

A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

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ABSTRACT

Background Actions of angiotensin II may contribute to the progression of heart failure despite treatment with currently recommended drugs. We therefore evaluated the long-term effects of the addition of the angiotensin-receptor blocker valsartan to standard therapy for heart failure.

Methods A total of 5010 patients with heart failure of New York Heart Association (NYHA) class II, III, or IV were randomly assigned to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined end point of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours.

Results Overall mortality was similar in the two groups. The incidence of the combined end point, however, was 13.2 percent lower with valsartan than with placebo (relative risk, 0.87; 97.5 percent confidence interval, 0.77 to 0.97; $P=0.009$), predominantly because of a lower number of patients hospitalized for heart failure: 455 (18.2 percent) in the placebo group and 346 (13.8 percent) in the valsartan group ($P<0.001$). Treatment with valsartan also resulted in significant improvements in NYHA class, ejection fraction, signs and symptoms of heart failure, and quality of life as compared with placebo ($P<0.01$). In a post hoc analysis of the combined end point and mortality in subgroups defined according to base-line treatment with angiotensin-converting-enzyme (ACE) inhibitors or beta-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.

Conclusions Valsartan significantly reduces the combined end point of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. However, the post hoc observation of an adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE inhibitor, and a beta-blocker raises concern about the potential safety of this specific combination. (N Engl J Med 2001;345:1667-75.)

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PHARMACOTHERAPY for heart failure has advanced considerably in recent years as clinical trials have demonstrated favorable long-term effects of angiotensin-converting-enzyme (ACE) inhibitors¹⁻³ and beta-blockers⁴⁻⁶ on morbidity and mortality. Despite the use of these potent drugs, heart failure remains the leading reason for hospitalization in the Medicare population,⁷ mortal-

ity among patients with heart failure is high, and the quality of life is low.

Angiotensin II, a potent vasoconstrictor and growth-stimulating hormone, may contribute to the impairment of left ventricular function and the progression of heart failure through increased impedance of left ventricular emptying,⁸ adverse long-term structural effects on the heart and vasculature,⁹ and potentially deleterious activation of other neurohormonal agonists, including norepinephrine, aldosterone, and endothelin.¹⁰ Since previous studies have shown that physiologically active levels of angiotensin II persisted despite long-term therapy with an ACE inhibitor,^{11,12} we undertook a study to determine whether the angiotensin-receptor blocker valsartan could further reduce morbidity and mortality among patients who were already receiving the pharmacologic therapy that was considered optimal by their physicians. Descriptions of the rationale for and design of this trial have been published elsewhere.¹³

METHODS**Study Design**

The Valsartan Heart Failure Trial (Val-HeFT) was a randomized, placebo-controlled, double-blind, parallel-group trial. Patients at 302 centers in 16 countries gave written informed consent for participation in the trial, which was approved by the institutional review board at each center. The investigation conformed to the principles of the Declaration of Helsinki. Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals. An independent end-points committee adjudicated all reports of primary end points. An independent data and safety monitoring board reviewed biannual interim analyses. The manuscript was prepared by the authors and reviewed by the steering committee and the sponsor.

Eligibility

Men and women 18 years old or older with a history and clinical findings of heart failure for at least three months before screening were eligible. Patients had heart failure of New York Heart Association (NYHA) class II, III, or IV and were clinically stable. To be eligible, they had to have been receiving for at least two weeks a fixed-dose drug regimen that could include ACE inhibitors, diuretics, digoxin, and beta-blockers. In addition, they had to have documented left ventricular dysfunction with an ejection fraction of less than 40 percent and left ventricular dilatation with an echocardiographically measured short-axis internal dimension at end diastole greater than 2.9 cm per square meter of body-surface area.

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Echocardiograms were analyzed locally after the technical and reader quality at each center had been validated by one of three core laboratories (in Los Angeles; Milan, Italy; or Stockholm, Sweden) that also monitored quality control during the study. Criteria for exclusion have been published previously.¹³

Placebo Run-in Period

Patients were assessed for two to four weeks to confirm their eligibility, clinical stability, and compliance while taking placebo in a single-blind fashion twice daily. Base-line evaluations included laboratory tests for hematologic variables and blood chemistry; urinalysis; echocardiography; 12-lead electrocardiography; and chest radiography. Quality of life was assessed with the Minnesota Living with Heart Failure questionnaire, which was administered to 60 percent of patients — that is, those in the United States, the United Kingdom, Australia, and Italy.

Randomization and Dose Adjustment

Eligible patients, stratified according to whether or not they were receiving a beta-blocker as background therapy, were randomly assigned to receive oral valsartan or matching placebo. Stratification was performed to ensure the equal distribution of patients receiving these drugs in the two groups. Randomization occurred after the base-line eligibility data were verified by the coordinating centers in Minneapolis and Milan. Valsartan was initiated at a dose of 40 mg twice daily, and the dose was doubled every two weeks until a target dose of 160 mg twice daily was reached. Placebo doses were similarly adjusted. The criteria for increasing the dose included a systolic blood pressure of 90 mm Hg or higher while the patient was standing, the absence of symptoms of hypotension, and a serum creatinine concentration of less than 2.0 mg per deciliter (177 μ mol per liter) or no more than 50 percent higher than the base-line concentration. Patients returned for follow-up visits at two, four, and six months and every three months thereafter.

Outcome Measures

The study was designed with two primary end points: mortality and the combined end point of mortality and morbidity, which was defined as cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. Secondary cardiovascular outcomes included the changes from base line to the last available observation after treatment had begun in ejection fraction, NYHA functional class, quality-of-life scores, and signs and symptoms of heart failure.

Statistical Analysis

Statistical analyses were performed at an overall significance level of 0.05, adjusted for the two primary end points. Each primary end point was tested at a two-sided significance level of 0.02532, on the basis of the Dunn–Sidak inequality: $\alpha' = 1 - (1 - \alpha)^{1/2}$. The significance level for the analysis of the time to death was further adjusted for five biannual interim analyses according to the O'Brien–Fleming alpha-spending function. Therefore, the final analysis for the time to death was performed at a two-sided significance level of 0.02.

The calculation of sample size was based on the time-to-death end point. The number of deaths that would be required to detect, with 90 percent power, a 20 percent difference between the death rate with valsartan and that with placebo (estimated at 12 percent per year) was calculated to be 906. We planned to enroll 2500 patients per treatment group.

Comparisons of the primary end points between treatment groups were performed by means of a log-rank test. To estimate the size of the effect, we used a Cox regression model with prespecified base-line covariates, including NYHA class, ejection fraction (above or below the median), cause of heart failure (ischemic or nonischemic), age (younger than 65 years or 65 years old or older), ACE inhibitor use or nonuse, and beta-blocker use or nonuse.

Confidence intervals of 98 percent and 97.5 percent were calculated for mortality and the combined end point of mortality and morbidity, respectively. To estimate the size of the effect on the secondary end points and in subgroups, relative risks with 95 percent confidence intervals were calculated with the use of the Cox regression model.

RESULTS

Of the 5010 patients who underwent randomization, 2511 were assigned to receive valsartan and 2499 to receive placebo, all with background therapy for heart failure. There were no clinically relevant differences in the base-line characteristics of the two groups (Table 1). A description of the base-line demographic characteristics of this diverse population has been published previously.¹⁴ At the time of randomization, 93 percent of the patients were being treated with ACE inhibitors. The average daily doses were 17 mg of enalapril, 19 mg of lisinopril, 80 mg of captopril, 6 mg of ramipril, and 23 mg of quinapril. Thirty-five percent of the patients were receiving beta-blockers (15 percent were receiving carvedilol, 12 percent metoprolol, and 3 percent atenolol), and randomization was stratified according to their use or nonuse; this percentage remained stable throughout the study. Only 5 percent of the patients were treated with spironolactone. The overall mean duration of follow-up was 23 months (range, 0 to 38).

The target dose was achieved in 84 percent of the patients receiving valsartan (mean dose, 254 mg) and 93 percent of those receiving placebo (mean equivalent dose, 283 mg). Systolic blood pressure was reduced to a greater extent with valsartan than placebo: at four months, it was reduced by a mean (\pm SD) of 5.2 ± 15.8 mm Hg in the valsartan group, as compared with 1.2 ± 14.8 mm Hg in the placebo group, and at one year the reductions were 5.2 ± 16.0 mm Hg and 1.3 ± 15.9 mm Hg, respectively. The mean heart rate was unchanged.

Primary End Points

Mortality was similar in the two treatment groups (Fig. 1 and Table 2). The adjudicated causes of death were also similar in the two treatment groups (there were 262 sudden deaths from cardiac causes in the valsartan group and 258 in the placebo group, and there were 118 deaths due to heart failure in the valsartan group and 125 in the placebo group).

The combined end point of mortality and morbidity was significantly reduced among patients receiving valsartan as compared with those receiving placebo ($P = 0.009$) (Fig. 2). The benefit appeared early after randomization and increased throughout the trial. Among the patients in the valsartan group, 723 (28.8 percent) reached the combined end point, as compared with 801 patients (32.1 percent) in the placebo group — a 13.2 percent reduction in risk with valsartan (relative risk, 0.87; 97.5 percent confidence interval, 0.77 to 0.97) (Table 2). The pre-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	VALSARTAN GROUP (N=2511)	PLACEBO GROUP (N=2499)
Age (yr)	62.4±11.1	63.0±11.0
Male sex (% of patients)	79.9	80.0
Race (% of patients)		
White	89.8	90.9
Black	7.2	6.5
Other	2.9	2.6
Primary cause of heart failure (% of patients)		
Coronary heart disease	57.6	56.8
Idiopathic	31.1	31.2
Hypertension	6.1	7.3
Other	5.2	4.7
NYHA class (% of patients)†		
II	62.1	61.4
III	36.1	36.3
IV	1.7	2.2
Diabetes (% of patients)	25.9	25.1
Atrial fibrillation (% of patients)	12.0	12.2
Ejection fraction (%)	26.6±7.3	26.9±7.0
Left ventricular internal diastolic diameter (cm/m ²)	3.7±0.5	3.7±0.5
Blood pressure (mm Hg)		
Systolic	123.0±18.4	124.0±18.6
Diastolic	76.0±10.5	76.0±10.7
Background therapy (% of patients)		
Diuretic	85.8	85.2
Digoxin	67.1	67.6
Beta-blocker	34.5	35.3
ACE inhibitor	92.6	92.8

*Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

†Five patients who were found to be in New York Heart Association (NYHA) class I are not shown.

dominant benefit in terms of the combined end point was a 24 percent reduction in the rate of adjudicated hospitalizations for worsening heart failure as a first event in those receiving valsartan (13.8 percent) as compared with those receiving placebo (18.2 percent) ($P<0.001$) (Table 2).

Secondary End Points

The risk of a hospitalization for heart failure (with censoring of the data for patients who died) was reduced by 27.5 percent with valsartan ($P<0.001$). There were 1189 nonadjudicated hospitalizations for heart failure in the placebo group and 923 in the valsartan group ($P=0.002$). Since hospitalizations for problems other than heart failure were unaffected, the rate of hospitalizations for any cause was reduced similarly — by 250 events, from 3106 in the placebo group to 2856 in the valsartan group ($P=0.14$). The mean change in ejection fraction from base line to the last observation was 4.0 percent in the valsartan

group and 3.2 percent in the placebo group ($P=0.001$). More patients in the valsartan group than in the placebo group had improvements in NYHA classification (23.1 percent vs. 20.7 percent) and fewer had worsening (10.1 percent vs. 12.8 percent) ($P<0.001$). Similarly, dyspnea, fatigue, edema, and rales were more favorably affected by valsartan than by placebo ($P<0.01$). Among the 1504 patients in the valsartan group to whom the Minnesota Living with Heart Failure questionnaire was administered, there was little change in scores from base line to the end point, but among the 1506 such patients in the placebo group, the mean score worsened by an average of 1.9 ($P=0.005$ for the comparison between the treatment groups).

Subgroup Analyses

The beneficial effect of valsartan on the combined mortality-morbidity end point was generally consistent among the predefined subgroups of patients. Valsartan improved the outcome in young and old patients, men and women, those with and without diabetes or coronary artery disease, those with ejection fractions or left ventricular dimensions above and below the median, and those with NYHA class II and class III or IV symptoms (Fig. 3). In the small, heterogeneous black population (which included 344 African-American and South African patients), there was a wide confidence interval for relative risk of the combined end point with valsartan that included 1.0 (relative risk, 1.11; 95 percent confidence interval, 0.77 to 1.61).

Background therapy with neurohormonal inhibitors appeared to influence the response to valsartan (Fig. 4). The patients were divided into four subgroups on the basis of the use or nonuse of ACE-inhibitor and beta-blocker therapy at base line. The global test for the interaction between treatment and subgroup among the four subgroups was statistically significant for mortality ($P=0.009$) and the combined end point of mortality and morbidity ($P=0.001$). In the three groups receiving neither drug or either ACE inhibitors or beta-blockers alone, there was a significantly favorable effect of valsartan on the rate of the combined end point ($P=0.003$, $P=0.002$, and $P=0.037$, respectively) and a favorable point estimate of the odds ratio for death. Mortality was significantly reduced in the 226 patients who were treated with neither an ACE inhibitor nor a beta-blocker ($P=0.012$). Among those who were receiving both drugs at base line, valsartan had an adverse effect on mortality ($P=0.009$) and was associated with a trend toward an increase in the combined end point of mortality and morbidity ($P=0.10$). Among all 366 patients who were not receiving an ACE inhibitor, whether or not a beta-blocker had been prescribed, there was a significantly lower risk of the combined end point in the valsartan group than in the placebo group (rel-

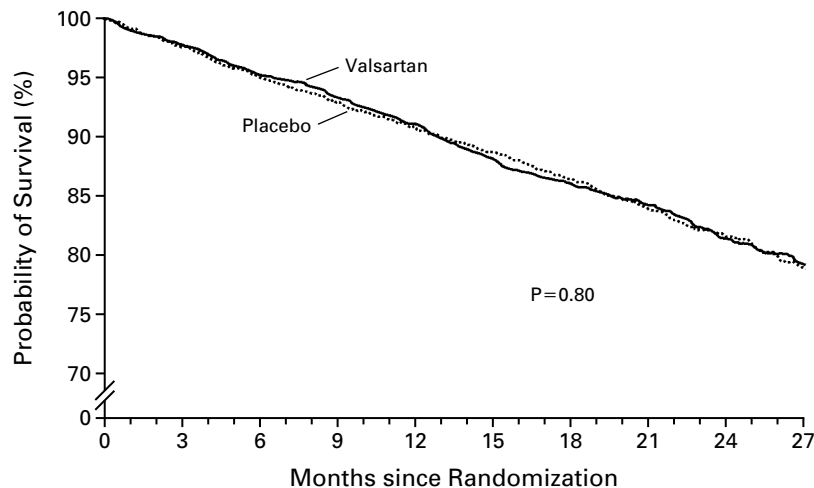


Figure 1. Kaplan–Meier Analysis of the Probability of Survival.

TABLE 2. INCIDENCE AND RELATIVE RISK OF THE PRIMARY END POINTS.

EVENT	VALSARTAN GROUP (N=2511)	PLACEBO GROUP (N=2499)	RELATIVE RISK (CI)*	P VALUE†
	no. with event (%)			
Death from any cause (during entire trial)	495 (19.7)	484 (19.4)	1.02 (0.88–1.18)	0.80
Combined end point	723 (28.8)	801 (32.1)	0.87 (0.77–0.97)	0.009
Death from any cause (as first event)	356 (14.2)	315 (12.6)		
Hospitalization for heart failure	346 (13.8)	455 (18.2)		
Cardiac arrest with resuscitation	16 (0.6)	26 (1.0)		
Intravenous therapy	5 (0.2)	5 (0.2)		

*The 98 percent confidence interval (CI) was calculated for the mortality end point (death from any cause), and the 97.5 percent confidence interval was calculated for the combined mortality–morbidity end point.

†P values were calculated by the log-rank test from time to first event.

ative risk, 0.56; 95 percent confidence interval, 0.39 to 0.81), as well as a lower risk of death (relative risk, 0.67; 95 percent confidence interval, 0.42 to 1.06).

Safety

Valsartan therapy was generally well tolerated. Adverse events leading to the discontinuation of the drug occurred in 249 of the patients receiving valsartan (9.9 percent) and 181 patients receiving placebo (7.2 percent) ($P<0.001$). The adverse events leading to discontinuation and occurring in more than 1 percent of the patients in the valsartan group included dizziness (in 1.6 percent of the patients and 0.4 percent of those in the placebo group; $P<0.001$), hypotension (1.3 percent and 0.8 percent, respectively; $P=0.124$), and renal impairment (1.1 percent and

0.2 percent, $P<0.001$). Overall, the mean change from base line in the blood urea nitrogen concentration was an increase of 5.9 mg per deciliter (2.1 mmol per liter) with valsartan and an increase of 3.3 mg per deciliter (9.2 mmol per liter) with placebo ($P<0.001$). The mean change in the serum creatinine concentration was an increase of 0.18 mg per deciliter (15.9 μ mol per liter) with valsartan and an increase of 0.10 mg per deciliter (8.8 μ mol per liter) with placebo ($P<0.001$). The mean change in the serum potassium concentration was an increase of 0.12 mmol per liter with valsartan and a decrease of 0.07 mmol per liter with placebo ($P<0.001$).

DISCUSSION

Our study was designed to assess the efficacy of the angiotensin-receptor blocker valsartan when add-

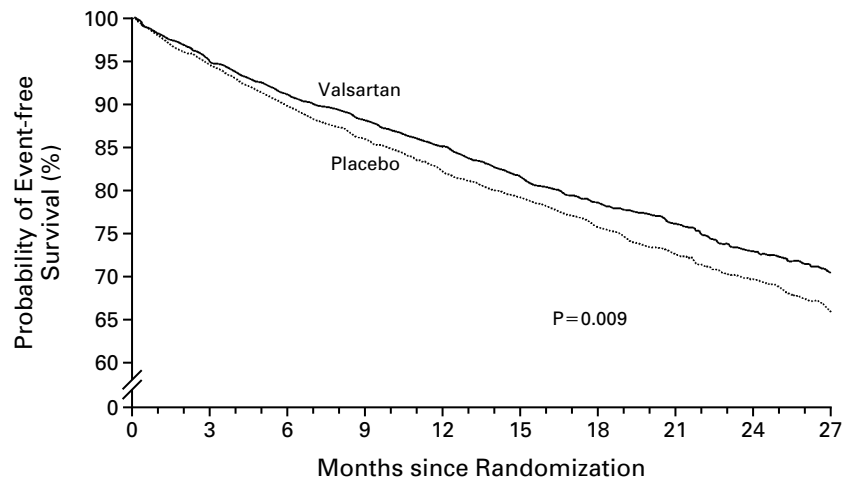


Figure 2. Kaplan–Meier Analysis of the Probability of Freedom from the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators).

ed to prescribed therapy for heart failure. The benefit in terms of morbidity and mortality was achieved in a population in which 93 percent of patients were treated with an ACE inhibitor and 35 percent were treated with a beta-blocker. The outcomes suggest that even with the use of currently prescribed therapy, angiotensin contributes to morbidity but not mortality in patients with heart failure. An unexpected finding emerged, however, from a post hoc analysis of the data on concomitant therapy. Within the 30 percent of the population that was being treated with both an ACE inhibitor and a beta-blocker at base line, there was a significant adverse effect of valsartan on mortality and a nearly significant adverse effect on morbidity. Clarification of whether this finding represents a true interaction or is attributable to chance must await the outcome of ongoing trials evaluating the combination of an angiotensin-receptor blocker with an ACE inhibitor and a beta-blocker. Since only 5 percent of the patients in the trial were receiving spironolactone, an aldosterone-receptor blocker,¹⁵ we cannot assess the efficacy or safety of valsartan when given in combination with spironolactone.

The protocol was designed with two primary end points and appropriate statistical adjustment. Although mortality was similar in the two treatment groups, a significant favorable effect of valsartan on cardiovascular morbidity was evident, primarily as a result of a 24 percent reduction in adjudicated (first) hospitalizations for heart failure and a similar reduction in all nonadjudicated (subsequent) hospitalizations for heart failure. The favorable effect was achieved with a target dose of 160 mg twice daily; this dose was chosen because of its hemodynamic and hormonal

effects, which were documented in a pilot study involving patients who were receiving ACE-inhibitor therapy.¹⁶ The dose was well tolerated; most patients achieved the target dose, and side effects were only slightly more prevalent than in the placebo group.

This study differed from previous trials of angiotensin-receptor blockers in heart failure, such as the Losartan Heart Failure Survival Study¹⁷ and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction,¹⁸ in terms of the high dose we used, our large sample size, and the use of valsartan as a balanced, placebo-controlled add-on to background therapy.

The reduction in cardiovascular morbidity has relevance for the economic burden of heart failure on the health care system. In addition, the moderate but statistically significant benefit in terms of the secondary end points — NYHA class, quality of life, signs and symptoms of heart failure, and left ventricular ejection fraction — is consistent with an overall incremental benefit of valsartan for patients with heart failure who are receiving medical therapy.

The negative effect of angiotensin II on heart failure could be mediated through a vasoconstrictor-induced increase in blood pressure or a direct effect on cardiac and vascular tissues. Since systolic blood pressure was an average of 5 mm Hg lower in patients who were randomly assigned to receive valsartan than in those assigned to receive placebo, a hemodynamic mechanism may account, at least in part, for the observed benefit. Nonetheless, the growth-promoting and apoptotic effects of angiotensin II have been well demonstrated^{9,19} and may contribute to the structural remodeling that promotes the progression of heart

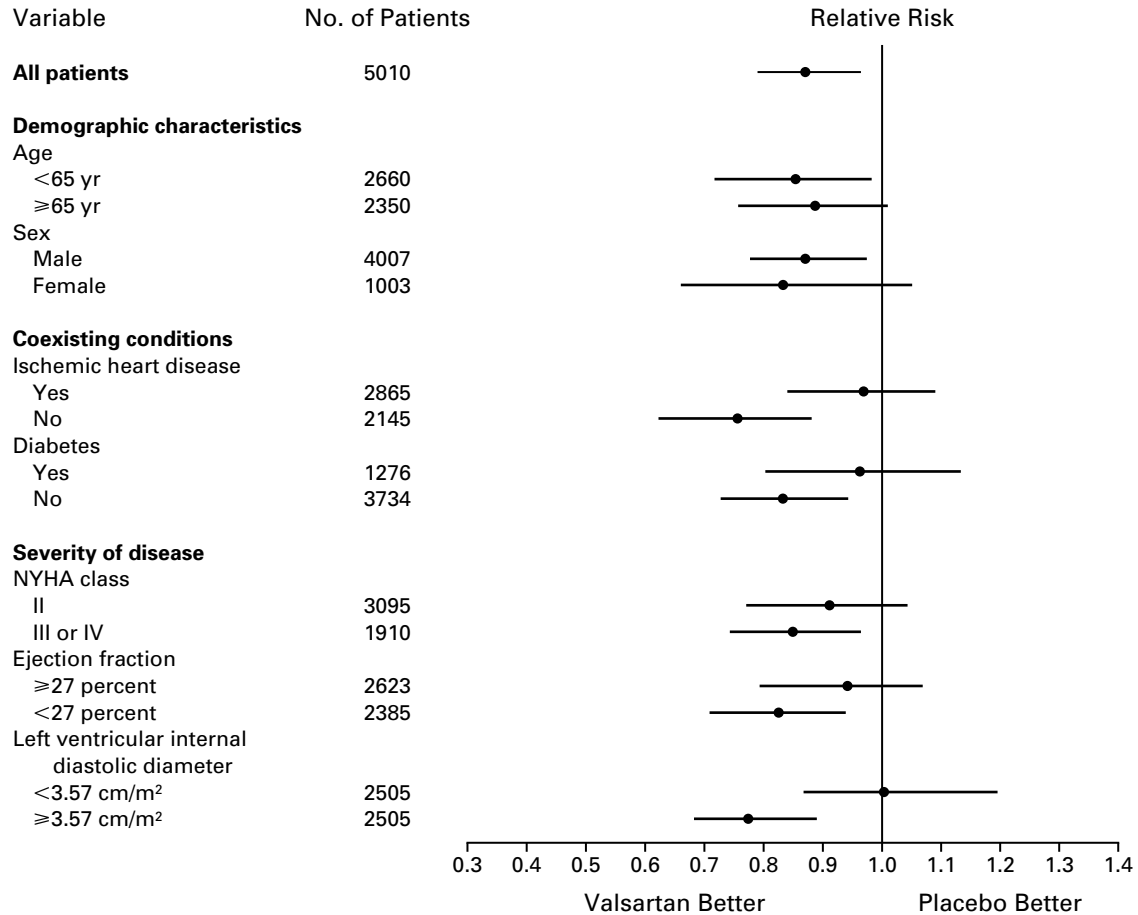


Figure 3. Relative Risks and 95 Percent Confidence Intervals for the Combined End Point, According to Demographic and Clinical Characteristics.

Patients found to be in New York Heart Association (NYHA) class I were not included in the analysis of severity of disease. Two patients did not have an ejection-fraction measurement at base line.

failure.²⁰⁻²⁴ A long-term increase in the ejection fraction has been identified as a marker of regression of left ventricular remodeling that is manifested as reduced chamber volume.^{25,26} This structural effect has been associated with an improvement in survival.^{27,28} In our study, the increase in the ejection fraction was more moderate than in previous trials of ACE inhibitors and beta-blockers and was not associated with reduced mortality. The absence of a more robust effect may be related to the effectiveness of the other therapy received by the patients (annual mortality in the placebo group was 9 percent, rather than the predicted 12 percent).

Subgroup analysis is used in large-scale trials to confirm the generalizability of the findings or, if inconsistencies are observed, to generate hypotheses about subgroup responses to be tested in subsequent studies. In our study, subgroups defined on the basis

of demographic characteristics or base-line clinical characteristics generally had responses that were similar to those in the study population as a whole. Background neurohormonal-inhibitor therapy, however, appeared to influence the outcome. Since this background therapy was not controlled and patients were only partially stratified according to its presence or absence at randomization (according to the use of beta-blockers but not ACE inhibitors), the data generated by this analysis must be interpreted with caution. Nonetheless, in the small subgroup of patients (7 percent) who were not being treated with an ACE inhibitor, there was a 44.0 percent reduction in the combined end point of mortality and morbidity and a 33.1 percent reduction in mortality.

The point estimate of the odds ratio favored valsartan in all subgroups except the subgroup of patients who were being treated with both an ACE in-

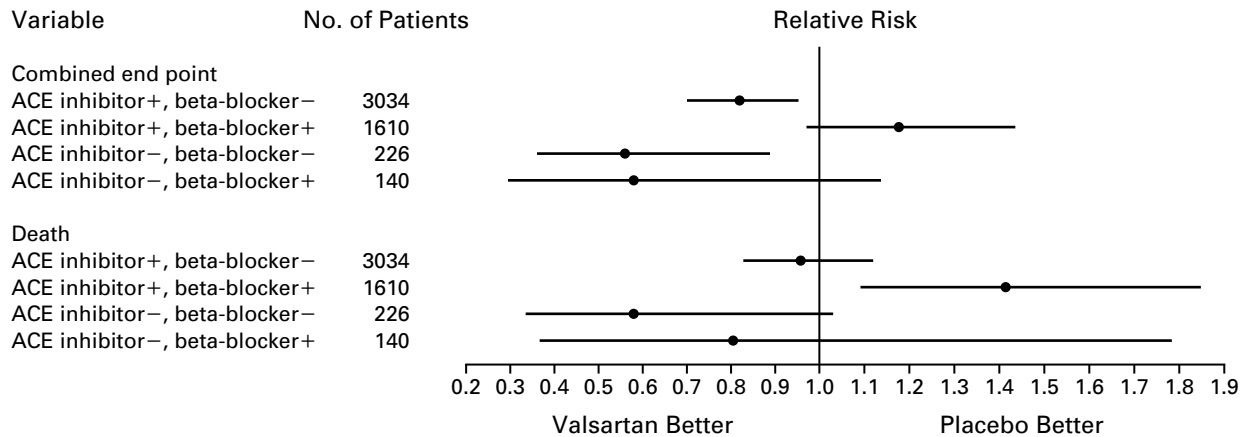


Figure 4. Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, as Calculated by Means of a Cox Regression Model.

ACE denotes angiotensin-converting enzyme, + the use of the drug, and - nonuse.

hibitor and a beta-blocker at base line. As previously noted, the apparent adverse effect of valsartan in this subgroup leads to the hypothesis that the extensive blockade of multiple neurohormonal systems in patients with heart failure could be deleterious. Recent clinical-trial experience with moxonidine,²⁹ endothelin-receptor antagonists, and cytokine inhibitors³⁰ is consistent with this hypothesis. Several trials involving substantial numbers of patients who are receiving these three classes of neurohormonal inhibitors are ongoing and can be expected to provide additional data relevant to this safety concern.

Although current guidelines recommend ACE inhibitors and beta-blockers as standard therapy for heart failure because of their demonstrated benefit in terms of mortality, only one third of the patients enrolled in our study were receiving both classes of drugs. Furthermore, patients who were already being treated with angiotensin-receptor blockers, which are widely prescribed for patients who are intolerant of ACE inhibitors, were excluded from the study. Improved compliance with the guidelines may reduce the number of inadequately treated patients. Nonetheless, the benefit of valsartan in terms of the combined end point of mortality and morbidity that was found in all subgroups except that receiving both ACE inhibitors and beta-blockers suggests that the drug could have a role in the management of the syndrome.

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APPENDIX

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