A COMPARISON OF ENALAPRIL WITH HYDRALAZINE–ISOSORBIDE DINITRATE IN THE TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE

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Abstract *Background and Methods.* To define better the efficacy of vasodilator therapy in the treatment of chronic congestive heart failure, we compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for heart failure. The patients were randomly assigned in a double-blind manner to receive 20 mg of enalapril daily or 300 mg of hydralazine plus 160 mg of isosorbide dinitrate daily. The latter regimen was identical to that used with a similar patient population in the effective-treatment arm of our previous Vasodilator–Heart Failure Trial.

Results. Mortality after two years was significantly lower in the enalapril arm (18 percent) than in the hydralazine–isosorbide dinitrate arm (25 percent) ($P = 0.016$; reduction in mortality, 28.0 percent), and overall mortality tended to be lower ($P = 0.08$). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (New York Heart Association class I or II). In contrast, body oxygen consumption at peak exercise was increased only by hydralazine–isosorbide dinitrate treatment ($P<0.05$), and left ventricular ejection fraction, which increased with both regimens during the 2 years after randomization, increased more ($P<0.05$) during the first 13 weeks in the hydralazine–isosorbide dinitrate group.

Conclusions. The similar two-year mortality in the hydralazine–isosorbide dinitrate arms in our previous Vasodilator–Heart Failure Trial (26 percent) and in the present trial (25 percent), as compared with that in the placebo arm in the previous trial (34 percent), and the further survival benefit with enalapril in the present trial (18 percent) strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine–isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination. (N Engl J Med 1991; 325:303-10.)

CHRONIC heart failure is a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life expectancy.[1] In recent years, vasodilator drugs have been widely used to supplement traditional therapy with digitalis and diuretic agents in the treatment of these patients.[2,3] Vasodilator drugs have been used because of their favorable early hemodynamic effects and their beneficial effects on exercise tolerance,[4-6] left ventricular function,[7-11] and survival.[12,13]

The first five-year, multicenter Veterans Administration Cooperative Vasodilator–Heart Failure Trial (or V-HeFT I) was completed in 1985. It demonstrated that as compared with placebo, the combination of the vasodilators hydralazine and isosorbide dinitrate reduced mortality in patients with mild-to-moderate heart failure who were treated with digoxin and diuretics.[9] The reduction in mortality with this therapy was 38 percent after 1 year, 25 percent after 2 years, and 28 percent over the entire follow-up period (mean, 2.3 years). During the course of that trial, converting-enzyme inhibitors were approved for the treatment of heart failure, and they became widely used as vasodilators among patients with this condition. Although the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial in patients with severe (New York Heart Association class IV) disease demonstrated a significant reduction in mortality with enalapril therapy (31 percent after one year),[13] no data were available on the long-term effects of enalapril in mild-to-moderate heart failure, a far more common medical condition. Accordingly, a second trial (V-HeFT II) was begun in 1986 to compare the effects of enalapril with those of hydralazine and isosorbide dinitrate in a population of patients similar to that in V-HeFT I and also treated with digoxin and diuretics. No placebo arm was included in the second trial, because after reviewing the findings of the earlier trial, the investigators thought it would be imprudent to leave a subgroup of patients untreated with vasodilators for a long period.

These trials have been designed as moderate-sized studies intended to explore the mechanisms of heart failure as well as morbidity and mortality. Since the present trial was an active-control study in which the new agent (enalapril) would be compared with a regimen already demonstrated to be effective, an important aspect of the trial was the comparison of sequential physiologic end points (peak oxygen consumption during exercise, left ventricular ejection fraction, and plasma norepinephrine levels) in addition to mortality in the two treatment arms.

METHODS

Men between the ages of 18 and 75 with chronic heart failure were recruited at 13 participating Veterans Affairs medical centers. The protocol was approved by the institutional review board at each center, and all patients gave informed consent. The study was moni-

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*For a complete list of institutions and individuals participating in the Vasodilator–Heart Failure Veterans Affairs Cooperative Study Group, see the Appendix.

tored by an external data-monitoring board and by the Human Rights Committee of the Cooperative Studies Program Coordinating Center. A patient's eligibility for the trial was determined on the basis of evidence of cardiac dysfunction (cardiothoracic ratio ≥0.55 on chest radiography, left ventricular internal diameter >2.7 cm per square meter of body-surface area at diastole on echocardiography, or ejection fraction less than 0.45 as determined with radionuclide methods) in association with reduced exercise tolerance, as assessed by a progressive maximal-exercise test with a bicycle ergometer during breath-by-breath monitoring of gas exchange. The ergometer load was increased in 25-W increments at two-minute intervals, and the volume and gas content of expired air were measured with a Medical Graphics system. Reduced exercise tolerance was defined as present when a test was terminated by dyspnea or fatigue occurring at a peak oxygen consumption of less than 25 ml per kilogram of body weight per minute. Reasons for exclusion from the study included myocardial infarction or cardiac surgery within the previous three months, angina pectoris limiting exercise or requiring long-term medical therapy, serious obstructive valvular disease, obstructive lung disease (ratio of forced expiratory volume in one second to forced vital capacity, <0.60), or other diseases likely to limit life expectancy. The patients were asked not to take vasodilators or antihypertensive drugs other than the study drugs.

After the patients were screened, a base-line period of at least four weeks was required to establish optimal therapy with digoxin and a diuretic agent and to allow any nonstudy drugs to be discontinued. Two consecutive exercise tests at least two weeks apart that showed respiratory stability (peak oxygen consumption, <25 ml per kilogram per minute, with a difference between tests of <4 ml per kilogram per minute) and a stable clinical state with respect to body weight and drug therapy were required before randomization. Venous-blood samples were obtained for determination in the central laboratory of plasma norepinephrine and plasma renin activity, and base-line radionuclide ejection fractions were measured. Other tests included sequential measurement of plasma norepinephrine, echocardiography, ambulatory electrocardiography, and questionnaires assessing quality of life. The randomization scheme was centrally controlled and used a randomized six-subject permuted-block design, with treatment assignments balanced within each participating medical center and also according to the patient's participation or nonparticipation in V-HeFT I. Randomization was required within four days of the completion of the base-line studies. The randomized patients received three bottles of medication, the first containing 5 mg of enalapril or matching placebo, the second containing 37.5 mg of hydralazine or matching placebo, and the third containing 40 mg of isosorbide dinitrate or matching placebo. Each patient received either a bottle of enalapril and two bottles of placebo or a bottle of hydralazine, a bottle of isosorbide dinitrate, and a bottle of placebo. They began treatment by taking one tablet two times daily from the first bottle, one tablet four times daily from the second bottle, and one-half tablet from the third bottle four times daily. After two weeks, if the patient tolerated these doses of each medication, the doses were doubled, so that the full daily treatment consisted of either 20 mg of enalapril or 300 mg of hydralazine plus 160 mg of isosorbide dinitrate.

Follow-up visits were scheduled at three-month intervals after the titration of the initial dose. In addition to clinical and laboratory evaluation, the following were performed at regular intervals: exercise testing with gas-exchange measurements (after 13 weeks and at 6-month intervals); chest radiography to determine cardiothoracic ratios, radionuclide measurement of ejection fractions, and assays of plasma norepinephrine levels (all yearly); and quality-of-life questionnaires (every 6 months).

Analysis of Deaths

The dates of all deaths were documented, and details of the events at the time of death and the preterminal condition of the patient were obtained from family members, friends, or medical personnel. Deaths were classified by the investigator at the local Veterans Affairs medical center as sudden (either observed or unobserved but assumed on the basis of the clinical setting); sudden, but with some premonitory worsening of cardiac status; due to progressive pump failure, even if the terminal episode was an arrhythmia; caused by another type of cardiovascular event; and noncardiovascular. All the deaths were reviewed blindly and with access to all supportive documentation by the study chairman and were reclassified if necessary to ensure consistency.

Statistical Analysis

All the survival analyses were performed according to the intention-to-treat method, as specified in the protocol. Data on patients who received heart transplants during the study were censored from the survival analysis as of the date of transplantation. The survival curves were compared by the log-rank test[14] calculated for the two selected mortality end points, overall and two-year mortality. The significance level for overall mortality was set at 0.042 after adjustment for four interim analyses with an O'Brien and Fleming group-sequential boundary.[15] Cumulative estimates of mortality were calculated by standard life-table techniques with one-month intervals. The size of effects during the follow-up period was estimated by dividing the mortality rates in the enalapril arm by the mortality rates in the hydralazine–isosorbide dinitrate arm, in order to express relative reductions in mortality at annual cutoff points. Survival analyses were performed for cause-specific events by censoring from the analysis at the time of their deaths data on the patients who had other causes of death. The Cox proportional-hazards model[16] was used to estimate treatment effects within strata of subgroups. Relative risk ratios (and 95 percent confidence intervals) were determined from coefficients of the life-table regression.

Justification for pooling the data on the newly screened patients with the data on the patients who had already participated in V-HeFT I was established by comparing base-line characteristics, testing for an interaction between previous participation and treatment with the Cox proportional-hazards model in the overall survival analysis, and comparing the survival curves of the previously randomized and new patients within each treatment arm.

The distributions of the base-line variables were compared between treatments with a t-test for continuous variables and a chi-square test for association for categorical variables. Changes over time in clinical measurements (ejection fraction, cardiothoracic ratio, peak oxygen consumption, blood-test results, heart rate, and blood pressure) were analyzed at each scheduled follow-up visit by comparing the mean changes from base line in the two treatment arms with use of a t-test. All P values reported are for two-tailed tests.

Results

Recruitment of patients began in March 1986 and ended on September 4, 1990. The screening process identified 2741 patients who met the screening criteria for eligibility; 1838 were excluded for various reasons, including angina requiring treatment with nitrates or calcium antagonists, severe pulmonary disease, inability to perform an exercise test, and inability to discontinue vasodilator therapy. Ninety-nine patients entered the run-in period but were not randomized because of angina, clinical instability, unimpaired exercise capacity, or intercurrent clinical events. The remaining 804 patients were enrolled in the trial and randomly assigned to enalapril (403 patients) or hydralazine–isosorbide dinitrate (401 patients). The base-line characteristics of the two groups were similar (Table 1). Since a low ejection fraction (<0.45) was one of three objective entrance criteria for left ventricular function, patients with a wide range of ejection fractions (0.06 to 0.68; mean, 0.29) were enrolled in the trial. Since angina limiting exercise during the bicycle ergometer test before randomization was a criterion for exclusion, patients with active ischemic heart disease were largely excluded. Coronary artery disease was thus defined as the pri-

Table 1. Base-Line Characteristics of the Treatment Groups.

Characteristic*	Enalapril (N = 403)	Hydralazine–Isosorbide Dinitrate (N = 401)
Historical data		
Age (yr)	60.6	60.5
	% of patients	
Duration of congestive heart failure		
<6 mo	17.7	16.0
6 mo–1 yr	18.5	17.2
1–2 yr	19.5	15.2
2–4 yr	19.5	20.7
>4 yr	25.0	30.7
New York Heart Association class		
I	6.0	5.5
II	49.6	52.4
III	44.2	41.6
IV	0.2	0.5
Race (white/black)	72.5/26.3	70.3/27.2
Coronary artery disease	54.3	51.9
Previous myocardial infarction	48.1	46.3
Coronary bypass surgery	21.1	21.7
Cerebrovascular accident	11.0	9.5
Hypertension	49.6	45.4
Diabetes	20.8	19.9
Excess use of alcohol	33.5	36.7
Tobacco use	33.5	32.9
Drug therapy (previous 6 mo)		
Vasodilators (including ACE inhibitors)	61.3	60.3
Nitroglycerin (sublingual)	15.9	16.7
Antiarrhythmic agents	24.8	26.4
Anticoagulants	20.8	21.9
Base-line clinical assessment†		
Arterial pressure — systole/diastole (mm Hg)	125.5/78.0	127.0/78.4
Heart rate (beats/min)	78.4	77.2
Ejection fraction	0.286	0.294
Cardiothoracic ratio	0.527	0.530
LVIDD (cm/m^2)	3.6	3.4
Atrial fibrillation (% of patients)	11.5	16.2
S_3 gallop (% of patients)	21.3	16.6
Peak oxygen consumption (ml/kg/min)	13.8	13.7
Plasma norepinephrine (pg/ml)	588.7	542.8
Plasma renin activity (ng/ml/hr)	20.0	15.7

*ACE denotes angiotensin-converting enzyme, and LVIDD left ventricular internal diastolic dimension (as measured by echocardiography).

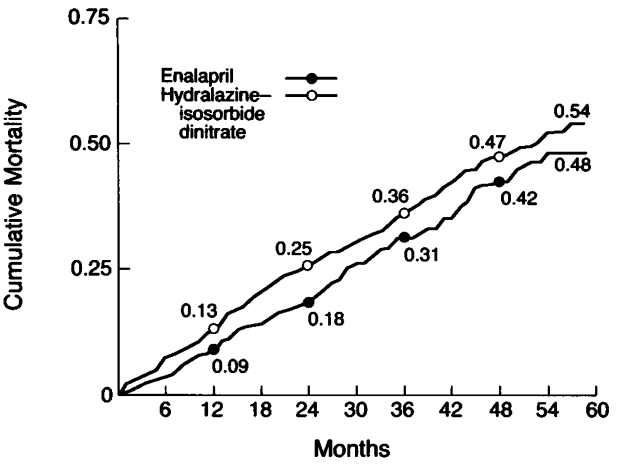
†Values shown are group means except as indicated.

mary cause of heart failure in only 53 percent of the randomized patients.

Mortality

The follow-up period ended on February 28, 1991, and ranged from 6 months to 5.7 years (average, 2.5 years). During this period 285 of the 804 patients died, 132 of those randomly assigned to enalapril (32.8 percent) and 153 of those randomly assigned to hydralazine–isosorbide dinitrate (38.2 percent). Eight patients (six in the enalapril arm and two in the hydralazine–isosorbide dinitrate arm) received heart transplants, and their data were censored from the analysis at that time; seven subsequently survived. The cumulative mortality curves for the two treatment arms are shown in Figure 1. Two years after randomization — a point predetermined to be a major end point of the trial — mortality in the enalapril group was significantly lower than in the hydralazine–isosorbide dinitrate group (P = 0.016 by a two-tailed test). This trend continued throughout the study but did not quite attain statistical significance for the duration of the follow-up period (P = 0.08). The mortality curves separated early and remained essentially parallel after reaching maximal separation after about two years. The reduction in mortality in the enalapril group was 33.6 percent after one year, 28.2 percent after two years, 14.0 percent after three years, 10.3 percent after four years, and 11.1 percent at the end of the follow-up period.

One hundred twenty-one of the 245 patients who had participated in V-HeFT I and had not been randomly assigned to hydralazine–isosorbide dinitrate in that trial met the eligibility criteria and were randomized in the present trial. Since concern had been raised about this strategy, the Cooperative Studies Evaluation Committee asked that the course of these formerly randomized patients be monitored separately to ensure homogeneity before the two cohorts were combined in the analysis. There was no difference between the survival curves for the new and the formerly randomized patients in the enalapril arm (P = 0.73 by the log-rank test) or the hydralazine–isosorbide dinitrate arm (P = 0.79). Nor could an interaction be detected between treatment and randomization status (P = 0.86 for new vs. formerly randomized patients). Therefore, the two cohorts were combined in the survival analyses. A survival analysis stratified according to previous randomization status also



Number Alive

Enalapril	403	344	262	165	85
Hydralazine–isosorbide dinitrate	401	329	239	152	84

Figure 1. Cumulative Mortality in the Enalapril and Hydralazine–Isosorbide Dinitrate Treatment Arms over the Entire Follow-up Period.

Cumulative mortality rates are shown after each 12-month period. For the comparison of the treatment arms after two years and overall, P = 0.016 and P = 0.08, respectively (log-rank test). The number of patients alive after each year is shown below the graph.

Table 2. Deaths Occurring during the Study, According to Cause.*

Deaths	Enalapril		Hydralazine–Isosorbide Dinitrate		P Value
	Deaths	Cumulative Mortality	Deaths	Cumulative Mortality	
	no. (%)	*%*	*no. (%)*	*(%)*	
All	132 (100)	—	153 (100)	—	0.08
Cardiac	*112 (85)*	—	*137 (89)*	—	—
Sudden, no warning	41 (37)	16	63 (46)	25	0.015
Sudden, with warning	16 (14)	7	29 (21)	12	0.032
Due to pump failure	50 (45)	23	40 (29)	19	0.44
Other or unknown	5 (5)	—	5 (4)	—	—
Noncardiac	*20 (15)*	*11*	*16 (11)*	*9*	*0.63*
Cancer	9 45)	—	9 (56)	—	—
Other	11 (55)	—	7 (44)	—	—

*Values for cumulative mortality were obtained from the cause-specific analysis of survival, which was performed by censoring the data for survivors and patients who died of other causes.

showed a similar level of significance for the overall treatment effect (P = 0.08).

The causes of death in the two treatment arms are shown in Table 2. The lower mortality in the enalapril arm was due to a lower incidence of sudden death, without or with premonitory worsening of cardiac status. The survival analyses for sudden death without premonitory symptoms (P = 0.015) and for sudden death with premonitory worsening (P = 0.032) both revealed a significant protective effect of enalapril, whereas there was no difference in mortality from pump failure.

The patients' mortality according to the presence or absence of coronary disease or initial New York Heart Association classification is shown in Table 3. With enalapril, there was a trend toward a preferential beneficial effect on mortality in patients without coronary disease and with less severe symptoms of heart failure. During follow-up, 20 patients in the enalapril arm and 22 in the hydralazine–isosorbide dinitrate arm had acute myocardial infarctions. Coronary bypass surgery was performed in six patients in the enalapril arm and seven patients in the hydralazine–isosorbide dinitrate arm.

Hemodynamic Effects

Blood pressure was reduced from the base-line values during follow-up in both treatment groups, but the reduction in systolic pressure (by 5 mm Hg) and diastolic pressure (by 4 mm Hg) with enalapril was significantly more than the reduction with hydralazine–isosorbide dinitrate (by 0 mm Hg systolic and 1 mm Hg diastolic) during the first 13 weeks. Thereafter, blood pressure in the two groups was similar. Heart rate was significantly higher in the hydralazine–isosorbide dinitrate group during the first year after randomization.

Ejection Fraction

Radionuclide ejection fractions measured at randomization, after 13 weeks, and annually after randomization were significantly increased in both treatment arms for three years after randomization (P = 0.0001) (Fig. 2). The increase after 13 weeks in the hydralazine–isosorbide dinitrate arm (0.033) was significantly greater (P = 0.026) than the increase in the enalapril arm (0.021).

Exercise Tolerance

Systemic oxygen consumption at peak exercise levels was measured before randomization, after 13 weeks, and at 6-month intervals after randomization (Fig. 3). The data plotted exclude the results of tests stopped for reasons other than dyspnea or fatigue and those of tests with uninterpretable gas-exchange measurements. Oxygen consumption was increased significantly by hydralazine–isosorbide dinitrate after 13 weeks (by 0.6 ml per kilogram per minute; P<0.0001) and after 6 months (by 0.8 ml per kilogram per minute; P<0.0001), but not by enalapril. After one year, oxygen consumption began to decline progressively in both treatment arms. P values for the difference between hydralazine–isosorbide dinitrate and enalapril with respect to peak exercise capacity during the first 2 years were 0.01 after 13 weeks, 0.02 after 6 months, 0.1 after 1 year, and 0.02 after 2 years.

Cardiothoracic Ratio

Chest films obtained at base line, after 13 weeks, and annually after randomization were analyzed to determine cardiothoracic ratios. The transverse diameter of the heart was reduced in both treatment arms after 13 weeks and after 1 year (P<0.0001), and there was no significant difference between treatment arms.

Adherence to Medical Regimen

Twenty-two percent of the patients assigned to enalapril had discontinued this medication by the time of their final clinic visit, and an additional 8 percent had reduced the dose. In the hydralazine–isosorbide dinitrate group, 29 percent of the patients had discontinued hydralazine, and 10 percent had reduced the dose, whereas 31 percent had discontinued isosorbide dinitrate and an additional 10 percent had reduced the dose. Compliance with the prescribed regimen (determined on the basis of pill counts) averaged 86 percent. The average daily dose of enalapril was 15 mg, that of hydralazine 199 mg, and that of isosorbide dinitrate 100 mg. Only 25 patients in the hydralazine–isosorbide dinitrate arm received long-term treatment with known converting-enzyme inhibitors during follow-up, whereas in the enalapril arm 5 patients were placed on a regimen of hydralazine and 15 on one of isosorbide dinitrate.

Hospitalization

During the follow-up period, 76 of the patients assigned to enalapril (18.9 percent) and 78 of those assigned to hydralazine–isosorbide dinitrate (18.4 percent) required hospitalization for the treatment of heart failure. In addition, 107 patients in each group

Table 3. Mortality According to the Presence or Absence of Coronary Artery Disease and Initial New York Heart Association (NYHA) Class.*

	Enalapril		Hydralazine–Isosorbide Dinitrate		Risk Ratio (95% CI)
	No. dead/ no. at risk	Annual mortality rate (%)	No. dead/ no. at risk	Annual mortality rate (%)	
Coronary artery disease					
No	55/184	10.7	75/193	12.6	0.74 (0.52–1.05)
Yes	77/219	14.1	78/208	14.3	0.87 (0.64–1.19)
NYHA class					
I	6/24	8.2	9/22	14.9	0.52 (0.18–1.49)
II	48/200	8.2	66/210	11.9	0.68 (0.47–0.98)
III or IV	78/179	16.5	78/169	16.8	0.99 (0.72–1.35)

*Annual mortality rates shown assume exponential survival. The risk ratios (and 95 percent confidence intervals [CI]) were calculated from coefficients from the life-table regression; they represent the ratio of mortality in the enalapril group to that in the hydralazine–isosorbide dinitrate group.

(26.7 percent) were hospitalized for other cardiac reasons. There was no significant difference in the number of patients hospitalized in the two groups. Additional analysis of the frequency and duration of hospitalization is planned.

Side Effects

The frequency of side effects and of alterations in the dose of the study drug due to side effects is outlined in Table 4. An excess of headache was noted in the hydralazine–isosorbide dinitrate group, and an excess of symptomatic hypotension and cough in the enalapril group. The incidence of joint symptoms or positive antinuclear-antibody tests was similar in the two treatment groups. Laboratory values revealed a higher incidence of azotemia in the enalapril group. Blood levels of urea nitrogen were increased in the enalapril group after four weeks (by 0.9 mmol per liter [2.6 mg per deciliter]) and after one year (by 1.2 mmol per liter [3.4 mg per deciliter]), but not in the hydralazine–isosorbide dinitrate group ($P<0.01$). Serum creatinine levels also rose more in the enalapril group than in the hydralazine–isosorbide dinitrate group after four weeks ($P = 0.08$) and after one year ($P = 0.02$). Serum sodium levels were lower in the enalapril group ($P<0.01$), and serum potassium levels higher ($P<0.01$).

Discussion

Both angiotensin-converting–enzyme inhibitors and nonspecific vasodilators exert favorable short-term hemodynamic effects in patients with heart failure.[7-11] Their similarity in vascular action, consisting of the relaxation of both arterial resistance and venous capacitance, has led to the classification of all these agents as vasodilators that lower the impedance to left ventricular ejection and reduce the ventricular preload. The beneficial long-term clinical effects of angiotensin-converting–enzyme inhibitors have been demonstrated more clearly than those of nonspecific vasodilators, at least partly because few trials of long-term efficacy have been carried out with vasodilator drugs other than angiotensin-converting–enzyme inhibitors. V-HeFT I monitored sequential exercise capacity and demonstrated a small improvement in patients randomly assigned to hydralazine–isosorbide dinitrate as compared with placebo or prazosin.[17] Smaller trials have suggested that angiotensin-converting–enzyme inhibitors might exert a more prominent effect on symptoms and exercise performance in heart failure.[4,6,9,11,18] Since hydralazine–isosorbide dinitrate had caused a sizable, though only marginally significant, reduction in mortality in the first trial and since enalapril had been studied over a long period only in patients with severe class IV heart failure, it was important to compare the efficacy of these drugs in patients with mild-to-moderate heart failure. Furthermore, since the power of the first trial to detect a difference in mortality was limited by the small size of its hydralazine–isosorbide dinitrate arm, the random assignment of additional patients to this treatment might serve to replicate the results of the earlier study.

The present study has revealed that the reduction in mortality with enalapril was significantly greater than that with hydralazine–isosorbide dinitrate, but surprisingly, the nonspecific vasodilators produced significantly more improvement in exercise performance and left ventricular function. These observations suggest that all therapeutic end points may not be affected similarly by a treatment and that angiotensin-converting–enzyme inhibitors and vasodilators may act at least partly by independent mechanisms.

Analysis of the mechanism of death provides some insight into the different long-term effects of these two treatments. The reduction in mortality associated with enalapril therapy as compared with hydralazine–isosorbide dinitrate therapy was due to a reduc-

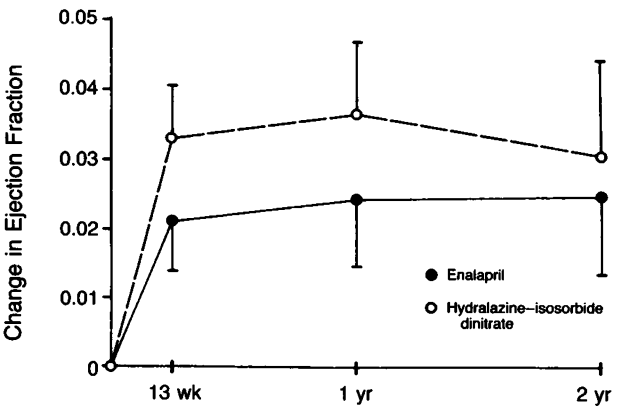


Figure 2. Mean Change from Base Line in Left Ventricular Ejection Fraction over the First Two Years of the Study in Each Treatment Arm.

Vertical bars represent 95 percent confidence intervals. The increase after the first 13 weeks in the hydralazine–isosorbide dinitrate arm was greater than in the enalapril arm ($P<0.05$).

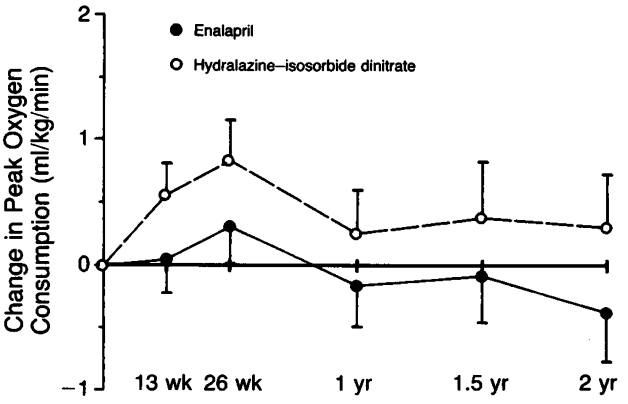


Figure 3. Mean Change from Base Line in Peak Oxygen Consumption over the First Two Years of the Study in Each Treatment Arm.

The increase in the hydralazine–isosorbide dinitrate arm was significant for the first six months ($P<0.01$) and was greater than in the enalapril arm.

tion in the incidence of sudden death. This observation is contrary to the results of the CONSENSUS trial, in which only mortality from pump failure was reduced by treatment with enalapril.[13] However, that study group consisted only of patients with severe class IV heart failure, and the incidence of sudden death was low. In the present study, 46 percent of the cardiac deaths in the hydralazine–isosorbide dinitrate arm were sudden and unexpected, without premonitory symptoms — a proportion almost identical to that in the earlier study[9] — whereas only 37 percent of the deaths in the enalapril arm were sudden and unexpected. The preferential reduction with enalapril of cardiac mortality not due to worsening pump failure raises the possibility that the added benefit of the converting-enzyme inhibitor as compared with the hydralazine–nitrate combination may be due to a nonvasodilator mechanism.

Table 4. Incidence of Side Effects in the Two Treatment Groups.*

Side Effect	Enalapril			Hydralazine–Isosorbide Dinitrate		
	Symptom Reported	Dose Reduced	Drug Stopped	Symptom Reported	Dose Reduced	Drug Stopped
	percent of patients					
Nausea	52	6	7	44	5	10
Fatigue	79	11	14	76	13	16
Headache	54	6	7	73†	19†	21†
Palpitations	46	3	2	51	3	5†
Symptomatic hypotension	28†	6	5	20	4	4
Taste disturbance	28	2	1	28	1	3
Joint pain	65	3	4	63	3	6
Rash	33	3	2	31	1	3
Nasal congestion	63	3	2	63	2	4†
Cough	37†	0	1	29	0	1

*Values shown are the percentages of patients reporting the specific symptom in any degree at any time during follow-up, the percentages in whom the dose of one or more study medications was reduced because of this symptom, and the percentages in whom one or more study medications were stopped because of this symptom.

†This value was significantly higher than the corresponding value for the other treatment ($P<0.05$).

The magnitude of the effect of these drugs on mortality deserves additional attention. No placebo group was included in the present study, but the hydralazine–isosorbide dinitrate arm should be comparable to the same treatment arm in the earlier trial, since the criteria for entry into the two studies and the treatment regimens were identical. As shown in Figure 4, the survival curves for these two groups are nearly identical. The homogeneity of the patient populations in the two trials and the reproducibility of the survival curves make it reasonable to compare mortality results. As shown in Table 5, the mortality at annual intervals in the placebo arm of the first trial was considerably higher than that in the hydralazine–nitrate arms in both trials and was reduced even further

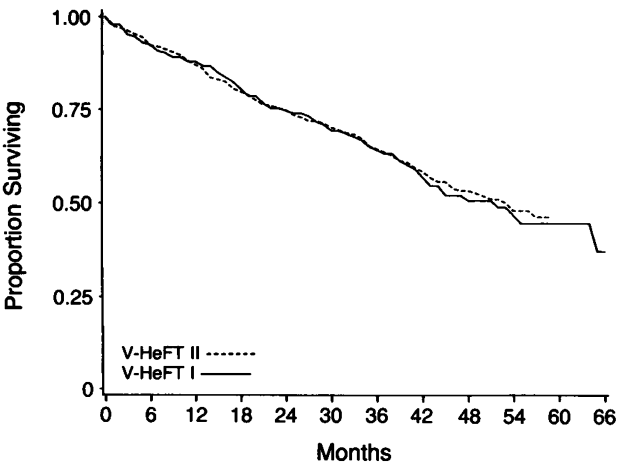


Figure 4. Survival Curve for the Hydralazine–Isosorbide Dinitrate Arm in the Earlier Trial (Solid Line) Superimposed on the Survival Curve for the Same Treatment Arm in the Current Trial (Dashed Line).

with enalapril. Since the placebo arm in the earlier trial (n = 273) was larger by design than the hydralazine–isosorbide dinitrate arm (n = 186), the similar mortality in the 401 patients randomly assigned to the combination of vasodilators in the present trial is further evidence of the reliability of the difference in mortality identified in the earlier trial. Although enalapril reduced one-year mortality to 9 percent from 13 percent in the hydralazine–isosorbide dinitrate arm and from the historic rate of 20 percent in the placebo arm in the earlier trial, the mortality in subsequent years increased comparably in the two treatment arms, reaching over 40 percent by the end of the fourth year of follow-up. Therefore, both enalapril and the combination of vasodilators delay death in patients with heart failure, but neither is completely effective in halting the progressive worsening process leading to death.

The early separation and subsequently parallel

Table 5. Cumulative Mortality at Annual Intervals in the Two Vasodilator–Heart Failure Trials.

Study Group	No. of Patients	Cumulative Mortality			
		1 YR	2 YR	3 YR	4 YR
		percent			
First trial					
Placebo	273	20	34	47	54
Hydralazine–isosorbide dinitrate	186	12	26	36	50
Current trial					
Hydralazine–isosorbide dinitrate	401	13	25	36	47
Enalapril	403	9	18	31	42

course of the mortality curves for the two treatment arms in the present study imply that the drug effect persisted throughout the study. Parallel curves after an initial separation imply a continued benefit of treatment, because the larger number of survivors in the effective-treatment arm should result in a higher number of deaths in that group if the risk were equal, and because saving patients at higher risk in the effective-treatment arm should lead to a population at intrinsically higher risk in this group over time. These statistical and biologic forces would tend to cause the curves to converge unless the drug was still effective or the course of the disease had been altered in some way by the therapeutic intervention.

Since enalapril and hydralazine–isosorbide dinitrate appear to have independent beneficial effects, one possible strategy would be to use the drugs together. Another attractive strategy would be to intervene earlier in an attempt to abort the disease process before it results in overt heart failure. This strategy is being tested in two ongoing clinical trials.[19,20] Alternatively, it may be necessary to devise more selective and more potent interventions to prevent the progression of heart failure, in order to allow patients with ventricular dysfunction a more normal life expectancy.

Appendix

The following individuals and institutions participated in the second Vasodilator–Heart Failure Veterans Affairs Cooperative Study Group (V-HeFT II): *Study Chairman's Office* (Minneapolis) — Jay N. Cohn, M.D., study chairman; Susan Ziesche, R.N., study coordinator; Pam Rossini, secretary; *Department of Veterans Affairs medical centers (VAMCs)* in the following cities: Cincinnati — Geetha Bhat, M.D., Kathleen Flohr, M.D.,* Judy Nelson, R.N., Nancy Sloan, R.N., Marge Egan, R.N.,* and Lequita Yvette Pierce (clerk); Durham, N.C. — Frederick Cobb, M.D., Jean Wilson, R.N., Johnny Etheridge, R.N., and Donna Bowen, R.N.*; Hines, Ill. — Henry Loeb, M.D., Christine Lawless, M.D.,* Ann Henrick, R.N., and Sandra Rome, Pat Lutcher,* and Janeen Dunst* (clerks); Little Rock, Ark. — James Doherty, M.D., Bonnie Baker, M.D.,* Barbara Cotter, L.P.N., Norma Tellez, R.N., Sherry Killingsworth, R.N.,* and Wilma Faye Hill (clerk); Minneapolis — Gary Francis, M.D., Michelle Berg, R.N., Janet Nelson, R.N.,* and JoAnn Underhill and Sandra Thiesse*(clerks); Nashville — Raphael Smith, M.D., Barbara Smith, R.N., Kathy Blankenship, R.N., and Lisa Manning, R.N.*; Philadelphia — W. Bruce Dunkman, M.D., Nancy Wagner, R.N., Laura Farrell, R.N., Lynn Georgepoulos, R.N.,* Rick Jones, R.N.,* and Marilyn Weddle and Deborah Jennings (clerks); Tucson, Ariz. — Steven Goldman, M.D., Richard Gay, M.D.,* Julia Brandt, R.N., Janet Acuna, L.P.N., and Michelle Dent (clerk); Washington, D.C. — Peter Carson, M.D., Marc Wish, M.D.,* Joseph Orndorff, R.N., and Mary Jo Bell (clerk); West Los Angeles — Maylene Wong, M.D., Pravin Shah, M.D.,* Becky Lopez, R.N., Patricia Carter, R.N.,* Jill James, Ph.D.,* Nancy Sadler, R.N.,* and Margaret Thomas and Katherine Cherry* (clerks); Milwaukee — Felix Tristani, M.D., C. Vincent Hughes, M.D., Sandra Laedtke, R.N., and Grace Daniels, L.P.N.; Tampa, Fla. — Guillermo Cintron, M.D., Joyce Eason, R.N., Lydia Manning, R.N.,* Scott Tanner, R.N.,* and Margie Morgan (clerk); San Diego, Calif. — Ralph Shabetai, M.D., Rosemary Cremo, R.N., Maribeth Cacha, R.N., and Nancy Miljan (clerk).

Executive Committee — Jay N. Cohn, M.D. (study chairman), Minneapolis; Susan Ziesche, R.N. (study coordinator), Minneapolis; Gary R. Johnson, M.S. (study biostatistician), West Haven, Conn.; Clair Haakenson, R.Ph., M.S. (study pharmacist), Albuquerque, N.M.; Ross Fletcher, M.D., Washington, D.C.; Gary Francis, M.D., Minneapolis; Maylene Wong, M.D., Los Angeles; Frederick Cobb, M.D., Durham, N.C.; Donald G. Archibald, M.Phil., West Haven, Conn.*; and Pravin Shah, M.D., Los Angeles.* *Cooperative Studies Program Coordinating Center (CSPCC)*, West Haven, Conn. — Dorothea Collins, M.S. (chief); Yick-Kwong Chan, Ph.D.*; Margaret Antonelli (administrative officer); Gary R. Johnson, M.S., and Donald G. Archibald, M.Phil.* (biostatisticians); Mary Ann Hope, M.D. (programmer); Raymond Kilstrom, M.B.A. (statistical assistant); Lillie Franklin, Stella Marcinauskis, and Mary E. Smith (data entry); and Darrell Burns (travel clerk). *Cooperative Studies Program Central Research Pharmacy Coordinating Center*, Albuquerque, N.M. — Mike R. Sather, R.Ph., M.S. (chief), Clair Haakenson, R.Ph., M.S. (research pharmacist), and Steve Simpson (research pharmacy technician). The core laboratories included the *Central Norepinephrine Laboratory*, Minneapolis — Jay N. Cohn, M.D.; director: Ada Simon, Ph.D.; technician: Flor Dizon, Linda Dahl*; *Central ECG Holter Tape Laboratory*, VAMC, Washington, D.C. — director: Ross D. Fletcher, M.D.; *Central Echocardiographic Laboratory*, VAMC, West Los Angeles — director: Maylene Wong, M.D., Pravin Shah, M.D.;* technician: Becky Lopez, R.N.; *Central Exercise Metabolic Measurements Laboratory*, VAMC, Durham, N.C. — director: Frederick Cobb, M.D.

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*Past members of the study.

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