EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

THE SOLVD INVESTIGATORS*

Abstract *Background.* It is not known whether the treatment of patients with asymptomatic left ventricular dysfunction reduces mortality and morbidity. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on total mortality and mortality from cardiovascular causes, the development of heart failure, and hospitalization for heart failure among patients with ejection fractions of 0.35 or less who were not receiving drug treatment for heart failure.

Methods. Patients were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial. Follow-up averaged 37.4 months.

Results. There were 334 deaths in the placebo group, as compared with 313 in the enalapril group (reduction in risk, 8 percent by the log-rank test; 95 percent confidence interval, −8 percent [an increase of 8 percent] to 21 percent; P = 0.30). The reduction in mortality from cardiovascular causes was larger but was not statistically significant (298 deaths in the placebo group vs. 265 in the enalapril group; risk reduction, 12 percent; 95 percent confidence interval, −3 to 26 percent; P = 0.12). When we combined patients in whom heart failure developed and those who died, the total number of deaths and cases of heart failure was lower in the enalapril group than in the placebo group (630 vs. 818; risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (434 in the enalapril group vs. 518 in the placebo group; risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P<0.001).

Conclusions. The angiotensin-converting–enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction. There was also a trend toward fewer deaths due to cardiovascular causes among the patients who received enalapril. (N Engl J Med 1992;327:685-91.)

ANGIOTENSIN-converting–enzyme inhibitors reduce mortality and the need for hospitalization and improve functional status in patients with symptomatic congestive heart failure.[1-3] Despite such treatment, however, the mortality and morbidity rates associated with this condition are still high. Efforts to prevent the development of heart failure in patients with asymptomatic left ventricular dysfunction are therefore warranted.

Angiotensin-converting–enzyme inhibitors improve the ejection fraction and exercise tolerance in asymptomatic patients with myocardial infarction and low ejection fractions.[4,5] The effects of such drugs on survival, the incidence of heart failure, and the frequency of hospitalization for heart failure are not known, however. This Prevention Trial, a part of the Studies of Left Ventricular Dysfunction (SOLVD), was designed to determine whether an angiotensin-converting–enzyme inhibitor, enalapril, could reduce mortality, the incidence of heart failure, and the rate of related hospitalizations in patients with ejection fractions of 0.35 or less who were not receiving therapy for heart failure (henceforth referred to as patients with asymptomatic left ventricular dysfunction).

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

METHODS

Organization of the Study

The SOLVD Prevention Trial was a randomized, double-blind, placebo-controlled trial. A total of 4228 patients with asymptomatic left ventricular dysfunction were randomly assigned to receive either enalapril or placebo at one of 83 hospitals linked to 23 centers in the United States, Canada, and Belgium. All data were collected and analyzed at the coordinating center at the University of North Carolina at Chapel Hill. The study was organized and conducted by the project office located at the Clinical Trials Branch of the National Heart, Lung, and Blood Institute and by a steering committee consisting of principal investigators from the centers.[6] An independent Data and Safety Monitoring Board oversaw the progress of the study. The study was approved by the institutional review board of each hospital, and all the patients provided informed consent.

Eligibility of Patients, Run-in Period, and Randomization

Patients known to have heart disease who had ejection fractions of 0.35 or less and who were not receiving diuretics, digoxin, or vasodilators for the treatment of heart failure were eligible for the Prevention Trial. Patients were allowed to receive diuretics for hypertension, digoxin for current or past atrial fibrillation, or nitrates for angina. Details of the measurement of the ejection fraction, exclusion criteria, screening procedure, and the run-in period have been reported previously.[1,6] Patients who had no evidence of overt heart failure at the end of the three-week run-in period, during which they were given enalapril for the first week and placebo for the remainder, were entered into the Prevention Trial. Patients were randomly assigned to receive enalapril at an initial dose of 2.5 mg twice daily, which was gradually increased to 10 mg twice daily unless side effects developed, or a matching placebo. After randomization, the patients were seen after two weeks, six weeks, and four months, and every four months thereafter.

Follow-up and Outcome Measures

At the time of this report, the vital status of four patients in the enalapril group and three in the placebo group was unknown. For all patients not lost to follow-up, information on clinical status, the

development of heart failure, use of medications other than those prescribed as part of the study, hospitalizations, adherence to the study regimen, and side effects was systematically recorded at each follow-up visit. For patients who died, were hospitalized, or had heart failure, the cause of death, the primary reason for hospitalization, and the development of heart failure were ascertained and classified by the principal investigator at each center, who was unaware of the patients' treatment, using standardized forms. Four overlapping definitions of heart failure, of increasing severity, were used: (1) heart failure, identified by the study physician on the basis of symptoms, signs, or the need for changes in therapy; (2) heart failure requiring the addition of a diuretic, digoxin, or a vasodilator to the patient's regimen (in the case of patients already receiving any one of these drugs at base line, the additional drug had to be prescribed for this indication); (3) heart failure requiring hospitalization; and (4) progressive heart failure causing death. When heart failure developed, the patients' physicians could use treatments at their discretion, but it was recommended that angiotensin-converting–enzyme inhibitors be used only after other drugs had been tried.

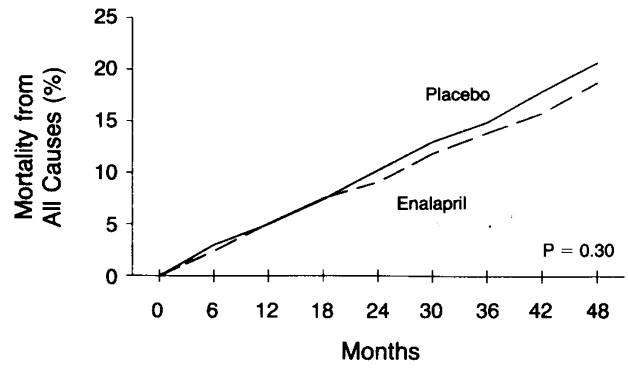
Table 1. Base-Line Clinical Characteristics and Drug Therapy, According to Treatment Group.

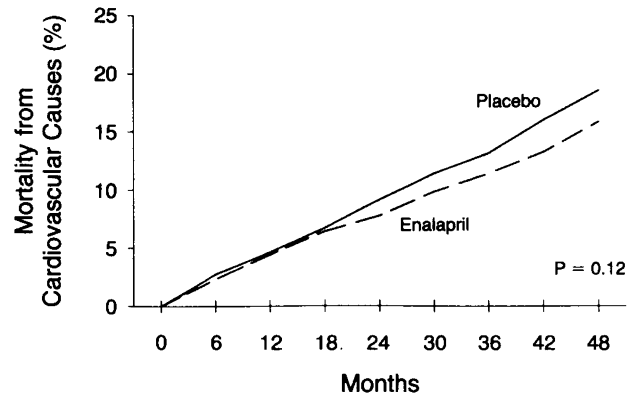
Characteristic	Placebo (N = 2117)	Enalapril (N = 2111)
	mean value	
Age (yr)	59.1	59.1
Weight (kg)	81.6	80.9
Ejection fraction	0.28	0.28
Blood pressure (mm Hg)		
Systolic	125.6	125.3
Diastolic	78.0	77.9
Heart rate (beats/min)	75.2	74.6
Serum sodium (mmol/liter)	140.2	140.3
Serum potassium (mmol/liter)	4.4	4.3
Serum creatinine (mg/dl)*	1.2	1.2
	% of group	
Male sex	88.6	88.5
Race		
White	86.5	86.4
Black	9.7	9.2
Other	3.4	4.1
NYHA functional class†		
I	67.1	66.3
II	32.7	33.4
History		
Ischemic heart disease	82.9	83.5
Myocardial infarction	79.4	80.5
Hypertension	37.3	36.8
Diabetes mellitus	15.1	15.4
Idiopathic dilated cardiomyopathy	10.1	8.6
Cigarette smoking‡	24.1	22.8
Angina‡	33.8	33.8
Atrial fibrillation‡	4.0	3.9
Cardiothoracic ratio >0.50	40.2	39.6
Drug therapy		
Neither digoxin nor diuretics	72.3	74.9
Digoxin	13.2	11.7
Diuretics	17.0	16.2
Potassium-sparing diuretic	4.0	3.9
Any vasodilator	45.7	47.1
Nitrates	29.9	30.6
Antiarrhythmic drugs	15.7	14.4
Beta-blockers	23.7	24.3
Calcium-channel blockers	34.1	35.6
Anticoagulant agents	12.3	11.2
Antiplatelet agents	52.7	55.7
Potassium supplements	6.4	5.5

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

†Five patients in NYHA class III were inadvertently enrolled in the Prevention Trial and have been retained in the analyses. No deaths or hospitalizations occurred among these five patients.

‡At base line.





Placebo	2117	2054	2009	1854	1566	1234	934	627	399
Enalapril	2111	2059	2000	1837	1580	1244	955	684	436

Figure 1. Total Mortality (Upper Panel) and Mortality from Cardiovascular Causes (Lower Panel) in the Prevention Trial.
The numbers at the bottom of the figure are the numbers of patients in each group who were alive at base line and after each six-month period.

Statistical Analysis

The primary hypothesis of the Prevention Trial was that enalapril would reduce total mortality. A subsidiary hypothesis was that enalapril would reduce the incidence of heart failure and the rate of hospitalization for heart failure. The last two end points were combined with mortality to avoid the problem of competing risks.[7] Such analyses are more conservative and methodologically more correct than analyses of secondary outcomes alone. However, data on the incidence of heart failure and hospitalization are also provided in the tables. A one-sided test with a significance level of 0.025 (equivalent to a nominal two-sided P value of 0.05) was specified in the protocol; however, at the request of the *Journal*, two-sided significance levels are reported. We estimated that a sample of 4100 patients followed for an average of three years would provide a 90 percent power to detect a 25 percent reduction in mortality.[1,6] The sample size was increased to 4600 in order to protect against unexpectedly low event rates or poor compliance. We recruited 4228 patients from July 1986 through May 1990. A termination date of August 31, 1991, was set for the study in advance. Deaths occurring between the patients' final follow-up visits and this date are also

reported. Details of monitoring, adjustment of the critical z value, and tests for heterogeneity have been reported earlier.[1] A stratified log-rank statistic was used to compare the life-table survival curves and the development of heart failure for all patients randomly assigned to the two groups.[8,9]

Results

The clinical characteristics of the two study groups were similar at base line (Table 1). The mean left ventricular ejection fraction was 0.28; 67 percent of the patients were in New York Heart Association (NYHA) functional class I, and 33 percent were in class II; one third of the patients had angina, and 74 percent were not receiving diuretics or digoxin for any reason. The average follow-up was 37.4 months (range, 14.6 to 62.0).

Mortality

There were 334 deaths in the placebo group, as compared with 313 in the enalapril group, for a reduction in risk of 8 percent as calculated from the log-rank test (95 percent confidence interval, −8 percent [an increase of 8 percent] to 21 percent; P = 0.30) (Fig. 1 and Table 2). The difference was entirely due to a reduction in deaths due to cardiovascular causes (298 in the placebo group, as compared with 265 in the enalapril group; risk reduction, 12 percent; 95 percent confidence interval, −3 to 26 percent; P = 0.12). Among the deaths from cardiovascular causes, the difference in mortality between the groups was observed mainly in terms of those classified as due to progressive heart failure (106 in the placebo group vs. 85 in the enalapril group); there was little difference between the groups in the number of deaths presumed to be due primarily to arrhythmia (105 vs. 98).

Hospitalization for Heart Failure

Altogether, 518 patients in the placebo group (24.5 percent) and 434 in the enalapril group (20.6 percent) died or were hospitalized for new or worsening heart failure (risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P<0.001) (Table 2 and Fig. 2). By one year, there had been 218 such events in the placebo group (10.3 percent), as compared with 167 in the enalapril group (7.9 percent) (risk reduction, 25 percent; 95 percent confidence interval, 8 to 38 percent). After one year there were a further 300 such events among the 1899 remaining patients in the placebo group (15.8 percent), as compared with 267 among the 1944 in the enalapril group (13.7 percent).

There were 454 hospitalizations for heart failure in the placebo group, as compared with 306 in the enalapril group; 102 patients in the placebo group (4.8 percent) and 58 patients in the enalapril group (2.7 percent) were hospitalized more than once for worsening heart failure (risk reduction, 44 percent; 95 percent confidence interval, 23 to 59 percent). The median length of time to the first hospitalization for heart failure was 13.2 months in the placebo group. The length of time before there were a similar number of hospitalizations in the enalapril group was 27.8 months.

Development of Heart Failure

In the placebo group, 818 patients had heart failure or died (38.6 percent), as compared with 630 in the enalapril group (29.8 percent) (Fig. 2) (risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P<0.001). The median length of time to the development of heart failure was 8.3 months in the placebo group. The length of time to the development of a similar number of events in the enalapril group was 22.3 months. Significant reductions in the incidence of heart failure were observed regardless of the definition of heart failure used. The difference in the rates of heart failure was seen as early as three months after randomization (143 patients in the pla-

Table 2. Deaths, Causes of Death, Development of Heart Failure, and Hospitalizations for Heart Failure, According to Treatment Group.

Cause of Death or Type of Event	Placebo (N = 2117)	Enalapril (N = 2111)	Reduction in Risk (95% CI)*	z Score	P Value†
	no. (%)		%		
Death‡					
All causes	334 (15.8)	313 (14.8)	8 (−8 to 21)	1.02	0.30
Cardiovascular causes	298 (14.1)	265 (12.6)	12 (−3 to 26)	1.57	0.12
Cardiac	271 (12.8)	238 (11.3)	13 (−3 to 27)	1.63	0.10
Arrhythmia without worsening CHF	105 (5.0)	98 (4.6)	7 (−22 to 30)	0.54	NS
Progressive heart failure (pump failure or arrhythmia with CHF)	106 (5.0)	85 (4.0)	21 (−5 to 41)	1.64	0.10
Myocardial infarction	52 (2.5)	46 (2.2)	14 (−28 to 42)	0.74	ND
Other	8 (0.4)	9 (0.4)	—	—	ND
Stroke	13 (0.6)	10 (0.5)	—	—	ND
Other vascular cause or unknown	14 (0.7)	17 (0.8)	—	—	ND
Noncardiovascular causes	36 (1.7)	48 (2.3)	—	—	ND
Morbidity and combined outcomes					
Development of CHF	640 (30.2)	438 (20.7)	37 (28 to 44)	7.47	<0.001
Development of CHF and anti-CHF therapy	477 (22.5)	293 (13.9)	43 (33 to 50)	7.59	<0.001
First hospitalization for CHF	273 (12.9)	184 (8.7)	36 (22 to 46)	4.65	<0.001
Multiple hospitalizations for CHF	102 (4.8)	58 (2.7)	44 (23 to 59)	3.61	<0.001
Death or development of CHF	818 (38.6)	630 (29.8)	29 (21 to 36)	6.55	<0.001
Death or hospitalization for CHF	518 (24.5)	434 (20.6)	20 (9 to 30)	3.46	<0.001

*By the log-rank test. CI denotes confidence interval. A negative number indicates an increase in risk.

†NS denotes not significant, and ND not done (i.e., no statistical test was performed).

‡After August 31, 1991, but before the final follow-up visits, there were eight additional deaths in the placebo group and four in the enalapril group. Therefore, the total numbers of deaths were 342 in the placebo group and 317 in the enalapril group (risk reduction, 9 percent; z = 1.23; P = 0.22). The corresponding numbers for mortality from cardiovascular causes were 304 and 269 (risk reduction, 13 percent; 95 percent confidence interval, −2 to 26; z = 1.71; P = 0.09). CHF denotes congestive heart failure.

cebo group vs. 82 in the enalapril group), and the groups continued to diverge until the end of the study.

The Development of Heart Failure and Hospitalization for Heart Failure in Relation to Subsequent Mortality

The difference in mortality between the groups was attributable only to the lower incidence of heart failure among patients assigned to enalapril (Table 3); 156 patients in the placebo group and 121 in the enalapril group died after heart failure developed (mortality among patients with heart failure, 24.4 percent and 27.6 percent, respectively). Among patients who did not have heart failure, the mortality rates were 12.1 percent in the placebo group and 11.5 percent in the enalapril group. Similar analyses of deaths among patients who died after hospitalization for heart failure (89 deaths in the placebo group and 63 in the enalapril group) also demonstrated a difference, whereas there was little difference in mortality among patients not hospitalized for heart failure (245 deaths in the placebo group and 250 in the enalapril group). Therefore, the difference in the incidence of heart failure accounted for the lower mortality with enalapril. However, 40.9 percent of the patients in the placebo group who had heart failure subsequently received an angiotensin-converting–enzyme inhibitor.

Table 3. Mortality and Use of Angiotensin-Converting–Enzyme (ACE) Inhibitors at the End of the Study Period among Patients Who Had Congestive Heart Failure (CHF) or Patients Hospitalized for CHF, As Compared with Patients without CHF or Hospitalization.

Variable	Patients with CHF		Patients without CHF		Patients Hospitalized for CHF		Patients Not Hospitalized for CHF	
	Placebo	Enalapril	Placebo	Enalapril	Placebo	Enalapril	Placebo	Enalapril
No. of patients	640	438	1477	1673	273	184	1844	1927
Died								
No.	156	121	178	192	89	63	245	250
Percent	24.4	27.6	12.1	11.5	32.6	34.2	13.3	13.0
Alive								
No.	484	317	1299	1481	184	121	1599	1677
Percent	75.6	72.4	87.9	88.5	67.4	65.8	86.7	87.0
Use of ACE inhibitors*								
No.	262	147	134	107	139	89	257	165
Percent	40.9	33.6	9.1	6.4	50.9	48.4	13.9	8.6
Average mo. of follow-up†	27.7	25.8	36.0	36.6	25.3	22.1	36.9	37.2

*Includes those receiving open-label ACE inhibitors.

†For patients in whom CHF developed or who were hospitalized for CHF, the duration of follow-up is calculated from time of the event to the end of the trial. For those without an event, follow-up is calculated from randomization to the end of the trial.

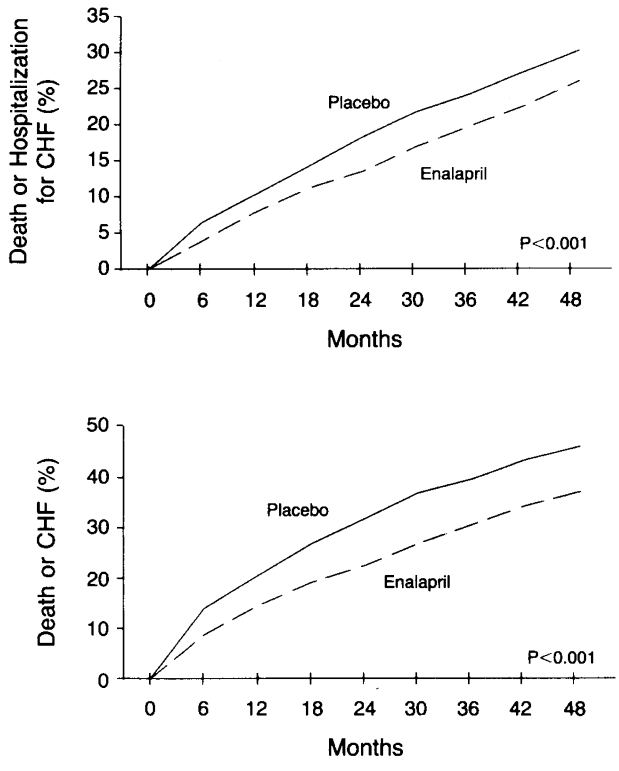


Figure 2. Death or Hospitalization for Congestive Heart Failure (CHF) and Death or Development of Heart Failure in the Prevention Trial.

See Figure 1 for the numbers of patients at risk at each time point.

The rate of mortality among patients who were hospitalized for heart failure (regardless of their treatment assignment) was about 33 percent, as compared with 13 percent among those who had not been hospitalized by the end of the study. After adjustment for differences in length of follow-up, the relative risk of death at one year among those who were hospitalized, as compared with those who were not hospitalized, was 4.6 (95 percent confidence interval, 3.4 to 6.3), indicating that hospitalization for heart failure was associated with a substantially higher risk of death.

All Hospitalizations

Altogether, 967 patients in the placebo group (45.7 percent) and 876 in the enalapril group (41.5 percent) were hospitalized primarily for a cardiovascular reason ($P = 0.006$), whereas 534 patients in the placebo group (25.2 percent) and 595 patients in the enalapril group (28.1 percent) were hospitalized for a noncardiovascular reason. The total number of patients hospitalized for any reason was 1202 in the placebo group, as compared with 1167 in the enalapril group ($P = 0.34$). The total number of hospitalizations was 2839 in the placebo group and 2645 in the enalapril group ($P = 0.12$).

Outcomes in Subgroups

The effect of treatment on various outcome measures was examined in several subgroups specified by the protocol; these were defined by base-line serum sodium levels, use of vasodilators, ejection fraction, and cause of ventricular dysfunction. We also exam-

ined the effects of treatment among patients with no functional disability (NYHA functional class I) and among those who were not receiving digoxin or diuretics at entry. Because the overall results regarding mortality in the Prevention Trial did not reach conventional levels of statistical significance, analysis of mortality in subgroups is less reliable than similar analyses of data on the rates of heart failure or hospitalizations for heart failure. There was a significant trend toward less benefit from enalapril among patients with a higher ejection fraction (Fig. 3). The benefits of treatment in terms of the frequency of hospitalization or the development of heart failure were consistent in most of the other specified subgroups. The benefits among those who were not receiving digoxin or diuretics (reduction in the frequency of death or hospitalization, 25 percent [95 percent confidence interval, 12 to 36 percent]; reduction in the incidence of heart failure, 39 percent [95 percent confidence interval, 29 to 47 percent]) and among those in functional class I (reduction in mortality or hospitalization, 21 percent [95 percent confidence interval, 7 to 33 percent]; reduction in mortality or development of heart failure, 28 percent [95 percent confidence interval, 18 to 37 percent]) were similar to the overall results.

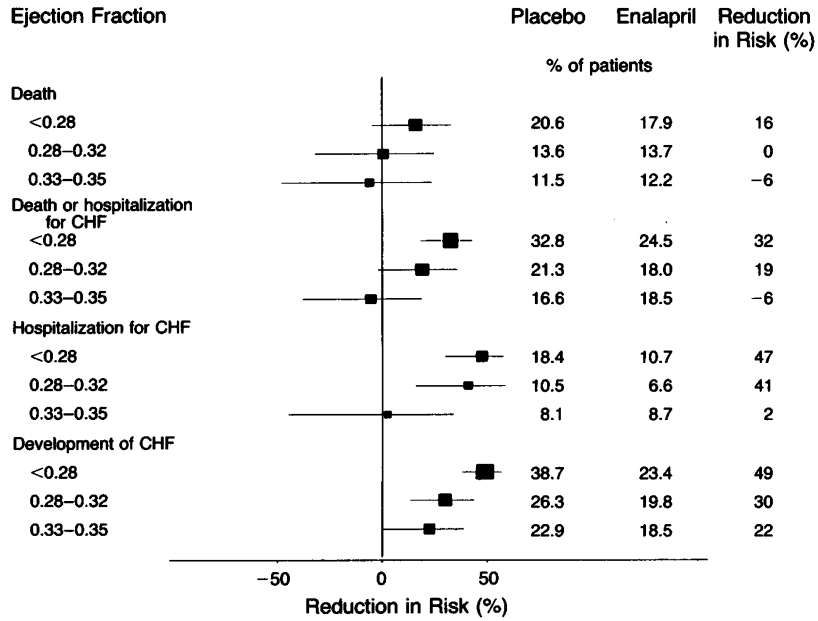


Figure 3. Effect of Enalapril on Mortality, Incidence of Congestive Heart Failure (CHF), and Hospitalization for Heart Failure in Various Subgroups Defined According to the Ejection Fraction.

Each subgroup composes one third of the study population. For each subgroup, the reduction in risk with enalapril is shown as a percentage (squares). (A negative value for risk reduction indicates an increase in risk.) The horizontal lines indicate the 95 percent confidence intervals. The size of each square is proportional to the number of events in the subgroup. The vertical line corresponds to a finding of no effect. The chi-square statistic for the interaction of the ejection fraction with the effect of enalapril on the risk of death was 2.16 (P = 0.34); that for the interaction with the effect of enalapril on the combined end point of death or hospitalization for CHF was 9.30 (P = 0.009); that for the interaction with its effect on hospitalization for CHF alone, 8.76 (P = 0.012); and that for the interaction with its effect on the development of CHF, 9.87 (P = 0.007).

Adherence to the Study Regimen, Side Effects, and Changes in Blood Pressure, Serum Electrolyte Levels, and Renal Function

The final mean daily dose of enalapril among all randomized patients was 12.7 mg. Among the patients in the enalapril group who were taking enalapril, the mean daily dose was 16.7 mg. At the last visit, 1.9 percent of the enalapril group was receiving 2.5 mg daily, 6.9 percent was receiving 5 mg daily, 11.1 percent was receiving 10 mg daily, and 56.1 percent was receiving 20 mg daily. Twenty-four percent of the patients in the enalapril group and 27 percent in the placebo group had stopped taking blinded medication by the end of the study. The study medication was discontinued in 218 patients in the placebo group and 102 in the enalapril group because of worsening heart failure. More patients were receiving diuretics and digoxin in the placebo group than in the enalapril group at one year (diuretics: 30 percent vs. 22 percent; digoxin: 19 percent vs. 15 percent), at two years (diuretics: 33 percent vs. 24 percent; digoxin: 23 percent vs. 17 percent), and at three years (diuretics: 35 percent vs. 27 percent; digoxin: 24 percent vs. 18 percent).

A high proportion of patients in both groups reported side effects during the trial (76 percent in the enalapril group vs. 72 percent in the placebo group). There were significantly more reports of dizziness or fainting (45.8 percent vs. 39.2 percent) and cough (33.8 percent vs. 27.3 percent) in the enalapril group. There was no difference in the frequency of angioedema (1.4 percent in each group); most cases of angioedema were mild and did not require the discontinuation of medication. Overall, 8 percent of the patients in the enalapril group and 45 percent in the placebo group permanently discontinued the study medication because of side effects. Forty-three patients in the enalapril group and 41 in the placebo group were given a diagnosis of cancer. Of these, 19 patients in the enalapril group and 13 in the placebo group were identified as having a cancer of the gastrointestinal tract, liver, gallbladder, or pancreas.

When averaged over all follow-up visits, systolic and diastolic blood pressures were significantly lower in the enalapril group than in the placebo group (by 5.2 and 3.2 mm Hg, respectively). Serum potassium and creatinine levels were slightly but significantly

higher in the enalapril group (by 0.1 mmol per liter and 0.04 mg per deciliter [3.5 μmol per liter], respectively).

Discussion

Although a significant reduction in total mortality with enalapril treatment was not observed in the Prevention Trial, enalapril, an angiotensin-converting–enzyme inhibitor, significantly reduced the incidence of heart failure and the need for hospitalizations for heart failure among patients with asymptomatic left ventricular dysfunction. There was also a trend (albeit not a significant one) toward fewer deaths due to cardiovascular causes. Although the relative reductions in total mortality and mortality from cardiovascular causes were smaller in the Prevention Trial (8 percent and 12 percent, respectively) than in the previously reported Treatment Trial (16 percent and 18 percent, respectively),[1] the direction of the effects was similar in both trials. However, the effects on the frequency of hospitalization for heart failure (a 36 percent reduction in both trials) and deaths from progressive heart failure (a 19 percent reduction in the Treatment Trial and a 21 percent reduction in the Prevention Trial) were similar.

The effect of enalapril in preventing the development of heart failure was evident as early as six weeks after randomization, and the difference between the two groups continued to increase until the end of the study. Similar results were observed for the rates of hospitalization for heart failure and death. After the development of heart failure or after hospitalization for heart failure, the mortality rates increased substantially as compared with those in patients in whom heart failure had not developed. This difference indicates that the development of heart failure has a serious adverse effect on prognosis.[10]

There were consistent reductions in the proportion of patients hospitalized for cardiovascular reasons in both the Treatment Trial and the Prevention Trial. There was a significant reduction in the proportion of patients in the enalapril group hospitalized for noncardiovascular reasons in the Treatment Trial,[1] whereas the opposite was observed in the Prevention Trial. The contradictory differences in the frequency of hospitalization for noncardiovascular reasons are probably due to chance. In the two trials combined, the number of hospitalizations for noncardiovascular reasons was virtually identical in the two groups (996 in the placebo groups vs. 997 in the enalapril groups). No significant difference in hospitalizations in any specific noncardiovascular category was observed in either trial.

During the study, more patients randomly assigned to the placebo group than to the enalapril group received digoxin, diuretics, or angiotensin-converting–enzyme inhibitors that were not part of the study regimen. In all, 40.9 percent of patients in whom heart failure developed and 50.9 percent of those who were hospitalized in the placebo group were prescribed an angiotensin-converting–enzyme inhibitor, generally after the development of heart failure. Because the reduction in mortality with enalapril was chiefly attributable to a lower incidence of heart failure, the frequent use of angiotensin-converting–enzyme inhibitors and perhaps other drugs in this group is likely to have led to the underestimation of the reduction in mortality with enalapril. Our data can also be interpreted as indicating that there may be only a small difference in mortality between asymptomatic patients treated preventively and those treated with careful follow-up and initiation of therapy if heart failure develops.

The reductions in the frequency of hospitalization and the incidence of heart failure were of approximately the same magnitude among patients who were receiving diuretics or digoxin at entry and those who were not receiving such agents; the reductions were also similar among patients in NYHA functional classes I and II. The benefits of enalapril in preventing heart failure and hospitalization were greatest among the patients with the lowest ejection fractions. Similar trends toward lesser benefit among patients with higher ejection fractions were observed in the SOLVD Treatment Trial,[1] suggesting that caution be exercised in extrapolating the results of the SOLVD trials to patients with ejection fractions above 0.35.

The major side effects observed in this study — hypotension, cough, and elevated serum potassium levels — are similar to those observed in the SOLVD Treatment Trial and other trials of angiotensin-converting–enzyme inhibitors in similar patients.[1-3] The frequency of side effects in the SOLVD trials may be higher than in other studies because of our substantially longer follow-up and the fact that patients were asked about these side effects at each visit. The proportion of patients who reported skin rashes, taste disturbances, or any other side effect was no higher in the enalapril group than in the placebo group in either SOLVD trial. The excess rate of gastrointestinal cancer is similar to that observed in the Treatment Trial.[1] When the data from both trials were combined, there were 38 cases of gastrointestinal cancer in the enalapril group as compared with 22 in the placebo group. Although this difference would be nominally significant when taken in isolation, this was one of numerous comparisons and the tests of significance are therefore less reliable. The frequency of these cancers did not increase with longer drug exposure (there were 20 cases in the first two years and 18 thereafter in the enalapril group, as compared with 12 and 10 in the placebo group), and the cancers were widely dispersed throughout the gastrointestinal tract (rectum, cecum, and colon: 26 in the enalapril group vs. 17 in the placebo group; esophagus and stomach: 5 vs. 1; gallbladder, pancreas, and liver: 7 vs. 4). For these reasons, the excess gastrointestinal cancers in the enalapril group were probably not causally related to the study treatment but rather a chance finding. It would be prudent, how-

ever, to examine this relation in other studies.

In the SOLVD Prevention Trial, enalapril was well tolerated by patients with asymptomatic left ventricular dysfunction; it reduced the incidence of heart failure and related hospitalizations, with a trend toward fewer cardiovascular deaths. However, the lack of a statistically significant effect on overall mortality or on the rate of deaths presumed to be due to arrhythmia emphasizes the need to explore more effective means, or additional means, of treating patients with left ventricular dysfunction.

Appendix

The following investigators and institutions participated in the SOLVD Prevention Trial. Principal investigators are indicated with asterisks.

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