The New England
Journal of Medicine

Volume 325 AUGUST 1, 1991 Number 5

EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

Abstract *Background.* Patients with congestive heart failure have a high mortality rate and are also hospitalized frequently. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on mortality and hospitalization in patients with chronic heart failure and ejection fractions ≤0.35.

Methods. Patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n = 1284) or enalapril (n = 1285) at doses of 2.5 to 20 mg per day in a double-blind trial. Approximately 90 percent of the patients were in New York Heart Association functional classes II and III. The follow-up averaged 41.4 months.

Results. There were 510 deaths in the placebo group (39.7 percent), as compared with 452 in the enalapril group (35.2 percent) (reduction in risk, 16 percent; 95 percent confidence interval, 5 to 26 percent; P = 0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (251 in the placebo group vs. 209 in the enalapril group; reduction in risk, 22 percent; 95 percent confidence interval, 6 to 35 percent). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26 percent; 95 percent confidence interval, 18 to 34 percent; P<0.0001).

Conclusions. The addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic congestive heart failure and low ejection fractions. (N Engl J Med 1991; 325:293-302.)

CONGESTIVE heart failure is a major and growing public health problem. About 2 million patients have congestive heart failure in the United States, and the number is expected to increase substantially in the next few decades.[1] The one-year mortality ranges from 15 percent among relatively unselected patients[2] to 50 percent among those in New York Heart Association functional class IV.[3] About 35 percent of all patients with a diagnosis of congestive heart failure are hospitalized every year (unpublished data).

The Veterans Administration Cooperative Vasodilator Heart Failure Trial[4] reported a lower mortality in patients with congestive heart failure treated with hydralazine and isosorbide dinitrate than in patients receiving placebo (P = 0.093). No benefit was observed in the group randomly assigned to prazosin. Angiotensin-converting–enzyme inhibitors appeared to be particularly promising in improving hemodynamic indexes[5] and symptoms.[6] The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[3] and a retrospective review of several short-term trials indicated that angiotensin-converting–enzyme inhibitors reduced mortality.[7] However, CONSENSUS was confined to patients who remained in New York Heart Association class IV despite two weeks of therapy that did not include an angiotensin-converting–enzyme inhibitor, and no data on mortality were available for patients with mild congestive heart failure or asymptomatic left ventricular dysfunction.

Given the frequent occurrence of congestive heart failure, its increasing incidence, and the high rates of mortality and hospitalization associated with it, we postulated that even a moderately effective agent (one yielding a reduction of 15 to 20 percent in the number of events) could prevent thousands of hospitalizations and premature deaths each year.[1,8] Therefore, the Studies of Left Ventricular Dysfunction (SOLVD) were designed to address whether intervention with an angiotensin-converting–enzyme inhibitor, enalapril, in patients with low ejection fractions (≤0.35) would reduce mortality.[8] Patients with overt congestive heart failure were entered in the treatment trial, and those without overt congestive heart failure were entered in the prevention trial. The primary aim of both trials was to assess the effect of enalapril on

*The investigators and institutions participating in the SOLVD study are listed in the Appendix.

Address reprint requests to Dr. Salim Yusuf at the Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, Federal Bldg., Rm. 5C08, 7550 Wisconsin Ave., Bethesda, MD 20892.

Supported under contracts from the National Heart, Lung and Blood Institute and by a gift from Merck Sharp and Dohme, which had no part in the design, conduct, or monitoring of the study or in the analysis, interpretation, or reporting of the results.

mortality. Key secondary aims included assessment of the effect of treatment on hospitalization for congestive heart failure, the incidence of myocardial infarction, mortality due to specific causes, and a combined analysis of mortality and morbidity based on data from both trials. This paper presents the data on mortality and hospitalizations for congestive heart failure for the 2569 patients enrolled in the treatment trial.

Methods

Study Organization

The SOLVD study was randomized, double-blind, and placebo-controlled. Patients with congestive heart failure were randomly assigned to treatment groups separately at each of 83 hospitals linked to 23 centers in the United States, Canada, and Belgium. All data were collected and analyzed centrally at the coordinating center at the University of North Carolina, Chapel Hill. The study was organized by the Project Office, located at the Clinical Trials Branch of the National Heart, Lung and Blood Institute. A steering committee consisting of principal investigators from each center and the Project Office developed and implemented the protocol.[8] An independent Data and Safety Monitoring Board monitored the progress of the study. The study was approved by the institutional review board of each hospital, and the patients provided informed consent.

Eligibility of Patients

Patients with congestive heart failure and ejection fractions of 0.35 or less who were already taking drugs other than an angiotensin-converting–enzyme inhibitor as part of conventional therapy for congestive heart failure were eligible for the study. The ejection fraction was measured with radionuclide techniques (for 68 percent of the patients), contrast angiography (11 percent), and two-dimensional echocardiography (21 percent) with the area–length method or Simpson's rule.[9] Patients were ineligible if they were over 80 years of age or had any of the following: hemodynamically serious valvular disease requiring surgery, unstable angina pectoris, angina thought to be severe enough to require revascularization procedures, myocardial infarction during the previous month, severe pulmonary disease, serum creatinine level higher than 177 μmol per liter (2 mg per deciliter), or any other disease that might substantially shorten survival or impede participation in a long-term trial. A screening log was maintained from April 1986 through March 1989. During this period, 39,924 patients with ejection fractions of 0.35 or less were identified. Of these, 6.4 percent were enrolled in the treatment trial, and 7.4 percent in the prevention trial. Among those excluded, the reasons for exclusion were as follows: use of an angiotensin-converting–enzyme inhibitor (28 percent), cardiovascular problems (12 percent), contraindications to the use of an angiotensin-converting–enzyme inhibitor (11 percent), lack of consent by the patient (11 percent), administrative reasons (21 percent), cancer or other life-threatening disease (12 percent), and other reasons (5 percent).

Run-in Period and Stabilization of Patients

All the patients eligible for either trial entered a run-in and stabilization phase. We initially gave 2.5 mg of enalapril twice daily in a single-blind fashion for two to seven days to identify patients who could not tolerate even a small dose of the drug for a short period and those who were unable to comply with the regimen. Treatment was begun in the hospital for only 1.2 percent of patients. A total of 310 of 7402 patients (4.2 percent) were excluded from the study during this phase (0.2 percent with worsening renal function, 2.2 percent with symptomatic hypotension, and 2.5 percent because of noncompliance). After this phase of active dosing, the patients were placed on a regimen of matching placebo in a single-blind fashion for 14 to 17 days so that those whose clinical condition worsened when the drug was withdrawn and those who complied poorly with the regimen could be identified. A total of 295 of 7092 patients (4.2 percent) were excluded from the study during this phase (1.8 percent for worsening congestive heart failure or worsening angina and 2.4 percent for poor compliance). Four patients died during the run-in period for the active drug (average, six days). Thirty-four patients died during the run-in period for placebo (average, 15 days). At the end of the run-in period for placebo, the patients were classified either as having overt congestive heart failure (and enrolled in the treatment trial) or as not having overt congestive heart failure (and enrolled in the prevention trial).

Randomization and Dose Titration after Randomization

Randomization was performed with a computer-generated allocation schedule that had a block size of 16 patients stratified according to hospital. Treatment with enalapril or placebo was started at 2.5 mg or 5 mg twice daily on the basis of the patient's clinical condition and the participating physician's judgment. The dose was titrated up to a maximum of 10 mg twice daily if the patient did not have symptomatic hypotension or worsening renal function. After randomization, the patients were seen after two weeks, six weeks, four months, and then every four months until the end of the study. In patients with worsening symptoms of congestive heart failure, an increase in the dose of diuretic agents or the addition of other vasodilators was generally recommended as the first step. If the patient remained symptomatic despite maximal therapy with such medications, open-label treatment with an angiotensin-converting–enzyme inhibitor was allowed, and the blinded medication was discontinued. However, all randomized patients were retained in the analysis.

Follow-up and Outcome Measures

At the time of this report, the vital status of one patient in each study group was unknown. The cause of a patient's death was classified by the principal investigator at each center on the basis of the blinded review of the circumstances surrounding the death, as obtained from a review of the hospital chart or from interviews with relatives. At each follow-up visit, a record was made of changes in the patient's clinical and functional status, the use of nonstudy drugs, any hospitalizations since the preceding visit, adherence to the study drug, and side effects. For each hospitalization, the patient's chart was reviewed by a study physician blinded to the treatment assignment in order to ascertain the diagnosis. Data on hospitalizations for congestive heart failure were based on the primary diagnosis at discharge.

Statistical Analysis

The hypothesis of the treatment trial was that treatment with enalapril would reduce mortality; hence, a one-sided test with a significance level of 0.025 (corresponding to a level of 0.05 with a two-sided test) was used for all analyses. A stratified log-rank statistic (with the 23 clinical centers as strata) was used to compare the life-table survival curves for all patients randomly assigned to the two groups.[10,11] A sample of 2500 patients was estimated; the details have been published elsewhere.[8] A termination date of January 31, 1991, for all events was set in advance. Deaths occurring between this date and the completion of the patients' final visits were also reported. The data were reviewed every six months by the Data and Safety Monitoring Board. The board chose to rely chiefly on the Lan–DeMets boundary[12] for formal statistical guidelines during the interim analyses. In view of these analyses, the critical Z value used at the end of the study for a one-sided test with a significance level of 0.025 was 2.11 rather than the usual 1.96. The Kaplan–Meier[13] method was used to construct life-table plots. The percentage reduction in mortality was reported as

$$(1 - \mathrm{RR}) \times 100,$$

where RR is the estimated relative risk of an event in the enalapril group as compared with the placebo group estimated from the life tables. The uniformity of treatment effects across subgroups was

assessed by the likelihood-ratio test on the basis of the proportional-hazards model.[14]

Results

From June 1986 to March 1989, 2569 patients were enrolled in the treatment trial. The clinical characteristics of the two groups were similar at base line (Table 1). The follow-up ranged from 22 to 55 months (average, 41.4).

Total Mortality

The cumulative mortality rates over a period of 48 months are shown in Figure 1. At the end of the scheduled follow-up of the study, 510 patients had died in the placebo group as compared with 452 patients in the enalapril group (risk reduction, 16 percent as calculated from the log-rank test; 95 percent confidence interval, 5 to 26 percent; P = 0.0036) (Table 2). The difference in mortality appeared to be most marked in the first 24 months (Table 3). Thereafter, there were similar numbers of deaths in each group.

Causes of Death

There were 461 cardiovascular deaths in the placebo group as compared with 399 in the enalapril group (risk reduction, 18 percent; 95 percent confidence interval, 6 to 28 percent) (Table 2). The chief difference in mortality was in deaths due to progressive heart failure (251 deaths in the placebo group as compared with 209 in the enalapril group; risk reduction, 22 percent; 95 percent confidence interval, 6 to 35 percent) (Fig. 2). There were 53 fatal myocardial infarctions in the placebo group as compared with 40 in the enalapril group. There was little difference in the number of deaths classified as due to arrhythmia without worsening congestive heart failure and the number of deaths due to noncardiovascular causes.

Hospitalization for Heart Failure

Overall, 736 patients in the placebo group (57.3 percent) died or were hospitalized for worsening congestive heart failure, as compared with 613 in the enalapril group (47.7 percent) (risk reduction, 26 percent; 95 percent confidence interval, 18 to 34 percent; P<0.0001) (Table 3 and Fig. 3). After one year, there were 401 such events in the placebo group (31.2 percent) as compared with 262 (20.4 percent) in the enalapril group (risk reduction, 40 percent; 95 percent confidence interval, 30 to 48 percent). After two years the corresponding numbers were 559 (43.5 percent) and 434 (33.8 percent) (risk reduction, 30 percent; 95 percent confidence interval, 21 to 38 percent). Subsequently, a further 24.4 percent of the placebo group and 21.0 percent of the enalapril group died or were hospitalized for congestive heart failure.

Table 4 provides further details about the patients requiring hospitalization for congestive heart failure. There were 971 hospitalizations for congestive heart failure in the placebo group as compared with 683 in the enalapril group. Two hundred thirty-four patients in the placebo group (18.2 percent) and 157 in the enalapril group (12.2 percent) were hospitalized more than once for worsening heart failure. The difference in mortality was observed only among the patients hospitalized at least once during the trial. Of the patients who died, 244 in the placebo group and 171 in the enalapril group were hospitalized for congestive heart failure during the trial. The proportions of patients who died without such a hospitalization were similar in the placebo and enalapril groups (20.7 and

Table 1. Base-Line Clinical Characteristics and Drug Therapy of the Patients in the Two Study Groups.

Characteristic	Placebo (N = 1284)	Enalapril (N = 1285)
	mean	
Age (yr)	61.0	60.7
Weight (kg)	79.6	79.9
Ejection fraction (%)	24.9	24.8
Blood pressure (mm Hg)		
Systolic	124.5	125.3
Diastolic	76.4	77.3
Heart rate (beats/min)	79.9	80.0
Serum sodium (mmol/liter)	139.7	139.7
Serum potassium (mmol/liter)	4.3	4.3
Serum creatinine (mg/dl)*	1.2	1.2
	percent of group	
Male sex	79.8	80.9
Race		
White	81.1	79.2
Black	14.5	16.2
Other	4.2	4.4
NYHA functional class†		
I	10.5	11.4
II	56.6	56.8
III	30.7	30.1
IV	1.9	1.5
Disease history		
Ischemic heart disease	72.1	70.2
Myocardial infarction	65.0	66.3
Hypertension	41.5	42.8
Diabetes mellitus	26.7	24.9
Idiopathic dilated cardiomyopathy	17.9	18.6
Current smoker	21.4	22.8
Current angina	38.9	36.1
Atrial fibrillation	7.9	11.5
Cardiothoracic ratio >0.50	55.6	57.6
Drug therapy		
Digitalis	68.2	65.7
Diuretics	85.3	85.6
Potassium-sparing diuretic	9.1	9.2
Vasodilators		
Any	52.4	49.7
Nitrates	43.8	39.6
Others	14.8	15.2
Antiarrhythmic drugs	20.8	22.8
Beta-blockers	7.0	8.3
Calcium-channel blockers	32.4	29.4
Anticoagulants	15.9	15.8
Antiplatelet agents	34.0	32.9
Potassium supplements	48.8	51.5

*To convert to micromoles per liter, multiply by 88.4.

†NYHA denotes New York Heart Association.

21.9 percent, respectively). Among the patients who were alive at the end of the study, a smaller proportion of those receiving active treatment were hospitalized at least once (29.2 percent in the placebo group vs. 19.3 percent in the enalapril group) or more than once (13.3 and 7.9 percent, respectively).

All Hospitalizations

Nine hundred fifty patients in the placebo group (74 percent) and 893 patients in the enalapril group (69 percent) were hospitalized at least once (P = 0.006). Eight hundred ten patients in the placebo group (63 percent) and 729 patients in the enalapril group (57 percent) were hospitalized for primarily cardiovascular reasons (P<0.001). Four hundred sixty patients in the placebo group (36 percent) and 399 in the enalapril group (31 percent) were hospitalized for noncardiovascular reasons. Although this difference was statistically significant (P = 0.006), it may be due to chance, because it was observed in many unrelated categories. The total numbers of hospitalizations were 2833 in the placebo group and 2396 in the enalapril group.

Effects in Subgroups

The protocol identified subgroups in which the effect of treatment on mortality and on the combined outcome of mortality or hospitalization would be examined, according to (1) the base-line sodium level, by tertiles; (2) whether or not patients used vasodilators other than angiotensin-converting–enzyme inhibitors at base line; (3) the base-line ejection fraction, by tertiles; and (4) the cause of congestive heart failure. When the results of CONSENSUS[3] were published, it was decided in addition to examine the effect of treatment in subgroups of patients divided according to New York Heart Association functional status at base line. Figure 4 shows that the effects of enalapril were consistent among most of these subgroups. The benefit with respect to the combined end point of death or hospitalizations appeared to be significantly smaller among the patients in the highest tertile for ejection fraction (chi-square for interaction, 6.93; P = 0.031). Even in this subgroup, however, there was a trend toward fewer deaths or hospitalizations in the enalapril group than in the placebo group (risk reduction, 12 percent; 95 percent confidence interval, −8 to +29 percent). Although there appeared to be slightly more deaths in the enalapril group among those with ejection fractions of 0.30 to 0.35 and among those in New York Heart Association class IV, these differences were not statistically different from those in the group as a whole, and the confidence intervals of the apparent effects were wide and included 15 percent risk reductions. The reductions in mortality and in the combined end point of death or hospitalizations with enalapril were almost the same whether or not patients used vasodilators

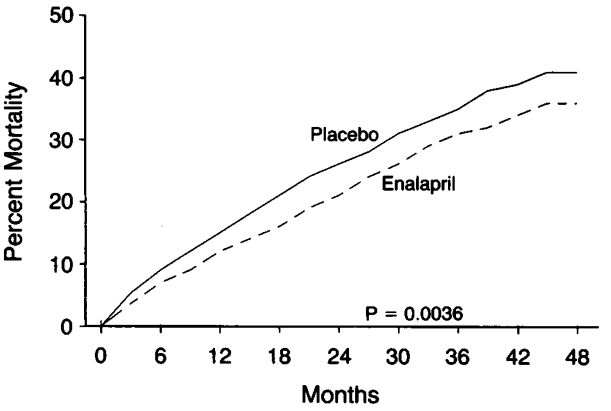

Figure 1. Mortality Curves in the Placebo and Enalapril Groups.

The numbers of patients alive in each group at the end of each period are shown at the bottom of the figure. P = 0.0036 for the comparison between groups by the log-rank test.

Table 2. Number of Deaths, Their Causes, and Number of Patients Who Died or Were Hospitalized for Congestive Heart Failure (CHF), According to Treatment Assignment.

Variable	Placebo	Enalapril	Risk Reduction (95% CI)*	Z Score	One-Sided P Value†
	number (percent)		*percent*		
Randomized patients	1284 (100.0)	1285 (100.0)	—	—	—
Deaths‡	510 (39.7)	452 (35.2)	16 (5 to 26)	2.69	<0.0036
Deaths or hospitalizations for CHF	736 (57.3)	613 (47.7)	26 (18 to 34)	5.65	<0.0001
Cardiovascular deaths	461 (35.9)	399 (31.1)	18 (6 to 28)	2.87	<0.002
Cardiac	441 (34.3)	376 (29.3)	19 (7 to 29)	3.02	<0.0015
Arrhythmia without worsening CHF	113 (8.8)	105 (8.2)	10 (−17 to 31)	0.81	—
Heart failure or arrhythmia with CHF	251 (19.5)	209 (16.3)	22 (6 to 35)	2.61	<0.0045
Myocardial infarction	53 (4.1)	40 (3.1)	28 (−8 to 52)	1.59	<0.07
Other	24 (1.9)	22 (1.7)	—	—	—
Stroke	11 (0.9)	10 (0.8)	—	—	—
Other vascular or unknown§	9 (0.7)	13 (1.0)	—	—	—
Noncardiovascular deaths	49 (3.8)	53 (4.1)	—	—	—

*Risk reductions were calculated from the log-rank analysis, reflecting the reduction in risk over the entire follow-up period. Ninety-five percent confidence intervals (CI) correspond to a two-sided P value of 0.05 or a one-sided P value of 0.025.

†Two-sided P values can be derived by doubling the values shown. For example, the two-sided P value for the difference in total mortality is 0.0072.

‡After January 31, 1991, but before the patients' last visits, there were eight additional deaths in the placebo group and six in the enalapril group. The inclusion of these deaths increased the total number of deaths to 518 in the placebo group and 458 in the enalapril group (Z = 2.74; P<0.003).

§For one death in the placebo group and one in the enalapril group, no detailed classification of the cause of death was available. Because 90 percent of deaths in patients with congestive heart failure are cardiovascular, it was decided in advance to include deaths from no known cause with the cardiovascular deaths.

other than angiotensin-converting–enzyme inhibitors at entry into the trial.

Adherence to Study Drug, Use of Nonstudy Drugs, and Side Effects after Randomization

When all randomized patients were considered, the final mean daily dose of enalapril was 11.2 mg, and the corresponding dose of matching placebo was 10.6 mg. Among the patients taking the study medication, the mean daily prescribed dose of enalapril was 16.6 mg, and that of placebo 18 mg. At the final visit, 1.8 percent of the patients in the enalapril group were receiving 2.5 mg daily, 6.7 percent were receiving 5 mg daily, 9.5 percent were receiving 10 mg once daily, and 49.3 percent were receiving 10 mg twice daily. The corresponding proportions in the placebo group were 0.6, 3.2, 5.5, and 49.1 percent. By the end of the study, 32.5 percent of the patients in the enalapril group and 41.4 percent of those in the placebo group had stopped taking blinded medication. The proportions of patients consuming at least 75 percent of the prescribed dose after one year were 77 percent in the placebo group and 80 percent in the enalapril group. After two years, the corresponding proportions were 67 and 74 percent, and after three years they were 60 and 69 percent. Open-label angiotensin-converting–enzyme inhibitors were used after one year in 12.4 percent of the patients receiving placebo as compared with 6.4 percent of those receiving enalapril; after two years, the corresponding proportions were 20.4 and 10.1 percent, and after three years, 23.0 and 13.9 percent. The study medication was discontinued in 320 patients in the placebo group and 182 patients in the enalapril group because of worsening congestive heart failure. Vasodilators other than angiotensin-converting–enzyme inhibitors were used more frequently in the placebo group than in the enalapril group (in 57.1 vs. 51.4 percent, respectively, after one year, 52.9 vs. 46.6 percent after two years, and 54.3 vs. 48.9 percent after three years).

The majority of the patients reported apparent side effects during the trial (87 percent in the enalapril group and 82 percent in the placebo group). In the enalapril group, there was significantly more dizziness or fainting (57 percent, vs. 50 percent in the placebo group) and cough (37 percent, vs. 31 percent). There was no excess of angioedema (3.8 percent in the enalapril group vs. 4.1 percent in the placebo group); most of the cases observed were mild and did not require the discontinuation of the medication. Cancer developed in 34 patients in the enalapril group and 22 in the placebo group, an apparent difference that was largely due to the number of cancers of the gastroin-

Table 3. Effect of Treatment on Mortality and Hospitalization for Congestive Heart Failure, and Proportion of Patients Taking Angiotensin-Converting–Enzyme Inhibitors after Various Periods.*

Months of Follow-up	Mortality			Death or Hospitalization for Heart Failure			Proportion Taking Inhibitors†	
	Placebo	Enalapril	Risk Reduction (95% CI)	Placebo	Enalapril	Risk Reduction (95% CI)	Placebo	Enalapril
	number		*percent*	*number*		*percent*	*percent*	
3	69	47	33 (2–53)	164	92	46 (30–57)	6	91
6	126	91	29 (8–46)	259	150	45 (33–55)	10	88
12	201	159	23 (5–37)	401	262	40 (30–48)	12	86
24	344	277	23 (10–34)	559	434	30 (21–38)	20	83
36	450	396	16 (4–27)	680	555	28 (19–35)	23	82
48	504	443	17 (5–27)	731	607	27 (18–34)	30	83
Overall‡	510	452	16 (5–26)	736	613	26 (18–34)	—	—
	Z = 2.69; P = 0.0036			Z = 5.65; P<0.0001				

*The 95 percent confidence intervals (CI) correspond to a two-sided P value of <0.05 or a one-sided P value of <0.025. Risk reductions were calculated by the log-rank test from the data available at each specific time.

†Values shown for three and six months were based on data obtained after the visits at four and eight months, respectively. The inhibitors were angiotensin-converting–enzyme inhibitors.

‡The total numbers of deaths were 518 and 458 when deaths after January 31, 1991, but before the patients' last visits, were included. See notes to Table 2.

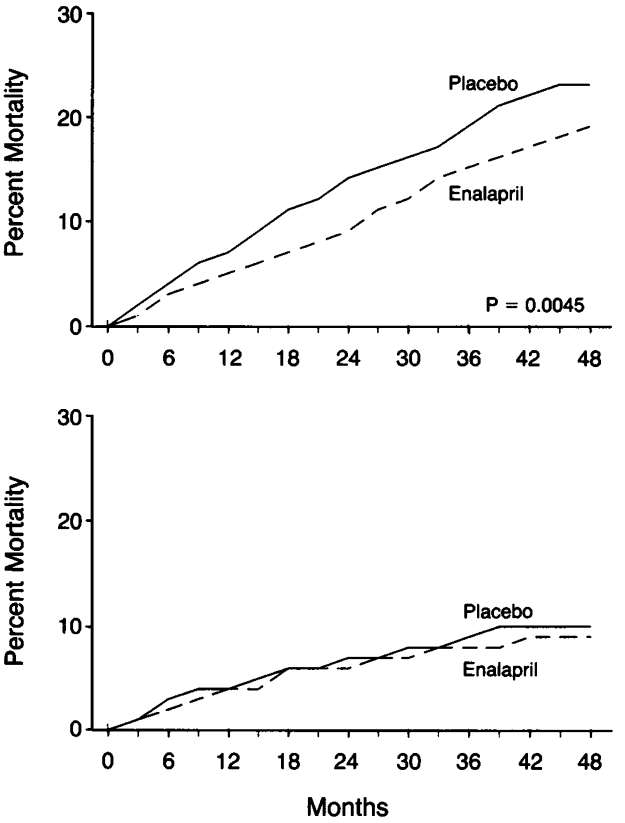

Figure 2. Mortality Due to Progressive Heart Failure (Upper Panel) (P = 0.0045) and Presumed to Be Due to an Arrhythmia but Not Preceded by Worsening Congestive Heart Failure (Lower Panel) (P Not Significant).

testinal tract, liver, gallbladder, and pancreas (18 and 9 in the respective groups; P not significant).

Changes in Blood Pressure, Electrolytes, and Renal Function

Systolic and diastolic blood pressures were significantly lower in the patients randomly assigned to enalapril than in the placebo group, by 4.7 and 4.0 mm Hg, respectively, when the results of all the follow-up visits were averaged. Although the serum sodium levels did not change on average, there were small but statistically significant increases in the serum levels of potassium and creatinine in the enalapril group (increases of 0.2 mmol per liter and 88 mmol per liter [0.1 mg per deciliter], respectively). The proportions of patients in whom the creatinine level increased to above 177 μmol per liter [2 mg per deciliter] or in whom the potassium level increased to above 5.5 mmol per liter were higher in the enalapril group than in the placebo group (10.7 vs. 7.7 percent, respectively, for creatinine, and 6.4 vs. 2.5 percent for potassium; $P<0.01$ for both).

Discussion

This study demonstrated a significant reduction in mortality and hospitalizations for congestive heart failure in patients treated with an angiotensin-converting–enzyme inhibitor, enalapril, in addition to conventional therapy for heart failure. Overall, enalapril therapy reduced mortality by 16 percent, an effect that is both clinically important and statistically significant. Besides the reduction in mortality, there were reductions in the proportions of patients hospitalized for congestive heart failure at least once or more than once. It appears that treating 1000 patients with congestive heart failure similar to those in this study with an angiotensin-converting–enzyme inhibitor for about three years would prevent about 50 premature deaths and an additional 350 hospitalizations.

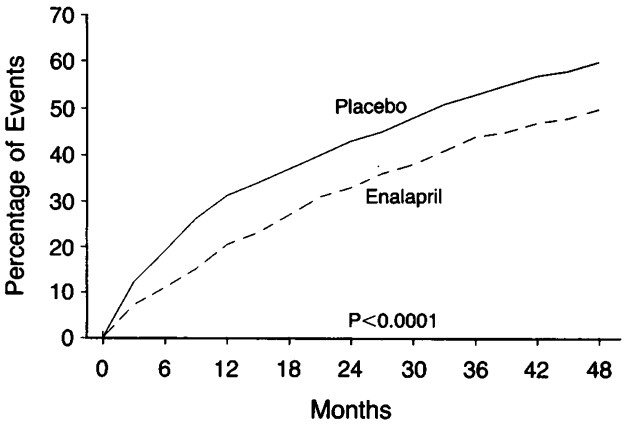

Figure 3. Percentage of Events, Defined as Death or Hospitalization for Congestive Heart Failure, Occurring in the Placebo and Enalapril Groups.

Table 4. Frequency of Hospitalization for Congestive Heart Failure, According to Vital Status at the End of the Study.*

Variable	Placebo	Enalapril
	number (percent)	
Vital status/no. of hospitalizations		
Alive		
0	548 (42.7)	672 (52.3)
1	123 (9.6)	95 (7.4)
2	48 (3.7)	31 (2.4)
3	27 (2.1)	15 (1.2)
≥4	28 (2.2)	20 (1.6)
Dead		
0	266 (20.7)	281 (21.9)
1	113 (8.8)	80 (6.2)
2	70 (5.4)	38 (3.0)
3	32 (2.5)	25 (1.9)
≥4	29 (2.2)	28 (2.2)
Patients hospitalized†		
At least once	470 (36.6)	332 (25.8)
Twice or more	234 (18.2)	157 (12.2)
All hospitalizations†	971 —	683 —
Patients dead or hospitalized†	736 (57.3)	613 (47.7)

*The distributions of patients with various numbers of hospitalizations were significantly lower in the enalapril group overall (chi-square of 37.2 with 4 df; $P<0.0001$), among the patients alive at the end of the study (chi-square of 22.5 with 4 df; $P<0.0001$), and among those who were dead by the end of the study (chi-square of 13.0 with 4 df; $P = 0.01$). There was no difference in the number of deaths among those who were not hospitalized during the trial for worsening congestive heart failure.

†All hospitalizations are tabulated, including those during which the patient died. If hospitalizations in which the patient died within seven days are excluded, then among those who died there were 202 patients in the placebo group as compared with 139 in the enalapril group who were hospitalized at least once for congestive heart failure. On the basis of these criteria, the total numbers of patients hospitalized would be 428 in the placebo group as compared with 300 in the enalapril group, the numbers hospitalized twice or more would be 208 and 135, respectively, and the total number of hospitalizations would be 869 and 593. All the differences are significant ($P<0.001$).

The reductions in mortality and rates of hospitalization for heart failure were observed soon after randomization, and the difference increased for as much as about 24 months. At that time, there was a 23 percent reduction in mortality and a 30 percent reduction in the risk of hospitalization or death. Subsequently, the mortality curves for the two study groups diverged slightly. Of the patients alive after 24 months, 17.7 percent of those receiving placebo and 17.4 percent of those treated with enalapril died by the end of the study. The possibility of further benefit after the first two years was supported by the data on the combined end point of hospitalization or death. After two years 559 of the placebo group (43.5 percent) and 434 of the enalapril group (33.8 percent) had reached this end point. An additional 24.4 percent of the placebo group and 21.0 percent of the enalapril group died or were hospitalized after two years, indicating a continued benefit from the active drug.

More patients taking placebo than taking enalapril received other vasodilators during the trial to treat worsening congestive heart failure. Therefore, the risk reductions of 16 percent for mortality and 26 percent for the combined outcome of mortality or hospitaliza-

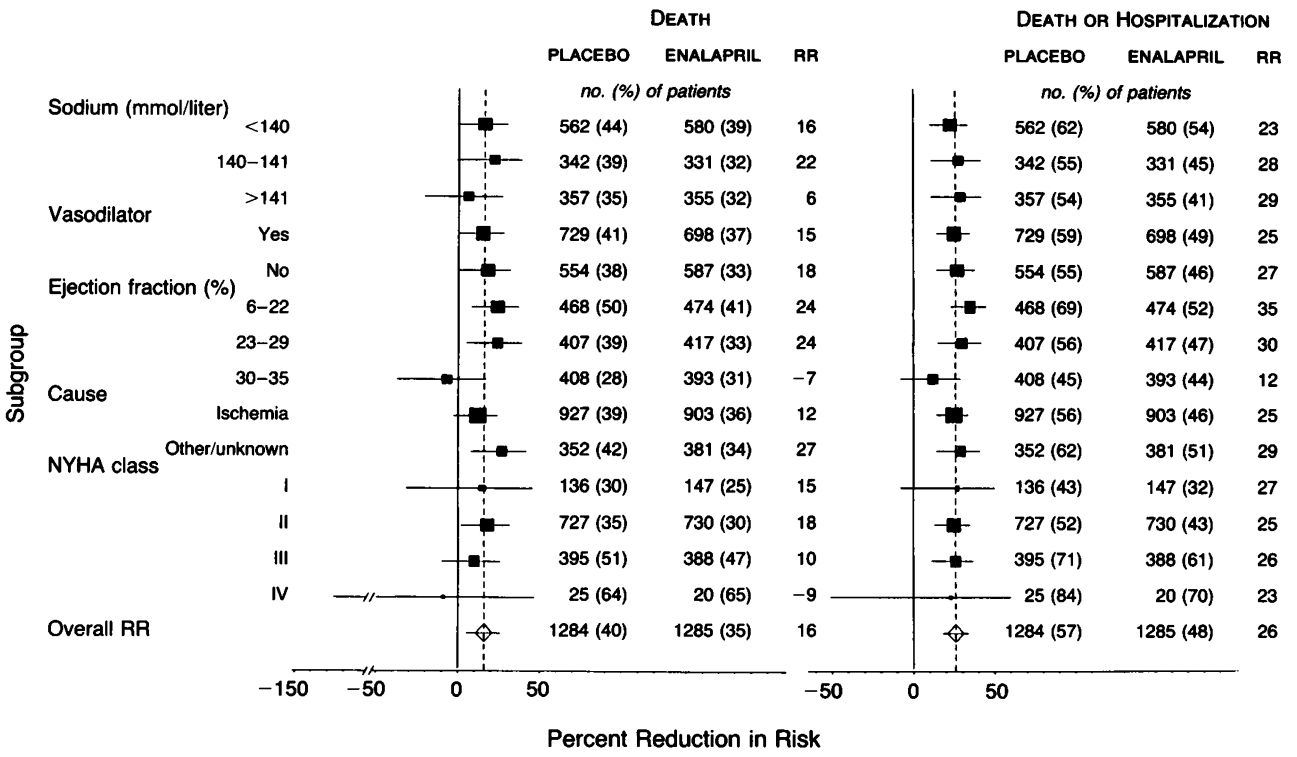

Figure 4. Effect of Enalapril on the Two Main Study End Points in Various Subgroups, Determined on the Basis of the Hypotheses Specified in the Protocol.

For each subgroup, the percentage of risk reduction (RR) with enalapril is plotted (solid squares). Horizontal lines represent 95 percent confidence intervals. The size of each square is proportional to the number of events in the subgroup. The diamonds at the bottom of each panel represent the overall result for each end point. The bold vertical line corresponds to a finding of no effect. The dashed vertical line is the RR observed overall, expressed as a positive number on the scale. The RRs in individual subgroups are mostly distributed around the dashed vertical line, except for the group in the highest tertile of ejection fraction (>0.30 to 0.35). The chi-square for interaction testing for the effect of enalapril on mortality in the tertiles of ejection fraction was 5.55 ($P = 0.06$), and for the combined end point of mortality or hospitalization, the corresponding value was 6.93 ($P = 0.03$). Given the number of subgroup hypotheses tested, this significant interaction between subgroups should be interpreted cautiously. Tests for interaction in the other subgroups were not significant. NYHA denotes New York Heart Association.

tion for congestive heart failure that were determined with the intention-to-treat analysis over the course of the trial probably underestimate the actual benefits of angiotensin-converting–enzyme inhibitors (Table 3).

The overall results of this trial are consistent with the results of CONSENSUS and an overview of other small trials of angiotensin-converting–enzyme inhibitors in congestive heart failure.[3,7] In previous studies, however, the average duration of treatment was only a few months, and entry was restricted to patients with severe congestive heart failure.[3,6,7] Our study extended these observations by providing information on a longer period of treatment (average, 41 months) and on hospitalizations in a broader range of patients with clinically stable congestive heart failure. As expected, the reduction in mortality resulted from a reduction in cardiac deaths. Within this category, the largest difference was observed among deaths classified as being due to progressive congestive heart failure, with little difference in presumed mortality from arrhythmia without previous worsening congestive heart failure. Although our classification system was somewhat different from that used in CONSENSUS, in both trials the greatest benefit of treatment involved deaths from progressive heart failure, and there was no effect on presumed deaths from arrhythmia. These results are consistent with the reduction in the rate of hospitalizations for congestive heart failure and with the observation that the difference in mortality occurred entirely among patients who had been hospitalized for congestive heart failure during the trial. Therefore, the prevention of hospitalization for congestive heart failure may be an effect of angiotensin-converting–enzyme inhibitors that is linked to their ability to reduce mortality. In addition, there was a worthwhile reduction in the number of patients who were hospitalized at least once or repeatedly for congestive heart failure among the patients who were alive at the end of the study. Reductions in deaths and rates of hospitalization from worsening heart failure may be related to improvements in ejection fraction and exercise capac-

ity, to a decrease in signs and symptoms of congestion,[6] and also to the known mechanism of action of the agent — i.e., a decrease in preload and afterload when the conversion of angiotensin I to angiotensin II is blocked.[5]

With enalapril treatment, the reductions in mortality and hospitalizations combined were not significantly different among the various subgroups examined, regardless of their serum sodium level at entry, New York Heart Association functional class, or use of other vasodilators. The effects in most subgroups were generally consistent with the results of the CONSENSUS trial. The benefits of the drug for mortality alone and for the combined end point appeared to be greatest in the patients in the lowest two tertiles of the ejection-fraction distribution. Even in the highest tertile, however, there was a trend toward fewer hospitalizations among those alive at the end of the study (placebo, 70; enalapril, 51), and the 95 percent confidence interval for the combined end point included the possibility of a risk reduction of 20 percent. Among those in New York Heart Association class IV, there appeared to be no difference in mortality between the study groups. This lack of benefit is probably due to chance, however, because of the small numbers of patients in this subgroup. Moreover, the 95 percent confidence interval included the possibility of a benefit, and a clearly significant benefit was observed in the CONSENSUS trial, which included only patients in class IV.

The most common side effects noted in this study were hypotension and increased serum creatinine levels. These side effects can be predicted on the basis of the pharmacologic effect of an angiotensin-converting–enzyme inhibitor. In patients who are critically dependent on high levels of angiotensin II to maintain blood pressure and renal perfusion, it would be prudent to start treatment with small doses of enalapril (e.g., 2.5 mg twice a day) with gradual increments, monitoring blood pressure and renal function and reducing the diuretic dose when necessary. For the majority of patients in this trial, treatment was begun on an outpatient basis. Of all patients entering the run-in period of the active drug, 1.2 percent were thought to be at risk of serious hypotension and were hospitalized for 24 hours during the initiation of the drug. Among such patients were those with "unstable" congestive heart failure who required high doses of diuretics or a number of vasodilators, patients in New York Heart Association class IV, and those with marked hyponatremia. The majority of patients with these conditions, however, were not hospitalized for the start of therapy. Symptomatic hypotension occurred not only during the start of treatment with enalapril but also later. These data indicate that although hypotension and prerenal azotemia are infrequent or not usually troublesome, careful monitoring is advisable, especially during changes in the dose of an angiotensin-converting–enzyme inhibitor or diuretics. It is also prudent to monitor potassium levels during the initiation of treatment with angiotensin-converting–enzyme inhibitors and if necessary to withdraw or reduce the doses of potassium supplements and potassium-sparing diuretics.

A small, nonsignificant difference in the sum of nonfatal cancers of the gastrointestinal tract, liver, gallbladder, and pancreas was observed, with more found in the enalapril group. This difference may well be due to chance, because of the multiplicity of sites involved and the large number of comparisons made. It is also possible that since the patients in the enalapril group had fewer symptoms of heart failure than those in the placebo group, they may have undergone more diagnostic procedures of the gastrointestinal tract, leading to a bias in detection. The frequency of gastrointestinal system neoplasia did not increase with longer drug exposure, as would be expected if there were a causal relation.

Although the results of this trial are encouraging with respect to mortality and morbidity and are consistent with the results of other smaller and shorter trials, there are a few sobering implications. The causes of death among patients with congestive heart failure were varied. The most common cause was worsening congestive heart failure, but it still constituted less than half of all deaths. Even a sizable reduction in the risk of this category of death (e.g., by one third) is likely to lead to only a moderate reduction (e.g., by one sixth) in the overall risk of death. These data suggest the need to explore several different approaches to reducing mortality in these patients. It is likely that most treatments will not reduce the risk of overall death by more than 10 percent or 20 percent unless they affect more than one mechanism of death. Nevertheless, given the high annual mortality rates in patients with congestive heart failure, an intervention that confers only a 15 percent risk reduction in mortality could potentially prevent at least as many premature deaths for every 100 patients treated as various treatments used in other common cardiovascular conditions, such as moderate hypertension or after a myocardial infarction.

The results of this trial should not be extrapolated to asymptomatic patients who have only low ejection fractions. Such patients have little activation of their serum renin–angiotensin system,[15] and for them angiotensin-converting–enzyme inhibitors may be less effective. The effects of enalapril in asymptomatic patients with low ejection fractions are currently being evaluated in the SOLVD Prevention Trial.

We are indebted to the patients for their willingness to volunteer for the trial; to the several hundred physicians who referred patients, for their cooperation; to Merck Sharp and Dohme for supplying drug and placebo; to Zola Hall for assistance in the preparation of the manuscript; and to John Allegretti, Susan Brooks, Michele Hyman, and Michael Kelly for their assistance.

Appendix

The following persons and institutions participated in the SOLVD study:

University of Michigan Medical Center, Ann Arbor — John M. Nicklas,* Bertram Pitt,* Gerald Timmis, Gerald Breneman, Syed Jafri, Wolf F.C. Duvernoy, Shukri W. Davis, Mark J. Goldberg, Joseph Blair, G.B. John Mancini, Terri Johnson, Cheryl Luckoff, Gregory Henry, Mary Beth Wlodkowski, Mary Czajka, Dori Reinstein, Judy Richards, Ruth Lewis, Debbi Davey, Corrine Mallott, Angie Moll, Laura Quain, Peter Thomasma, and Susan Schreiber; *University of Alabama at Birmingham Medical Center,* Birmingham — William J. Rogers,* Joaquin G. Arciniegas, Vera Bittner, Thomas M. Bulle, J. Bradley Cavender, Edgar D. Charles, Louis J. Dell'Italia, Milena Henzlova, William A. MacLean, Silvio E. Papapietro, Michael F. Salvia, L. Thomas Sheffield, Alfred W.H. Stanley, Eric Van Tassel, Herman A. Taylor, Kim Carlisle, Andrea Baker, Glenda Blackburn, Beth Bonville, Karen Bynum, Suzanne Deriso, Donna Kerns, Nancy Lambert, Lynn Merritt, Vally Nance, Elizabeth Reddy, Faye Atkins, and Melanie Cox; *University of Louvain,* Brussels, Belgium — Hubert Pouleur,* Michel F. Rousseau,* Jacques Melin, Baudouin Marchandise, Erwin Schroeder, and Sylvie Ahn; *Brigham and Women's Hospital, Harvard Medical School,* and *Brockton–West Roxbury Veterans Affairs Medical Center,* Boston — Kevin M. McIntyre,* Donald Tow, Daniel Pietro, Edward Gillie, G.V.R.K. Sharma, Patricia Woods, Mary Ellen C. Dondero, Robert Brown, W. Strauss, and Joseph Loscalzo; *Tufts–New England Medical Center,* Boston — Deeb Salem,* Marvin A. Konstam, James E. Udelson, Alan Weinshel, William Gaasch, Noreen Dolan, Ruth Hoshino, Cindy Lane, Susan Kelly, Lorraine Kilcoyne, and Linda Paradise; *Weiler Hospital, Albert Einstein College of Medicine,* Bronx, N.Y. — Thierry H. LeJemtel,* William H. Frishman, J. Wexler, Marie Galvao, Lee Ann Mills, and Margaret Jones; *Buffalo General Hospital,* Buffalo, N.Y. — Robert M. Kohn,* Philip D. Morey, Kenton E. Forte, Michael J. Hong, Joseph L. Maddi, Joseph A. Zizzi, Jr., Edward J. Bernaski, Nancy A. Roberts, Mary M. Bonora, Josephine A. Celano, Lois D. Banks, and Elaine M. Muffoletto; *University of Illinois School of Medicine,* Chicago — Stuart Rich,* Bruce H. Brundage,* Jeffrey G. Shanes,* Mary Ann Papp, James Mathew, Laurence Berarducci, Sandra Davidson, Barbara J. Dierenfeldt, Susan Stanford, Jalal K. Ghali, Patricia Mumby, and Towanda Adams; *University of Florida and Veterans Affairs Medical Center,* Gainesville — Carl J. Pepine,* C. Richard Conti, J.L. Mehta, Marian C. Limacher, Robert L. Feldman, Edward A. Geiser, James A. Hill, Charles R. Lambert, Xavier Prida, Kate McCoy, Ariel Miranda, Nancy K. Norvell, J. Russell Green, Jr., Alan B. Miller, D. Lynn Perchalski, Eileen Handberg, and Barbara Hall; *Victoria General Hospital,* Halifax, Canada — David E. Johnstone,* M.J. Gardner, T.J. Montague, L.D. Lalonde, G.A. Klassen, K.K. Teo, B.M. Chandler, Beryl Carew, Sharon Black, Sylvia Martin, and Monica Francis; *Baylor College of Medicine,* Houston — James B. Young,* Craig M. Pratt, Miguel A. Quinones, Robert Roberts, Connie Kingry, Deborah Gibson, Claudette Foreman, and Marilyn Francis; *Michigan State University,* Lansing — Philip C. Kirlin,* Park W. Willis, III,* John W. Jones, Walter M. Baird, Timothy Fritz, Benjamin Perry, Richard McNamara, Raymond H. Murray, Linda E. Scaffidi, Helen Boichot, Nancy Solis, Cheryl Bachman, Chrysanthe Fooy, Kristin McKay, Mary Van der Puy, Karen Hiner, Eileen Worden, and Patricia Hearns; *University of Minnesota Medical School,* Minneapolis — Jay N. Cohn,* Spencer H. Kubo, Gary S. Francis, Charles Peterson, Irvin F. Goldenberg, John W. McBride, David Berman, William Hession, Steven R. Goldsmith, Wes R. Pederson, Susan Holmer, Gina K. Bjerken, Kris Monson, Joanne Pearson, Barbara O'Toole-Brehm, and Linda Mensing; *Montreal Heart Institute,* Montreal — Martial G. Bourassa,* Claude Goulet, Michel Joyal, Gilbert Gosselin, Micheline Labbe, Margot Methe, Helene Benjamin, Suzanne Morin, and Diane Leclerc; *Vanderbilt University School of Medicine,* Nashville — Marvin W. Kronenberg,* Gottlieb C. Friesinger,* Benjamin F. Byrd III, W. Barton Campbell, John H. Nadeau, Stephen Schillig, Donna M. Howe, Tonya R. Edens, Yvonne D. Bernard, Louise A. Brown, and Raphael F. Smith; *University of Medicine and Dentistry of New Jersey* and *Robert Wood Johnson Medical School,* New Brunswick — John B. Kostis,* Daniel M. Shindler, Clifton R. Lacy, Sumathisena, Sophia Karstensen, Joanne Williams, Barbara Hill, Lee Wood, and Jeanette Steinhagen; *Temple University Hospital,* Philadelphia — Mariell Jessup,* Susan Brozena,* Mark Victor, John Hagaman, Miriam Cannon, Jeannie McDonough, Susan Luhmann, Andrew L. Smith, Joann Kelly, and Darlene Stinson; *Oregon Health Sciences University,* Portland — Barry Greenberg,* Henry DeMots, John Grover, Steven Reinhart, Deirdre Nauman, Diana Dutton, Maureen Guillotte, and Marita Schmit; *Brown University,* Providence, R.I. — Robert J. Capone,* Candace McNulty, Satish Sharma, Ara Sadaniantz, Larry Gorkin, Kathy Handshaw, Louise Erikson, Concetta Lamore, Linda Redfern, Patricia Rubbert, and Denise Tremblay; *University of Rochester Medical Center,* Rochester, N.Y. — William B. Hood, Jr.,* Chang-seng Liang, Patricia G. Fitzpatrick, J. Franklin Richeson, Kathryn J. Acciari, Lorrie D. Divers, Tanya M. Stone, Mary J. Farrell, Kathleen D. Miller, Karen L. Wellington, Robert M. Easley, Jr., Gerald F. Ryan, Serge Barold, John A. Gillespie, Lisa Cove, Michael P. Roache, and Julene M. Malcolm; *University of Washington Medical Center,* Seattle — Douglas K. Stewart,* J. Ward Kennedy, James H. Caldwell, John A. Murray, Ted D. Hegg, Robert Wallach, Roger Chumusco, Peter Kudenchuck, Stephen Olmstead, Harold Dash, Jay Gorham, Arthur Resnick, Linda Cahill, Rebecca Letterer, Therese Kempf, Polly Gardner, Joy Dalquist, and Michele Olsufka; *Overlook Hospital,* Summit, N.J. — John J. Gregory,* Donald C. Brock, Robert Lauer, Andrew Greene, Stephen J. Fischl, Robert Slama, Elliot Stein, Alan Kalischer, Linda Diehl, Susan Facchinei, Judith Romano, Elizabeth O'Leary, Gertrude Kimball, and Lisa Brock; *Westchester County Medical Center, New York Medical College,* Valhalla — Michael V. Herman,* Melvin B. Weiss, Richard H. Kay, Michael Evans, Kenneth Lerrick, Craig Unger, Steven Ripa, Jeffrey Blake, Marette Reid, Denise Braga, Nancy Treulieb, and Terri Cutrone.

The central laboratories and staff members participating in the study were as follows: Arrhythmia Laboratory, Baylor College of Medicine, Houston — Craig Pratt,* Marilyn Francis, Linda Miller, Kay Yang, and Gary Marks; Echocardiography Laboratory, Baylor College of Medicine — Miguel A. Quinones,* Helen Kopelen, and Augusto Galan; Exercise Laboratory, University of Rochester Medical School, Rochester, N.Y. — Chang-seng Liang* and Andrea W. Moore; Neurohumoral Laboratory, University of Texas Health Science Center, Houston — Claude Benedict,* O. Bryan Holland, Francis Bodola, David Cappolino, Wen Lu Sheng, Sreevatsa Chakravarthy, Azam A. Entezami, Cheryl Sullivan, and Chung-Wun Wu; Radionuclide Laboratory, Tufts University, Boston — Marvin A. Konstam,* James E. Udelson, Jeanne Metherall, Debra Kinan, and Hasida Toltsis.

Coordinating Center, University of North Carolina at Chapel Hill — Clarence E. Davis,* James D. Hosking, Shrikant I. Bangdiwala, Joan Fiorello Barrett, Carlos Garces, Kenneth M. Kral, Elizabeth R. Toretsky, Marston E. Youngblood, Dawn Stewart, Carol J. Hazard, Debra H. Weiner, Kirkwood F. Adams, Jr., Lars-Goran Ekelund, George Williams, Brent J. Shelton, Doris Jones, and Vickie Smith.

Project Office, Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, Bethesda, Md. — Salim Yusuf,* Jeffrey Probstfield, Joel Verter, Eleanor Schron, Sally Shumaker, Peter Held, Myron Waclawiw, Eileen Webster, Patricia Davis, and Linda Gardner.

Executive Committee — Bertram Pitt (chairman), Jay N. Cohn, Clarence E. Davis, William B. Hood, Jeffrey Probstfield, and Salim Yusuf (project officer). Data and Safety Monitoring Board — Elliot Rapaport (chairman), Byron W. Brown, Lawrence S. Cohen, Max Halperin (deceased), Milton Packer, Leroy Walters, Rolf Gunnar, and William Friedewald.

The following persons chaired the study subcommittees: Recruitment — William J. Rogers (chairman) and Michael Herman (vice-chair), Adherence/Follow-up — Deeb Salem (chairman) and Kevin M. McIntyre (vice-chair); Registry — Martial G. Bourassa (chairman) and Gottlieb C. Friesinger (vice-chair); and Substudies/Pub-

lications — Robert J. Capone (chairman) and Barry H. Greenberg (vice-chair). The members of the writing committee were Salim Yusuf, Bertram Pitt, Clarence E. Davis, William B. Hood, and Jay N. Cohn.

*Principal investigator.

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