.8 (n = 180)	0.974

*Statistically significant at $p < 0.05$. Data are presented as the least squares mean (LSM) change ± SEM by analysis of co-variance.

HR = heart rate; LSM = least squares mean; MLHFQ = Minnesota Living With Heart Failure Questionnaire; SBP = sitting systolic blood pressure.

drug relationship, were dizziness (excluding vertigo) (44 [23.9%] for valsartan vs. 34 [18.9%] for placebo) and hypotension (27 [14.7%] for valsartan vs. 10 [5.6%] for placebo).

With respect to renal function, serum creatinine levels increased from baseline to the last available evaluation in both the valsartan and placebo groups. The mean increase was slightly but significantly higher in the valsartan group than in the placebo group (0.18 ± 0.02 vs. 0.10 ± 0.02 mg/dl, $p = 0.009$).

DISCUSSION

The present analysis of Val-HeFT suggests that valsartan is effective in reducing all-cause mortality and hospital admissions for HF in patients not prescribed ACE inhibitors as part of their background therapy. This was accompanied by a significant increase in LVEF, a decrease in LVIDD/BSA and BNP levels, and an attenuation of the increase in the plasma norepinephrine concentration over time in the valsartan group as compared with the placebo group. Sitting systolic blood pressure was significantly lower in the valsartan group at one and two years and at study end. The overall incidence of adverse events was not significantly different between the valsartan and placebo groups. Quality of life was significantly improved in the valsartan group at one year, with a trend toward sustained improvement at two years and study conclusion. In patients receiving ACE inhibitors, there was a trend toward a reduction in the composite mortality/morbidity end point (relative risk 0.901, $p = 0.096$), although the effect on all-cause mortality was neutral (data on file at Novartis Pharma AG, Basel, Switzerland).

Previous studies have suggested that significant numbers of patients with HF are not being treated with ACE inhibitors, despite clear evidence of a benefit from their utilization (4,10–14). In the Study of Patients Intolerant of Converting Enzyme inhibitors (SPICE) registry (4) and other data bases, nearly 20% of patients with depressed left ventricular function, as monitored by cardiologists, were not prescribed ACE inhibitors because of a perceived drug intolerance (2,14). In Val-HeFT, the proportion of the population receiving an ACE inhibitor was high (93%). This was probably because patients who had been prescribed an ARB (increasingly used in ACE inhibitor–intolerant patients) were excluded.

Patients who were enrolled in Val-HeFT and not prescribed ACE inhibitors, most likely due to contraindications or drug intolerance, have a baseline risk profile that is worse than that of patients treated with ACE inhibitors. This observation is consistent with that seen in the SPICE registry, in which 9,580 patients at 105 centers in eight countries were included. In that study, patients not prescribed ACE inhibitors were older and had indicators of more severe HF, as well (4).

The small pilot trial that followed the SPICE registry showed that short-term treatment (12 weeks) with cande-

Table 4. Permanent Study Treatment Discontinuations

	Valsartan (n = 185)	Placebo (n = 181)	Total (n = 366)	p Value*
Adverse events	18 (9.7%)	23 (12.7%)	41 (11.2%)	0.367
Life-threatening laboratory abnormalities	1 (0.5%)	1 (0.6%)	2 (0.5%)	0.988
Hypotension†	1 (0.5%)	1 (0.6%)	2 (0.5%)	0.988
Other	12 (6.5%)	20 (11.1%)	32 (8.7%)	0.122
Total	32 (17.3%)	45 (24.9%)	77 (21.0%)	0.076

*By chi-square test. †Persistent standing systolic blood pressure <80 mm Hg or symptoms of hypotension.

sartan was tolerated as well as placebo in patients with a documented intolerance to ACE inhibitors (7). However, until now, evidence from randomized trials of the efficacy of ARBs on morbidity and mortality in this high-risk chronic HF population has been lacking.

Val-HeFT tested the effects of valsartan versus placebo on top of the prescribed therapy for patients with chronic symptomatic HF, depressed left ventricular function, and left ventricular dilation (8). In the patients not treated with an ACE inhibitor included in the present analysis, 80% were receiving diuretics, 38% beta-blockers, 59% digoxin, and 7% spironolactone. Analysis of this subgroup allowed a randomized comparison of the effect of valsartan on morbidity, mortality, and physiologic measures, such as the neurohormonal profile, left ventricular function, and quality of life.

Despite the relatively low number of patients included in this analysis, the significant reduction in morbidity and mortality with the use of valsartan in patients not prescribed ACE inhibitors confirms the pathogenetic role of the renin-angiotensin-aldosterone system in the progression of HF and its influence on the outcome of patients with HF.

Patients randomized to valsartan showed improvements in terms of physiologic end points, consistent with the beneficial effects on clinical events. These observations further strengthen the reliability of the results and provide information on the possible mechanisms that underlie the benefits of valsartan. The improved neurohormonal profile and the significant reduction in blood pressure confirm the importance of the modulation of the renin-angiotensin-aldosterone system and suggest that both hemodynamic and neurohormonal effects played a role in determining the beneficial effects of ARBs in these patients. These pharmacologic actions are also likely to be determinants of the improvement in left ventricular function, as documented by the significant increase in LVEF. Together, these positive effects were associated with a better quality of life and increased survival.

In this population of patients at high risk of clinical events, the favorable effect of valsartan appears to be similar to that obtained with ACE inhibitors, when these drugs were compared with placebo (15,16). In the present study, the patients not treated with an ACE inhibitor who were randomized to valsartan showed a reduction in the relative risk of all-cause mortality of 33%, a figure very similar to that observed (27%) for patients receiving enalapril in the COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS) (15). It is also interesting that the reduction in sitting systolic blood pressure was similar for the patients treated with valsartan (but not ACE inhibitors) in Val-HeFT and those treated with enalapril in the Studies Of Left Ventricular Dysfunction (SOLVD), thus confirming the importance of angiotensin in supporting blood pressure in HF.

An important feature of ARBs is their low adverse-effect profile. The favorable effects of valsartan were obtained without the occurrence of relevant adverse reactions. Nearly 83% of patients not treated with an ACE inhibitor who were randomized to valsartan completed the trial without permanently discontinuing treatment, and 77% were titrated to the target dose of 320 mg/day. Unexpectedly, the number of patients not treated with an ACE inhibitor who discontinued valsartan was lower than the number of patients randomized to placebo. A similar tolerability profile was observed in the SPICE trial, where 270 patients with HF intolerant to ACE inhibitors were treated with candesartan, but only for a short period (12 weeks) (7).

There are some limitations to be noted in the present analysis of patients not treated with an ACE inhibitor in the Val-HeFT data base. Although the size of the non–ACE inhibitor group was small, the consistent direction and magnitude of the effects favoring valsartan, in terms of clinical and physiologic end points, together with the pharmacologic and pathophysiologic rationale on its use in these patients, tend to make these observations interesting and potentially acceptable for recommendations in clinical practice. In any case, as suggested by previous contradictory conclusions derived from underpowered studies (17,18), these results should be interpreted with caution and need to be confirmed in larger randomized trials, and in this respect, the final results of the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) trial are awaited with great interest (19).

Clinical implications and conclusions. The findings of this analysis of the Val-HeFT data base suggest that valsartan can improve morbidity and mortality in patients not treated with ACE inhibitors, but with other background therapy, including beta-blockers. Valsartan not only inhibits this system effectively, but also has an excellent safety profile in this group of high-risk patients. Although this subgroup of patients from Val-HeFT is small, the preliminary findings suggest that valsartan can serve as a safe, effective substitute for ACE inhibitors in the management of HF.

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