The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

Abstract To evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart failure (New York Heart Association [NYHA] functional class IV), we randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for heart failure, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days (range, 1 day to 20 months). The crude mortality at the end of six months (primary end point) was 26 percent in the enalapril group and 44 percent in the placebo group — a reduction of 40 percent (P = 0.002). Mortality was reduced by 31 percent at one year (P = 0.001). By the end of the study, there had been 68 deaths in the placebo group and 50 in the enalapril group — a reduction of 27 percent (P = 0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50 percent), whereas no difference was seen in the incidence of sudden cardiac death.

A significant improvement in NYHA classification was observed in the enalapril group, together with a reduction in heart size and a reduced requirement for other medication for heart failure. The overall withdrawal rate was similar in both groups, but hypotension requiring withdrawal occurred in seven patients in the enalapril group and in no patients in the placebo group. After the initial dose of enalapril was reduced to 2.5 mg daily in high-risk patients, this side effect was less frequent.

We conclude that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of heart failure. (N Engl J Med 1987; 316:1429-35.)

CONGESTIVE heart failure is a common condition reported to affect 1 percent of the population, with an annual incidence of approximately 3 per 1000.[1] The prognosis of congestive heart failure is poor: annual mortality is in excess of 50 percent.[2]

Vasodilator therapy for severe congestive heart failure induces hemodynamic effects that are believed to be beneficial,[3-6] and it has become widely accepted during the past decade.[7,8] The introduction of inhibitors of angiotensin-converting enzyme has been associated with both hemodynamic and symptomatic improvements during long-term use.[9] The effect of these agents on survival in congestive heart failure, however, is unknown. Furberg and Yusuf[10] have pooled the results of the placebo-controlled trials of both vasodilators and angiotensin-converting-enzyme inhibitors. They found no overall effect of vasodilators on survival but suggested that angiotensin-converting-enzyme inhibitors may influence the prognosis beneficially. Recently, the combination of isosorbide dinitrate and hydralazine in a Veterans Administration trial was shown to reduce mortality over a three-year period.[11]

The CONSENSUS trial was designed to study the effect on mortality of enalapril[12] as compared with placebo, in addition to conventional therapy in severe congestive heart failure. This paper presents the data on survival among the 253 randomized patients.

METHODS

This was a randomized, double-blind, placebo-controlled, parallel-group trial in patients with severe congestive heart failure (New York Heart Association [NYHA] functional class IV). Patients were randomly assigned to treatment groups at each of 6 centers in Finland, 12 in Norway, and 17 in Sweden. The study organization consisted of a Steering Committee from the participating countries and national monitors who were in close contact with the study coordinator (K.S.). An international Ethical Review Committee monitored the progress of the study.

At the start of the trial, patients were receiving optimal treatment with digitalis and diuretics. Treatment with any other drug for heart failure — including vasodilators (e.g., nitrates, prazosin, hydralazine) — except angiotensin-converting-enzyme inhibitors was also permitted.

The diagnosis of congestive heart failure was based on clinical criteria: a history of heart disease with symptoms of dyspnea or fatigue or both, together with signs of fluid retention and no evidence of primary pulmonary disease. The patients were symptomatic at rest (NYHA functional class IV).

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Supported by a grant from Merck Sharp and Dohme Research Laboratories, Rahway, N.J.

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The heart size as determined radiologically had to be more than 600 ml per square meter of body-surface area in men (normal, <550) or more than 550 ml per square meter in women (normal, <500).[13] Measurements of myocardial function were not required. A period of not more than 14 days was allowed to stabilize the patients on digitalis and diuretics before the study began. Patients whose condition improved during this period to class III or less were not randomized.

Patients were excluded if any of the following were present: acute pulmonary edema, hemodynamically important aortic or mitral-valve stenosis, myocardial infarction within the previous two months, unstable angina, planned cardiac surgery, right heart failure due to pulmonary disease, or a serum creatinine concentration above 300 μmol per liter.

The computer-generated allocation schedule had a block size of two patients. At the time of random assignment, patients were stratified with regard to treatment with vasodilators. Blinded bottles of study drug or placebo were labeled only with the patient's allocation number. For each allocation number, a complete set of four bottles (one for each tablet strength) was available at each visit.

Treatment with enalapril or an identical placebo was started in the hospital with a dose of 5 mg twice a day. After one week, the dosage was increased to 10 mg twice a day if the patient did not have symptoms of hypotension or other side effects. According to the clinical response, a further increase in dosage could occur up to a maximal dose of 20 mg twice a day. The patients were evaluated after 1, 2, 3, 6, and 16 weeks, 6, 9, and 12 months, and at the end of the study. In patients with worsening symptoms, additional vasodilator therapy — with isosorbide dinitrate, hydralazine, or prazosin, in that sequence — was recommended.

Early in the trial, the occurrence of symptomatic hypotension in some patients led to a revision of the protocol after 67 patients had been randomly assigned. No patient's treatment was unblinded. Patients considered to be at high risk (serum sodium, <130 mmol per liter; serum creatinine, 150 to 300 μmol per liter; an increase in the dosage of diuretics within the previous week; or treatment with potassium-sparing agents) were given an initial dose of 2.5 mg daily. If hypotension or an increase in the serum creatinine level did not occur after three to four days, the dosage was increased to 2.5 mg twice a day for the remainder of the first week. Thereafter, the previous titration plan was followed.

The principal end points of the trial, as stated in the protocol, were the six-month mortality and the cause of death. The cause of death was classified by two investigators independently, on the basis of detailed reports, before the code was broken. Causes of death were described in accordance with a modified version of the American Heart Association's recommendations. Sudden death was defined as death within one hour of the onset of new symptoms.[14] Unwitnessed deaths were classified according to the length of time from the last observation when the patient was alive to the estimated time of death. Secondary end points were the 12-month and overall mortality during the entire trial period, according to the "intention-to-treat" principle.

The study was performed under the auspices of an independent Ethical Review Committee, which every three months reviewed (separately for the enalapril and placebo groups) the number of patients included, the number of deaths, and the instances of premature withdrawal of the test drug.

Statistical Considerations

A sample size of 400 patients was calculated on the assumption that the six-month mortality would be 40 percent in the placebo group and would be lowered to 24 percent by enalapril ($\alpha = 0.05$, power = 90 percent, two-tailed test). No formal rule was adopted governing the interruption of the trial for the purpose of interim analyses by the Ethical Review Committee.

The mortality status of each patient on the date of study termination was confirmed in writing by the investigator. All randomized patients were included in the mortality analyses, and all patients on whom data were available were included in the other analyses. All the reported P values are two-tailed. Within treatment groups, changes in vital signs from base-line levels were analyzed with the signed-rank test, and between-group differences were analyzed with the rank-sum test. Differences between the groups in NYHA classification were also analyzed with the rank-sum test; deaths were included in these analyses as the most severe category. Categories of change in electrolyte levels and renal function were analyzed with McNemar's test[15] for within-group comparisons, and by a method of analyzing ordered categorical data[16] for between-group comparisons.

Differences in mortality between the treatment groups were analyzed with use of life-table methods. The intention-to-treat approach was used, in which the survival information for each patient from the date of random assignment to the date of death or study termination was included in the analysis. The Kaplan–Meier survival curves were calculated,[17] and differences between the curves were analyzed with both the log-rank statistic[18] and a Cox regression model,[19] with treatment group as the only covariate. The two tests yielded results that were virtually identical (the P values were always within 0.002 of one another).

The study was approved by the institutional ethical committee at each participating center. Informed consent was obtained from each patient.

Table 1. Base-Line Clinical Characteristics of Patients in the Two Treatment Groups.

Characteristic	Treatment Group	
	Placebo (N = 126)	Enalapril (N = 127)
	mean	
Age (yr)	70	71
Weight (kg)	69	66
Heart size (ml/m^2)	853	875
Blood pressure (mm Hg)		
Systolic	121	118
Diastolic	76	74
Heart rate	80	79
Serum sodium (mmol per liter)	137	138
Serum potassium (mmol per liter)	4.1	4.0
Serum creatinine (μmol per liter)	124	132
	percent	
Sex		
Female	29	30
Male	71	70
Etiologic factors		
Coronary artery disease	74	72
Previous myocardial infarction	48	47
Cardiomyopathy	16	14
Valvular heart disease	22	23
Hypertension	19	24
Atrial fibrillation	47	53
Diabetes mellitus	21	24
Drug therapy		
Digitalis	94	92
Beta-blocker	2	4
Diuretics		
Furosemide (mean dose)	98 (200 mg)	98 (210 mg)
Spironolactone (mean dose)	55 (80 mg)	50 (80 mg)
Any other diuretic	10	14
Vasodilators		
Isosorbide dinitrate	45	47
Hydralazine	2	1
Prazosin	6	8
Antiarrhythmic agents	17	13
Anticoagulant agent	34	33
Duration of heart failure (mo)		
<6	9	4
6–17	16	24
18–47	21	23
≥48	52	47
Unknown	2	2

Results

The first patient was randomly assigned to treatment on April 19, 1985. On December 7, 1986, the

Ethical Review Committee reviewed data on 124 patients assigned to receive enalapril, of whom 44 were known to have died, and 120 patients assigned to receive placebo, of whom 66 were known to have died. The committee found both treatment groups well balanced as far as base-line characteristics were concerned, and observed a consistent difference in favor of enalapril from the beginning of the study and among various subgroups of clinical interest. The committee considered that chance alone could practically be ruled out as an explanation of the difference and recommended that both enrollment and follow-up be terminated ahead of schedule. This recommendation led to the termination of the study on December 14, 1986. On that date, 253 patients had been randomly assigned — 126 in the placebo group and 127 in the enalapril group. The clinical characteristics of the two groups were very similar at base line (Table 1). According to the entry criteria, all the patients were in NYHA functional class IV. Coronary artery disease was the most frequent cause of heart failure (73 percent). In 49 percent of the patients, vasodilator drugs other than angiotensin-converting-enzyme inhibitors were being used. The follow-up ranged from 1 day to 20 months, with an average of 188 days; no patients were lost to follow-up. Because of the premature termination, a six-month follow-up was achieved in only 194 patients, and a 12-month follow-up in 102 patients.

The cumulative mortality rate for up to 12 months is shown in Figure 1. For more than 12 months, the sample size was too small for meaningful interpretation. The overall crude mortality at six months was 44 percent in the placebo group and 26 percent in the enalapril group — a reduction of 40 percent (P = 0.002) (Table 2). At the end of one year, mortality was 52 percent and 36 percent in the two groups, respectively (P = 0.001). At the end of the study, 68 patients had died in the placebo group and 50 patients in the enalapril group — a reduction of 27 percent (P = 0.003).

Table 2. Mortality from Any Cause in the Two Groups.*

	Treatment Group				Reduction in Relative Risk	P Value (Life-Table Analysis)
	Placebo (N = 126)		Enalapril (N = 127)			
	no.	%	*no.*	%	%	
Mortality at six months (180 days)	55	44	33	26	40	0.002
Mortality at one year (360 days)	66	52	46	36	31	0.001
Total mortality	68	54	50	39	27	0.003

*In the placebo group, the mean period of follow-up was 237 days among the 58 survivors and 93 days among the 68 patients who died, for an overall mean of 160 days. In the enalapril group, the mean period of follow-up was 260 days among the 77 survivors and 147 days among the 50 patients who died, for an overall mean of 215 days.

The causes of death are shown in Table 3. Of the 118 patients in the study who died, 39 (33 percent) died within 24 hours of the development of new symptoms (28 of these were sudden deaths) and 66 (56 percent) died of progressive heart failure. There was no difference in the incidence of sudden cardiac death between the two treatment groups; however, there was a 50 percent reduction in mortality due to the progression of heart failure in the enalapril-treated group (P<0.001). An autopsy was performed in 48 percent of the patients.

In patients not being treated with vasodilators at the time of random assignment, the reduction in crude mortality was from 60 to 37 percent (P<0.02). The corresponding six-month life-table mortality figures were 50 and 34 percent (Fig. 2). Among the patients receiving vasodilator therapy at base line, the reduction was from 48 to 42 percent (P = 0.11), and the six-month life-table mortality figures were 46 and 24 percent, respectively.

Table 4 shows the distribution of the NYHA functional classes at the end of the study. The distribution was significantly different in the two groups, whether one considers all the patients (with death included as the most severe category) or just the surviving patients (P = 0.001). Twenty-two percent of the placebo-treated patients and 42 percent of the enalapril-treated patients had improvement in their NYHA classification.

Among the patients surviving at the end of the study, heart size was reduced in the placebo group from 867 ml per square meter at base line to 839 (−3.2 percent) and in the enalapril group from 910 to 823 ml per square meter (−9.6 percent). The reduction in heart size was significantly greater in the enalapril group (P = 0.02), although the fi-

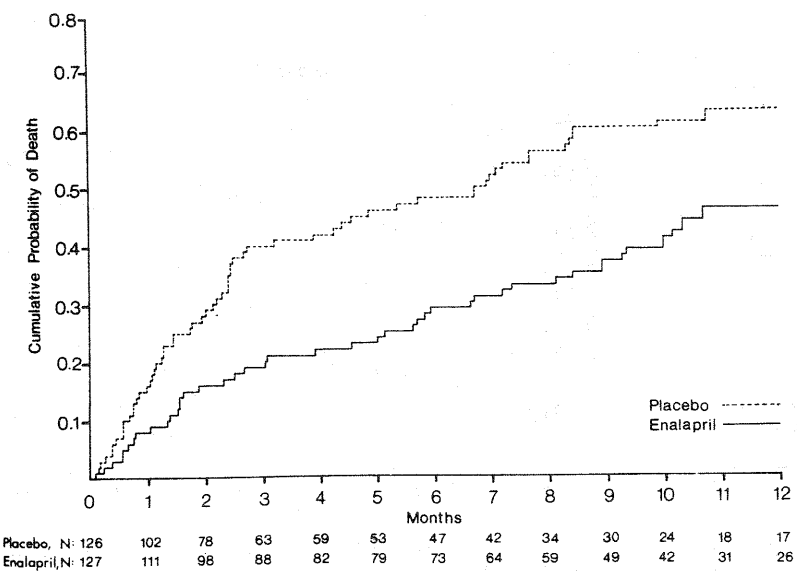

Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

Table 3. Causes of Death.

Cause	Treatment Group		P Value (Life-Table Analysis)
	Placebo (N = 126)	Enalapril (N = 127)	
	no. of patients		
Any cardiac death	64	44	0.001
Cardiac death within 24 hours of new symptoms	19	20	>0.25
Sudden cardiac death (within 1 hour of new symptoms)	14	14	>0.25
Progression of congestive heart failure	44	22	0.001
Other cardiac death	1	2	
Stroke	2	1	
Other cardiovascular deaths*	2	4	
Noncardiovascular death (perforated ulcer)	0	1	
Total mortality	68	50	0.003

*Includes deaths from renal-artery thrombosis, endocarditis, pulmonary emboli after leg amputation, bronchitis and concomitant heart failure, occlusion of femoral arterial graft, and heart failure in relation to melena (gastric ulcer).

nal heart sizes achieved in the two groups were similar.

We observed a significant fall in systolic blood pressure in both groups after the first dose, but the reduction was greater in the enalapril group (121 to 111 mm Hg, as compared with 118 to 98 mm Hg; $P<0.01$). The mean heart rate was unchanged in the placebo group (80 bpm) but decreased in the enalapril group (from 80 to 77 bpm; $P<0.05$).

The final mean dose level of enalapril was 18.4 mg, and of matching placebo, 27.3 mg ($P<0.001$). The dosage had been titrated to the maximal permitted level for 57 patients in the placebo group, as compared with 28 patients in the enalapril group. A comparison between the groups with respect to the concomitant use of cardiovascular drugs showed that the enalapril group had fewer initiations and more discontinuations of cardiovascular drugs than the placebo group.

The proportions of withdrawals from randomly assigned therapy were not significantly different in the two treatment groups (14 percent in the placebo group and 17 percent in the enalapril group). The reasons for withdrawal are shown in Table 5. Hypotension led to the withdrawal of seven patients in the enalapril group, but none in the placebo group. In two of the seven patients, hypotension developed after the initial dose of enalapril, whereas in the remaining five patients, it developed from 8 to 48 days after the start of therapy. One patient had prolonged hypotension and the development of a transient right-sided hemiparesis that persisted for two days. In the initial phase of the study, when a starting dose of 5 mg twice a day was used in all patients, 4 of the first 34 patients in the enalapril group were withdrawn from treatment because of hypotension (11.8 percent). When high-risk patients were identified and the starting dose was reduced to 2.5 mg, hypotension led to the withdrawal of only 3.2 percent of the remaining patients in the enalapril group.

A similar number of patients in each treatment group (four in the placebo group and six in the enalapril group) were withdrawn because of deterioration of renal function as assessed by measurement of the serum creatinine level. Changes in the serum creatinine level from base line to the last follow-up within six weeks are shown in Table 6. There was no significant difference between the two groups. Hypokalemia developed in 14 patients in the placebo group as compared with 3 in the enalapril group. Five patients in the placebo group and nine in the enalapril group had elevated serum potassium levels at follow-up. There was a significantly greater increase in the serum sodium level in the enalapril group ($P<0.02$).

The patients in the placebo group who were withdrawn had received blinded treatment before withdrawal for an average of 67 days (median, 28.5; range, 0 to 311). The corresponding period for the patients in the enalapril group was 75 days (median, 28.5; range, 0 to 275). The mortality among the patients withdrawn was 78 percent in the placebo group and 68 percent in the enalapril group. The average survival

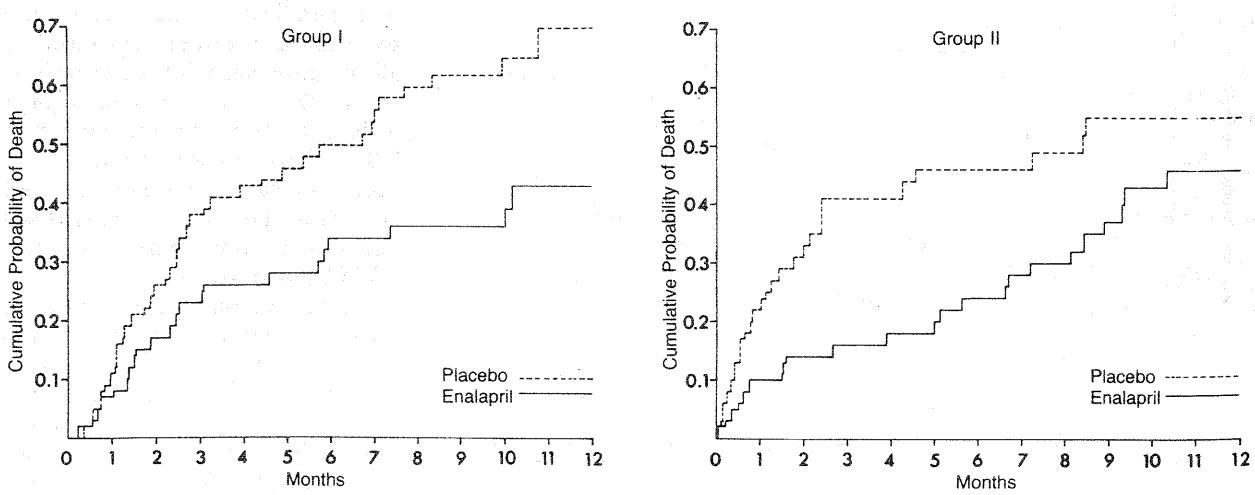

Figure 2. Cumulative Probability of Death in Patients Not Taking Vasodilators (Group I) and in Patients Taking Vasodilators (Group II) at the Time of Random Assignment.

Table 4. NYHA Classifications at End of Study.*

NYHA Class	Treatment Group	
	Placebo (N = 126)	Enalapril (N = 127)
	no. of patients	
I	0	3
II	2	13
III	25	38
IV	30	21
(Patient died)	68	50
Unknown	1	2

*For the difference between the groups, $P<0.001$. NYHA denotes New York Heart Association.

after withdrawal was 27 days in the placebo group (median, 28; range, 2 to 75) and 80 days in the enalapril group (median, 69; range, 2 to 287).

Discussion

This trial was discontinued ahead of schedule, as recommended by the Ethical Review Committee, which was of the opinion that its continuation was of limited scientific interest and unjustified from an ethical point of view. A detailed report by the committee is available upon request (from the National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20209). The trial demonstrates that treatment with enalapril improves survival in severe chronic congestive heart failure. A change from NYHA functional class IV to class I or II was observed in 16 patients in the enalapril group as compared with only 2 in the placebo group. The beneficial treatment effects were also reflected in a reduction in the concomitant use of cardiovascular drugs and a decrease in heart size in the enalapril-treated patients. The entire treatment effect was due to a reduction in mortality from the progression of heart failure. We observed no effect on sudden cardiac death.

Congestive heart failure is a serious condition with a high mortality rate,[20] as demonstrated by our placebo group. The 6-month and 12-month mortality rates calculated from the life table were 48 and 63 percent, respectively, in this group. These figures are even higher than were anticipated at the beginning of the study but are in agreement with survival rates in other functional class IV patients.[1]

A Veterans Administration trial compared placebo with prazosin and with a combination of hydralazine and isosorbide dinitrate.[11] Prazosin had no effect on the mortality rate, but on the basis of life-table estimates, the hydralazine–nitrate combination was found to reduce mortality after one year from 19.5 to 12.1 percent (−38 percent) and after three years from 46.9 to 36.2 percent (−23 percent). In the present trial, a similar calculation of life-table estimates shows a mortality after six months of 48 percent reduced to 29 percent (−40 percent) and a mortality after one year of 63 percent reduced to 47 percent (−25 percent). The six-month mortality in the present trial was similar to the mortality risk after three years in the Veterans Administration trial, suggesting that we were studying a more severely ill group of patients.

The most common adverse events in this study were hypotension and an increased serum creatinine level. A reduction in blood pressure has dual implications. Some reduction due to a reduced afterload is beneficial, and in clinical practice a low blood pressure in patients with heart failure may not cause further limitation of activity. On the other hand, pronounced hypotension may affect renal and myocardial perfusion. Hypotension after the addition of angiotensin-converting-enzyme inhibitors may be a problem in severe heart failure.[21] All the patients were therefore observed in the hospital for at least six hours after the initial dose and after dose increases. Seven patients in the enalapril group, but none in the placebo group, had to be withdrawn because of hypotension.

Four of the seven withdrawals due to hypotension occurred among the first 34 patients to be randomly assigned to receive enalapril, who were all given a starting dose of 10 mg daily. Accordingly, the protocol was changed, and a lower starting dose of 2.5 mg daily was recommended in high-risk patients, whose renin–angiotensin system was likely to have been most highly activated. In addition to severe heart failure itself, other factors that may stimulate the renin–angiotensin system and may lead the renal function to become dependent on angiotensin II include the use of high doses of diuretics, hyponatremia, and preexisting renal impairment. Serious side effects were reduced after these protocol adjustments, and only three (3.2 percent) of the subsequent patients in the enalapril group were withdrawn from the study because of hypotension.

Increases in the serum creatinine level resulting in withdrawal were similarly distributed in the placebo and the enalapril groups. In severe heart failure, an

Table 5. Reasons for Withdrawal from the Study.

Reason	Treatment Group	
	Placebo (N = 126)	Enalapril (N = 127)
	no. of patients	
Patient's decision	6	5
Side effects		
Hypotension	0	7
Increased serum creatinine	4	6
Rash	1	1
Other		
Weight gain	1	0
Progression of arteriosclerotic leg pain	0	1
Nausea and vomiting	1	0
Photosensitivity, taste disturbance, and coughing	1	0
Medical reasons		
Aortic stenosis	1	0
Acute myocardial infarction	1	1
Serious clinical condition	1	1
Unknown	1	0
Total	*18*	*22*

Table 6. Serum Creatinine Level at Base Line and at Six-Week Follow-up (or at Last Follow-up If the Patient Was Not Alive at Week 6).*

BASE-LINE LEVEL (μmol/liter)	FOLLOW-UP LEVEL (μmol/liter)					
	PLACEBO GROUP (N = 118)			ENALAPRIL GROUP (N = 120)		
	≤120	*121–150*	*>150*	*≤120*	*121–150*	*>150*
≤120	50	8	1	38	5	9
121–150	12	18	12	13	14	12
151–300	0	4	13	0	10	19

*P>0.25 for the difference between groups.

elevation in serum creatinine as a consequence of reduced renal perfusion is common. This is a situation quite similar functionally to that of renal-artery stenosis, in which glomerular filtration is maintained in the presence of reduced renal-perfusion pressure through selective vasoconstriction of the efferent arteriole by angiotensin II. The dependence of renal function on angiotensin II is heightened by the sodium depletion and dehydration that may occur with excessive diuresis. In such patients, a marked reduction in the angiotensin II level following angiotensin-converting-enzyme inhibition could be detrimental to renal function.[22,23]

Hyperkalemia was more common among patients in the enalapril group, all of whom were taking potassium-sparing agents or potassium supplements. There was no relation between hyperkalemia and an increase in the serum creatinine level or in mortality. In contrast, hypokalemia or hyponatremia developed in more patients in the placebo group than in the enalapril group.

The withdrawal of spironolactone was also more frequent in the active-treatment group. Angiotensin-converting-enzyme inhibitors attenuate the compensatory aldosterone mechanism that regulates the effect of spironolactone. It may, therefore, be safer to withdraw spironolactone before starting enalapril in severe congestive heart failure — an action that may reduce the risk of hyperkalemia and renal impairment.

It has been argued that patients with advanced heart failure are so ill and have such extensive myocardial damage that no important prolongation of survival by any medical treatment can be expected.[24] However, our data suggest that enalapril can reduce mortality. The limited follow-up period did not permit us to estimate the duration of this beneficial effect or its effects in less severe forms of heart failure.

Vasodilation reduces the load on the failing myocardium, but the pharmacologic means by which peripheral resistance is lowered may be a critical factor. Enalapril probably lowers peripheral resistance by reducing vasoconstriction induced by angiotensin II.[12] Conversely, conventionally acting vasodilators may actually stimulate the renin–angiotensin system.[25,26]

In summary, this study has shown that enalapril given to patients with severe congestive heart failure is associated with a considerable reduction in mortality. The treatment was well tolerated; however, it is important to initiate therapy with low doses of enalapril, particularly in high-risk patients.

APPENDIX

The CONSENSUS Trial Study group consisted of the following investigators (the city in which their institution is located and the number of patients are shown in parentheses):

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