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The European Journal of Heart Failure 6 (2004) 937–945

The European Journal of Heart Failure

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Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT

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Received 6 May 2004; received in revised form 12 August 2004; accepted 20 September 2004

Abstract

Aims: To investigate the effect of valsartan in the Valsartan-Heart Failure Trial (Val-HeFT) when added to angiotensin-converting enzyme inhibitor (ACEi) alone in patients with heart failure (HF).
Methods: Subjects in Val-HeFT receiving ACEi but not beta-blocker at baseline were analysed; 1532 were assigned to valsartan and 1502 assigned to placebo. Primary outcome events (all-cause mortality, hospitalisation for adjudicated heart failure, sudden death with resuscitation and need for >4 h of parenteral therapy for worsening heart failure) were monitored.
Results: Mortality was not affected by valsartan but morbidity endpoints were significantly reduced (36.3% in placebo, 31.0% in valsartan, p=0.002) in patients receiving an ACEi but no beta-blocker. Quality of life (QOL) was significantly improved, ejection fraction (EF) significantly increased, left ventricular (LV) diameter significantly reduced and plasma B-type natriuretic peptide, norepinephrine and aldosterone levels significantly reduced with valsartan compared to placebo. The morbidity benefit was significant in patients on ACEi doses below the median (22% reduction, p=0.003) and not statistically significant in those receiving ACEi doses above the median (14% reduction, p=0.143).
Conclusion: Valsartan reduces heart failure hospitalisations and slows LV remodelling in patients treated with an ACEi in the absence of beta-blockade, particularly in those on lower doses of ACEi.

Keywords: Chronic heart failure; Valsartan; Angiotensin receptor blockade; ACE-inhibition; Mortality

1. Introduction

Renin–angiotensin system (RAS) activation is characteristic of patients with heart failure (HF) [1] and angiotensin II exerts a variety of physiologic and structural effects that are likely to aggravate HF and contribute to its progression. Indeed, inhibition of the RAS has been the goal of angiotensin-converting enzyme inhibitor (ACEi) therapy. The efficacy of ACEi in reducing morbidity and mortality [2,3] has resulted in the recommendation that all patients with HF should be treated with these agents [4–6]. ACEi therapy is usually followed by beta-blocker (BB) treatment, although the most efficacious sequence of administration of the two drugs is currently under investigation [7].

In the Valsartan-Heart Failure Trial (Val-HeFT), the addition of the angiotensin receptor blocker (ARB) valsartan

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doi:10.1016/j.ejheart.2004.09.005

to background therapy in HF resulted in a 13.2% reduction in the combined endpoint of morbidity and mortality in comparison to placebo [8]. In the subgroup of patients not receiving an ACEi, a benefit on mortality as well as combined morbidity/mortality was noted [9]. However, background therapy with both ACEi and BB therapy unexpectedly influenced outcomes negatively in subgroups defined by these therapies. This interaction was not observed in the Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM)-Added trial [10] or the recently reported Valsartan in Acute Myocardial Infarction (VALIANT) trial [11]. These findings have stimulated us to examine the effect of RAS inhibiting therapies on clinical outcomes and physiologic parameters of patients in this trial.

Recent evidence indicates that ACEi administered in usually recommended doses does not produce sustained suppression of circulating angiotensin II levels [12,13]. On the other hand, BBs are potent renin inhibitors that have been reported to produce profound suppression of angiotensin II levels when administered in combination with an ACEi [14]. Thus, ARBs should block the persistent angiotensin II effect and exert clinical benefit when administered to patients with HF receiving ACEi but not BB.

We therefore have examined the Val-HeFT data to evaluate the efficacy of valsartan in patients already treated with an ACEi but not a BB. Furthermore, we have explored the effect of the background dose of ACEi on the response to valsartan in these patients.

2. Methods

The study design and overall results for Val-HeFT have previously been published [8,15]. In short, patients receiving prescribed background therapy for HF were eligible if they had NYHA class II–IV symptoms, an echocardiographic ejection fraction (EF) of <40% and a left ventricular internal diameter in diastole (LVIDd) of >2.9 cm/m^2 adjusted for body surface area (BSA).

After a 2–4-week single-blind placebo run-in period to confirm stability and reliability, patients were randomly assigned to receive placebo or valsartan at a starting dose of 40 mg b.i.d., doubled every 2 weeks to the target dose of 160 mg b.i.d., in addition to their existing background therapy. Up-titration criteria required standing systolic blood pressure ≥90 mm Hg, no serum creatinine increase >50% from baseline to a value >2.0 mg/dL and no hypotensive symptoms (syncope, faintness, orthostatic dizziness).

Patients were assessed at 2, 4 and 6 months, and every 3 months thereafter including quality of life (QOL) assessments, NYHA class, adverse events and occurrence of permanent discontinuation of study medication until trial end or death. Echocardiograms were performed at 4 and 12 months, then every 6 months thereafter. Neurohormonal parameters (B-type natriuretic peptide, norepinephrine and aldosterone) were measured at 4 and 12 months and every 12 months thereafter.

Table 1
Demographic and baseline characteristics of patients receiving ACEi without BB

	ACE inhibitors/no beta-blockers			Overall
	Valsartan (*n*=1532)	Placebo (*n*=1502)	Total (*n*=3034)	Total (*n*=5010)
Age (years)	63.0±10.8	63.9±10.8	63.4±10.8	62.7±11.1
Male (% pts)	80.4	79.3	79.9	80.0
Whites (% pts)	88.5	89.7	89.1	90.3
Primary cause of HF (% pts)				
CHD	54.8	55.2	55.0	57.2
Idiopathic	32.4	31.6	32.0	31.1
Hypertension	6.9	7.5	7.2	6.7
Other	5.9	5.7	5.8	5.0
NYHA class (% pts)				
II	60.4	61.1	60.7	61.8
III	37.5	36.8	37.1	36.2
IV	2.0	2.1	2.0	1.9
Diabetes (% pts)	27.0	24.8	25.9	25.5
SBP (mm Hg)	123.3±17.9	123.9±18.0	123.6±17.9	123.8±18.5
DBP (mm Hg)	75.3±10.4	75.4±10.6	75.4±10.5	75.5±10.6
HR (bpm)	75.4±12.9	76.0±12.5	75.7±12.7	73.4±12.6
LVEF (%)	26.2±7.3	26.5±6.9	26.3±7.1	26.7±7.2
LVIDd/BSA(cm/m^2)	3.7±0.5	3.7±0.5	3.7±0.5	3.7±0.5
BNP (pg/mL)	187.0±244.3	179.6±225.4	183.3±235.1	180.5±230.1
NE (pg/mL)	449.5±274.1	469.9±316.5	459.7±296.1	463.8±323.2
Aldosterone	137.6±117.9	143.5±126.1	140.5±122.0	143.8±142.9
MLHFQ overall score	33.1±23.4	31.4±22.7	32.3±23.1	32.4±23.0

CHD—coronary heart disease; NYHA—New York Heart Association; SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate; LVEF—left ventricular ejection fraction; LVIDd/BSA—left ventricular internal diastolic diameter corrected for body surface area; BNP—B-type natriuretic peptide; NE—norepinephrine; MLHFQ—Minnesota Living with Heart Failure Questionnaire.

Table 2
ACE inhibitor doses at baseline, year 1 and year 2 among Val-HeFT patients receiving ACEi without BB background therapy

ACEi therapy	Valsartan [mean dose±S.D. (*N*)]			Placebo [mean dose±S.D. (*N*)]		
	Baseline	Year 1	Year 2	Baseline	Year 1	Year 2
Enalapril	17.6±11.6 (463)	17.5±13.4 (348)	18.4±12.7 (206)	17.2±10.8 (467)	17.0±10.6 (395)	18.2±11.3 (227)
Lisinopril	17.6±13.2 (367)	18.2±13.8 (309)	19.0±14.3 (190)	19.1±14.5 (360)	20.4±14.8 (325)	20.7±15.0 (219)
Captopril	81.0±66.0 (309)	79.3±63.9 (231)	74.8±59.4 (141)	76.1±58.0 (304)	79.2±58.9 (224)	80.1±54.7 (131)
Ramipril	5.5±3.6 (111)	5.2±3.2 (91)	5.6±3.5 (58)	5.7±3.5 (99)	5.9±3.6 (88)	5.7±2.8 (45)
Quinapril	21.2±15.8 (93)	21.3±16.7 (77)	22.1±18.2 (42)	24.7±21.0 (93)	26.9±20.8 (81)	25.7±15.8 (38)

The two primary efficacy endpoints of Val-HeFT were time to death and time to first morbid event, defined as death, sudden death with resuscitation, requirement of intravenous therapy for HF or hospitalisation for HF. All potential primary endpoints were adjudicated by an Endpoint Committee. Secondary variables included: change from baseline to endpoint (last observation carried forward) in LVEF, LVIDd adjusted for BSA, QOL scores assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) with lower score indicative of improvement [16], and neurohormonal parameters (norepinephrine, aldosterone and B-type natriuretic peptide).

2.1. Statistical analysis

For the pre-specified Val-HeFT analyses, statistical analysis was performed for the two primary endpoints to achieve an overall significance of 0.05. A log-rank test was used for between-treatments comparisons and a Cox regression model (adjusted for NYHA class, LVEF category, age group, etiology and baseline use of ACEI and BB) was used for estimating relative risks between treatments. Between-treatments comparisons of change from baseline in LVEF, LVIDd adjusted for BSA, QOL and neurohormonal values were made using an analysis of covariance (ANCOVA) model with treatment effect adjusted for baseline, center, ACEI and BB use, and treatment-by-baseline interaction.

Exploratory post hoc analyses for the subgroups of patients receiving ACEi but not BB were based on these same methods. Cox regression analyses within the high-, low- and no-ACEi subgroups included adjustments for NYHA class, LVEF category, age group and etiology. A test of treatment-by-ACEi subgroup interaction was made in these combined subgroups, using this same Cox regression model plus effects for the ACEi subgroups and treatment-by-ACEi subgroup interaction. Treatment comparisons within demographic and baseline subgroups were made using a Cox regression model including adjustments for NYHA class, LVEF category, age group and etiology (with each of these four covariates dropped from the model for analyses performed within the corresponding subgroups).

ANCOVA models for patients receiving ACEi but not BB included adjustments for baseline, continent and treatment-by-baseline interaction.

A significance level of 0.05 was used for all exploratory analyses.

3. Results

3.1. Patient population

Of the 5010 patients enrolled in Val-HeFT, 3034 were receiving ACEi but not BB on entry, corresponding to 61.0% (*n*=1532) of patients randomised to valsartan and 60.1% (*n*=1502) of patients randomised to placebo. The demographic and baseline characteristics of this subgroup were similar to the overall Val-HeFT cohort (Table 1). Mean doses of ACEi at randomisation, during and at the

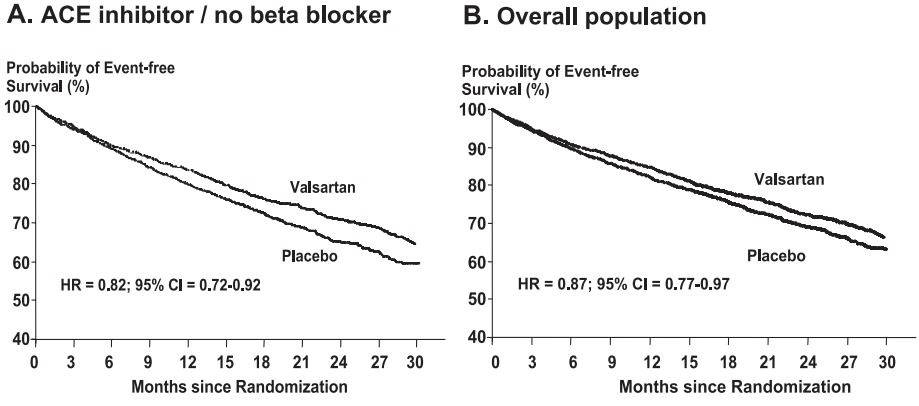

Fig. 1. Kaplan–Meier plot of time to first morbid event for valsartan and placebo in the ACE inhibitor without beta-blocker cohort of Val-HeFT (A) compared with the entire Val-HeFT cohort (B).

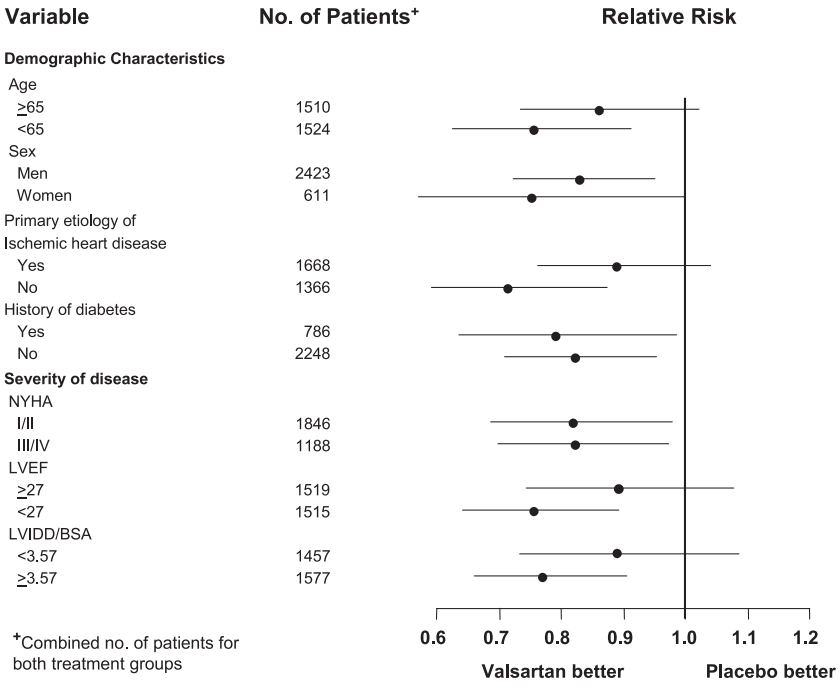

Fig. 2. Subgroup analysis of effect of valsartan and placebo on the morbidity endpoint in the ACE inhibitor without beta-blocker cohort. LVEF and LVIDd subgroups dichotomised above and below median. NYHA—New York Heart Association; LVEF—left ventricular ejection fraction; LVIDd—left ventricular internal diameter in diastole.

conclusion of the study are listed in Table 2. There was little change in mean dose of ACEi over the duration of the Val-HeFT study (average follow-up of 23.0 months). Furthermore, ACEi therapy was discontinued during follow-up in only 9.7% of patients in the valsartan arm and 6.5% in the placebo arm. In addition, 13.0% of patients in the valsartan arm and 16.5% in the placebo arm were commenced on BB therapy following randomisation.

3.2. Effect on mortality and morbidity

Mortality in patients receiving background ACEi but not BB therapy at baseline was similar in the valsartan group (21.8%, n=334) and the placebo group (22.5%, n=338). The hazard ratio for mortality (Cox proportional hazard model) was 0.959, 95% confidence interval 0.824–1.116.

Morbidity was significantly lower in the valsartan group (31.0%, n=475) than the placebo group (36.3%, n=545, p=0.002). The hazard ratio for morbidity was 0.817 (95% confidence interval 0.722–0.924) (Fig. 1). The benefit of valsartan on morbidity was observed in a variety of subgroups based on demographic parameters and severity of disease (Fig. 2).

3.3. Physiologic effects

LVEF rose and LVIDd fell significantly in the valsartan group compared to the placebo group (Table 3). Blood

Table 3
Least-squares mean (LSM) changes in echocardiographic, neurohormonal and haemodynamic measurements among patients receiving ACEi without BB in Val-HeFT

	Valsartan (N=1532)			Placebo (N=1502)			p Value[a]
	Baseline [mean (S.D.)]	Endpoint [mean (S.D.)]	LSM [change (S.E.M.)]	Baseline [mean (S.D.)]	Endpoint [mean (S.D.)]	LSM [change (S.E.M.)]	
SBP (mm Hg)	123.3 (17.9)	116.1 (19.4)	−7.37 (0.41)	124.0 (18.0)	120.0 (18.8)	−3.94 (0.41)	<0.00001
DBP (mm Hg)	75.3 (10.5)	70.7 (11.0)	−4.85 (0.24)	75.5 (10.5)	72.2 (10.9)	−3.44 (0.25)	0.00005
HR (bpm)	75.3 (12.9)	74.6 (13.0)	−0.89 (0.31)	76.0 (12.5)	75.0 (13.1)	−0.67 (0.31)	0.61433
LVEF (%)	26.2 (7.3)	30.2 (9.7)	3.88 (0.23)	26.5 (6.9)	29.2 (9.7)	2.72 (0.23)	0.00033
LVIDd/BSA (cm/m^2)	3.7 (0.5)	3.6 (0.6)	−0.08 (0.01)	3.6 (0.5)	3.7 (0.6)	−0.03 (0.01)	0.00143
BNP (pg/mL)	178.4 (236.4)	154.9 (240.8)	−21.56 (5.99)	168.9 (211.8)	197.0 (267.1)	27.20 (6.00)	<0.00001
NE (pg/mL)	445.1 (272.8)	462.4 (278.5)	9.95 (7.67)	458.7 (299.1)	505.1 (330.0)	44.56 (7.67)	0.00143
Aldosterone (pg/mL)	135.0 (116.1)	114.0 (110.4)	−22.68 (3.66)	141.0 (120.8)	160.8 (163.5)	20.76 (3.69)	<0.00001

SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate; LVEF—left ventricular ejection fraction; LVIDd/BSA—left ventricular internal diastolic diameter corrected for body surface area; BNP—B-type natriuretic peptide; NE—norepinephrine.

[a] p Value for difference in least-squares treatment means comparing valsartan vs. placebo from analysis of covariance (ANCOVA).

pressure fell more in the valsartan group and heart rate was unchanged. Plasma B-type natriuretic peptide, norepinephrine and aldosterone were all significantly lower during follow-up in the valsartan group compared to the placebo group.

3.4. First HF hospitalisation and quality of life

The risk of first hospitalisation for HF was reduced by 34.4% (p=0.0007) with valsartan compared to placebo. QOL (MLHFQ score) was also significantly improved in those patients assigned to valsartan compared to placebo (−0.96 vs. 1.82, p=0.0006) (Majani, G. et al., 2003, submitted).

3.5. Effect of valsartan with increasing ACEi dose

In order to explore the influence of background ACEi dose on the response to valsartan, patients receiving an ACEi without a BB at baseline were divided into two groups, those receiving doses above and those receiving doses below the median dose level for that particular ACEi. These two groups were compared to patients (n=226) treated with neither an ACEi nor a BB at baseline.

The mean doses above and below the median of the most frequently prescribed ACEi in these patients in Val-HeFT are shown in Table 4. Baseline characteristics of the patient subgroups receiving ACEi above and below the median dose compared to patients not receiving ACEi are shown in Table 5. Patients receiving ACEi doses above the median were the youngest, most likely to be Caucasian, least symptomatic based on NYHA classification, least likely to have an ischaemic aetiology and had the lowest neurohormonal levels of the three subgroups.

The greatest morbidity relative risk reduction with valsartan was observed in patients not on an ACEi (44%, p=0.003), as previously described [9]. Intermediate effects were observed in those on doses below the median (22%, p=0.003), and the smallest effect, which was not statistically significant, in those receiving ACEi doses above the median (14%, p=0.143) (Fig. 3). The risk of hospitalisation for HF was statistically significantly reduced by valsartan regardless of background ACEi dose (Fig. 3). The 95% confidence intervals for comparative risk of valsartan vs. placebo overlapped across all three ACEi groups, both for morbidity risk and HF hospitalization risk, suggesting similar treatment effects across all three groups. This was further supported by non-significant test results for treatment-by-ACEi subgroup interaction among the three ACEi subgroups (p=0.1632 for morbidity and p=0.7154 for HF hospitalization).

Table 5
Demographics and baseline characteristics of patients receiving ACEi (by dose above/below median) without BB compared to patients receiving no ACEi and no BB

	No ACEi (N=226)	ACEi dose<median (N=1388)	ACEi dose≥median (N=1626)
Age, years (mean±S.D.)	68.4±10.5	64.5±10.5	62.5±11.0
Females (%)	29.6	20.2	20.0
Caucasians (%)	95.1	92.7	86.1
NYHA III–IV (%)	51.8	40.6	38.0
Ischaemic aetiology (%)	63.7	59.9	50.9
Duration HF in months [mean (median)]	55.4 (38.0)	48.7 (35.0)	52.6 (36.0)
LVEF (%; mean±S.D.)	27.9±6.5	26.4±7.1	26.2±7.1
LVIDd/BSA (cm/m^2; mean±S.D.)	3.7±0.5	3.7±0.5	3.7±0.5
BNP (pg/mL; mean±S.D.)	211±238	203±255	167±217
NE (pg/mL; mean±S.D.)	487±317	477±295	445±297
Aldosterone (pg/mL; mean±S.D.)	228±280	138±121	129±111
MLWHF (mean±S.D.)	35.2±24.9	31.3±22.8	33.0±23.2

LVEF—left ventricular ejection fraction; LVIDd/BSA—left ventricular internal diastolic diameter corrected for body surface area; BNP—B-type natriuretic peptide; NE—noreprinephrine; MLHFQ—Minnesota Living with Heart Failure Questionnaire.

The benefits of valsartan on EF and LVIDd (Fig. 4), plasma B-type natriuretic peptide and norepinephrine (Fig. 5) and QOL (Fig. 6) did not appear to be dependent on ACEi dose. Statistically significantly greater benefit was demonstrated in all three subgroups with valsartan compared to placebo.

3.6. Safety and tolerability

Permanent discontinuation of study medication occurred in 18.7% of the valsartan group and 14.6% of the placebo group. Adverse experiences were the cause of discontinuation in 8.6% and 5.9%, respectively (Table 6).

4. Discussion

ARBs represent an alternative for ACEi in the management of hypertension [17] and, more recently, their use and

Table 4
Mean doses above and below median of most frequently used background ACEi at baseline in patients receiving ACEi BB

ACEi	ACEi dose<median		ACEi dose≥median	
	Valsartan	Placebo	Valsartan	Placebo
Enalapril (mg/day)	8.2±3.3 (n=210)	8.1±3.3 (n=212)	25.4±10.1 (n=253)	24.7±8.8 (n=255)
Lisinopril mg/day)	7.9±3.1 (n=195)	8.0±3.2 (n=172)	28.5±11.6 (n=172)	29.2±13.4 (n=188)
Captopril (mg/day)	34.7±13.1 (n=153)	36.1±12.8 (n=157)	126.3±65.7 (n=156)	118.9±56.9 (n=147)

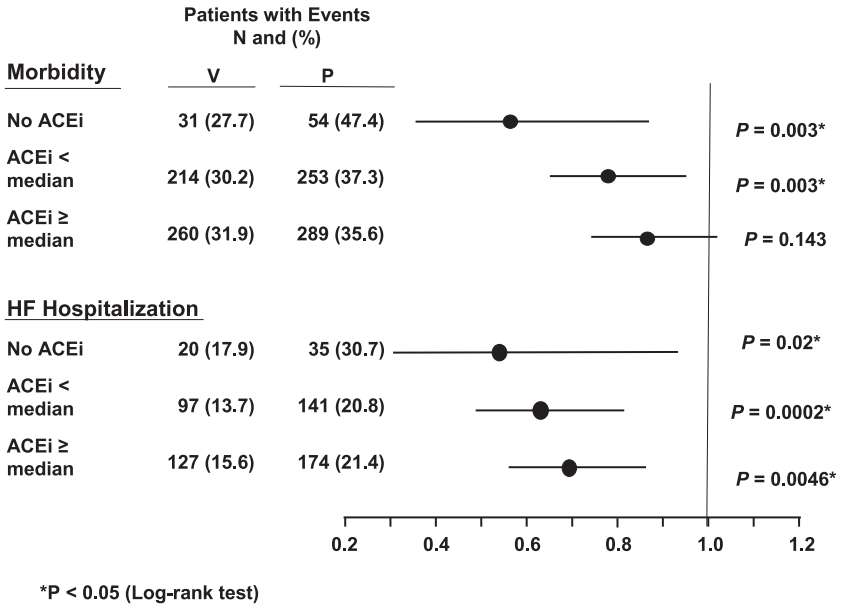

Fig. 3. Hazard ratio and 95% CIs for the morbidity endpoint and time to first HF hospitalisation in Val-HeFT, according to background use of ACE inhibitor (without beta-blocker), namely, patients receiving low dose (ACEi<median), high dose (ACEi≥median) or not receiving ACEi (No ACEi).

potential in HF has been increasingly recognised [18,19]. This concept is based on the perception that both pharmacologic agents exert similar effects by blocking the RAS. Recent evidence, however, indicates that recommended and prescribed doses of ACEi do not produce sustained suppression of plasma angiotensin II levels [12,13]. Indeed, studies by Jorde et al. [20] have demonstrated that higher doses than currently utilised can produce further suppression of physiologically active angiotensin II. Evaluation of this question is further complicated by the fact that beta-blockers, commonly prescribed in the treatment of HF, suppress angiotensin II levels when co-administered with ACEi [14]. We examined a subgroup of the Val-HeFT population that was treated with an ACEi but not a BB. A statistically significant 18% reduction in morbidity was observed in valsartan-treated patients receiving an ACEi without a BB. The CHARM-Added trial [10], designed specifically in ACEi-treated HF patients, also lends support

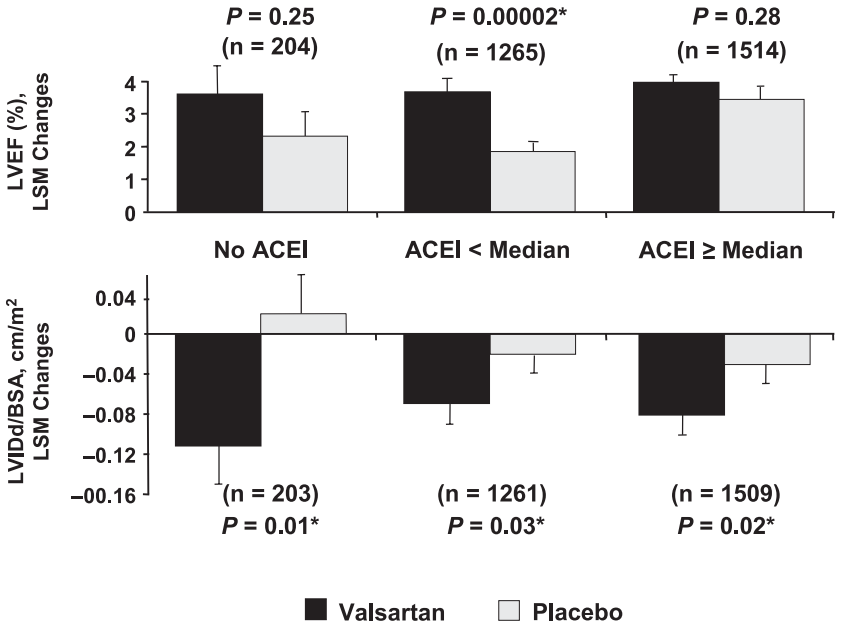

Fig. 4. Least-squares mean changes in LVEF and LVIDd from baseline to endpoint comparing valsartan and placebo in subgroups by background use of ACE inhibitor (without beta-blocker), namely, patients receiving low dose (ACEi<median), high dose (ACEi≥median) or not receiving ACEi (No ACEi).

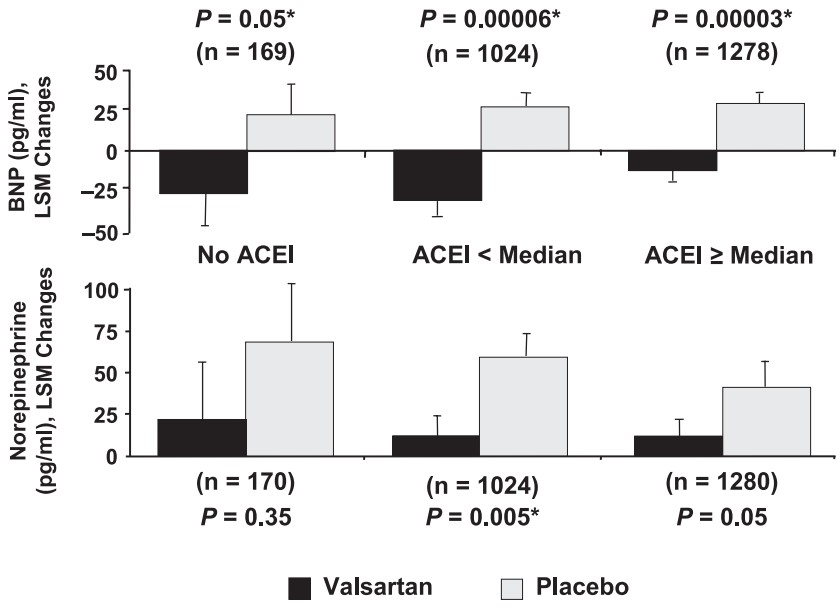

Fig. 5. Least-squares mean changes in B-type natriuretic peptide and norepinephrine from baseline to endpoint comparing valsartan and placebo in subgroups by background use of ACE inhibitor (without beta-blocker), namely, patients receiving low dose (ACEi<median), high dose (ACEi≥median) or not receiving ACEi (No ACEi).

to the morbidity benefits of combined ACEi and ARB therapy.

In Val-HeFT, the benefit of valsartan was most dramatic in patients not receiving an ACEi [9]. In addition, the present analysis suggests that the outcome benefit of valsartan may be greater in patients on low-dose than on high-dose ACEi therapy, although interaction tests indicated that there was no significant difference in treatment effect among the ACEi groups. In comparison, in the CHARM-Added trial, the relative risk reduction for the combined morbidity/mortality primary endpoint analysis was similar in patients receiving "recommended" doses of background ACEi to that observed in the overall trial. The results of the present analysis raise the possibility, as suggested by Jorde et al. [20], that a higher dose of an ACEi might substitute for an ARB in improving outcome in HF. Nonetheless, an earlier trial of high-dose ACEi did not demonstrate a

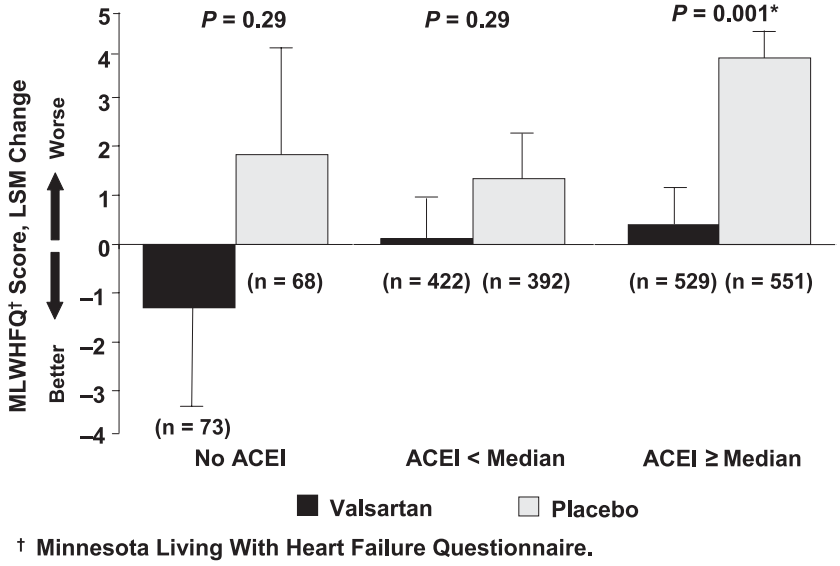

Fig. 6. Least-squares mean changes in Minnesota Living With Heart Failure Questionnaire score from baseline to endpoint comparing valsartan and placebo in subgroups by background use of ACE inhibitor (without beta-blocker), namely, patients receiving low dose (ACEi<median), high dose (ACEi≥median) or not receiving ACEi (No ACEi).

Table 6
Permanent discontinuation of study drug among patients receiving ACEi without BB in Val-HeFT

	Valsartan		Placebo	
	N	%	*N*	%
Patients randomised	1532	100.0	1502	100.0
Permanently discontinued trial treatment	286	18.7	219	14.6
Intolerable adverse experience(s)	131	8.6	88	5.9
Life-threatening laboratory abnormality	25	1.6	8	0.5
Persistent standing systolic blood pressure<80 mm Hg or symptoms of hypotension	19	1.2	6	0.4
Other	111	7.2	117	7.8

persuasively better response [21]. A limitation of the present analysis is the fact that the reasons patients were receiving lower rather than higher ACEi doses are not known.

The benefits observed in the valsartan treatment groups on LV remodelling and neurohormonal activation lend further credence to the favourable effect of ARBs on morbidity. These data support the hypothesis that angiotensin II contributes to progression of HF, even in patients taking an ACEi, and that its inhibition accounts for the favourable effect of valsartan. Indeed, it has previously been reported in the Studies of Left Ventricular Dysfunction (SOLVD) that patients whose LVEF fell despite ACEi therapy exhibited higher neurohormonal levels than those who remained stable [22].

Several mechanisms may contribute to the recovery of angiotensin II during chronic ACEi therapy. Alternate pathways of angiotensin II formation through the chymase and other systems (e.g., tonin, cathepsin, CAGE) have been reported [23]. However, overproduction of angiotensin I and inadequate suppression of its conversion to angiotensin II is another possibility. The latter mechanism is supported by the data of Jorde et al. [20] and by our present observation that the magnitude of the beneficial effect of valsartan on clinical endpoints tended to be smaller in patients receiving higher doses of ACEi. However, the fact that the benefits of valsartan on neurohormones and LV function and size was not related to background ACEi dose precludes any definitive conclusions being made.

There was no interaction effect on clinical outcomes observed between ARBs and beta-blockers in CHARM-Added or VALIANT. Therefore, it is likely that the adverse ARB/beta-blocker interaction observed in Val-HeFT represented a statistical aberration.

A limitation of the present study is the lack of angiotensin I and angiotensin II levels in these patients. These levels would have been of considerable interest to mechanistically support the effects of ARBs when added to differing background doses of ACE inhibitors.

5. Conclusions

The combination of ACEi and BB is the currently recommended therapy to slow progression of HF [4–7]. This combination produces profound suppression of angiotensin II. However, some patients have contraindications to or are intolerant of BBs. The Val-HeFT data demonstrate a beneficial effect of valsartan in patients receiving ACEi therapy without BB. Therefore, HF patients unable to take BB may derive considerable morbidity benefit from valsartan added to a regimen of ACEi therapy.

Acknowledgements

This study was supported by a grant from Novartis Pharma, Basel, Switzerland.

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