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Role of Converting Enzyme Inhibitors in the Treatment of Heart Failure

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Treatment with angiotensin-converting enzyme inhibitors has proved to be effective in relieving symptoms of congestive heart failure. With recognition of the high mortality rate that accompanies heart failure, the question has arisen whether angiotensin-converting enzyme inhibitors may also improve survival. Early trials of the vasodilator combination hydralazine plus nitrates (V-HeFT trial) showed a strong trend toward a reduction in mortality, and a subsequent trial of the angiotensin-converting enzyme inhibitor enalapril in a population of patients with end-stage heart failure (CONSENSUS trial) showed a highly significant reduction in the mortality. The SOLVD trial was begun in 1986 to determine whether enalapril could reduce morbidity and mortality in patients with mild to moderate congestive failure (primarily New York Heart Association classes II and III), as well as in asymptomatic patients with a low ejection fraction.

This report presents the results in patients with symptoms of congestive failure who were studied in the SOLVD treatment trial. A total of 2,569 patients were recruited into the trial, with an average follow-up period of 41.4 months. There was a 16% reduction in mortality in the enalapril-treated group compared with that of patients receiving placebo ($p = 0.0036$), as well as a 26% reduction in the combined end point of death plus hospital admission for congestive failure ($p < 0.0001$). Compared with placebo, enalapril significantly reduced the incidence of death due to progressive heart failure but apparently had no effect on sudden death. The results clearly indicate that the angiotensin-converting enzyme inhibitor enalapril can reduce both morbidity and mortality in symptomatic congestive heart failure. However, the mechanism of action of angiotensin-converting enzyme inhibitors remains to be fully established.

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Congestive heart failure is a major public health problem. It is also a disease with a high mortality rate, as shown by the prospective analysis of patients with congestive failure of new onset in the Framingham Study (1), which revealed a 5-year death rate of ≈50%. The current review focuses on ongoing attempts to reduce this high mortality rate with vasodilator therapy and particularly with use of the converting enzyme inhibitor enalapril.

Early Studies

Over the past decade, investigators have sought to reduce both symptoms and death associated with congestive heart failure through the use of vasodilator therapy. By reducing the work load of the heart, it was theorized that this treatment might cause the disease to progress more slowly and reduce both morbidity and mortality. It has been known for more than a decade that vasodilator therapy can lessen symptoms of congestive heart failure. With the discovery that the renin-angiotensin-aldosterone system is activated in congestive heart failure and the development of angiotensin-converting enzyme inhibitors in the 1980s, it was hoped that a highly effective form of vasodilator therapy would become available. Several short-term (3 to 6 months) trials carried out in the early 1980s showed that the angiotensin-converting enzyme inhibitor captopril lessened symptoms and increased exercise tolerance in patients with congestive heart failure (2,3) and in some cases improved ejection fraction as well (2), with a relatively low incidence of side effects. The effect on exercise tolerance appeared to be a class effect of the angiotensin-converting enzyme inhibitors because similar results were obtained using enalapril (4).

Large Scale Trials

Vasodilator–Heart Failure Trial. Large-scale randomized double-blind trials of vasodilator therapy to reduce mortality from congestive heart failure began with the Vasodilator–Heart Failure Trial (V-HeFT) in the early 1980s. In that study (5), 642 patients with predominantly New York Heart Association class II and III congestive heart failure were randomized to long-term treatment with placebo, prazosin or a combination of hydralazine and isosorbide dinitrate. The mortality rate in the placebo- and prazosin-treated groups was approximately 50% at the end of 3.5 years of the study, but in the hydralazine and nitrate–treated group, there was a strong trend toward a reduction in mortality. This early study, which was of borderline statistical significance, nonetheless supported the concept of using vasodilators to reduce mortality in patients with congestive heart failure.

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Table 1. Sample Size Estimates

	Treatment	Prevention
% mortality (3 yr)		
Placebo group	32	17
Enalapril group	25	13
Sample size* (no.)	2,100	4,000

*Adherence 80% to 85%, alpha 0.025 (one-sided), power 90%.

Studies of Left Ventricular Dysfunction (SOLVD) trial. *Patients and protocol.* The SOLVD study, begun in 1986 (6), was designed to determine whether mortality could be reduced by the angiotensin-converting enzyme inhibitor enalapril in a group of patients with diminished left ventricular ejection fraction who had symptomatic congestive failure (treatment trial) and a group of patients who had a reduced ejection fraction but remained asymptomatic (prevention trial). The primary end point of SOLVD was all-cause mortality; secondary end points were cardiovascular mortality, mortality from sudden death, incidence of myocardial infarction and cerebrovascular accident, hospital admission for congestive heart failure, quality of life; and, for patients in the prevention trial, the onset of symptomatic congestive failure. Inclusion criteria included an ejection fraction ≤0.35 and age 21 to 80 years. Exclusion criteria (6) included intolerance to angiotensin-converting enzyme inhibitors, inability to discontinue these agents, recent myocardial infarction, candidacy for a cardiac surgical procedure including heart transplantation, advanced pulmonary or cerebrovascular disease or other life-threatening condition, renal dysfunction with serum creatinine >2.5 mg/dl, women of child-bearing age unprotected by contraception, use of other investigational drugs and unstable or severe angina pectoris. Patients with an average of two or fewer attacks of angina/day were not excluded. Patients in the treatment trial were allowed to take conventional drugs for heart failure, including digitalis, diuretic drugs and nonangiotensin-converting enzyme inhibitor vasodilators.

Sample size calculations for SOLVD are shown in Table 1. The 3-year mortality rate in the treatment and prevention trials were projected to be 32% and 17%, respectively, based on data obtained in the Coronary Artery Surgery Study Registry (6). To detect a 25% reduction in mortality to 25% and 13%, respectively, in the two trials, a sample size of 2,100 patients was required for the treatment trial and of 4,000 patients for the prevention trial. These numbers were arbitrarily increased to 2,500 and 4,600 to provide a margin of safety. The actual number of patients recruited for the treatment trial was 2,569, with an average follow-up period of 41.4 months; for the prevention trial, it was 4,228 patients with an average follow-up period of 37.4 months.

Patients considered eligible for SOLVD were initially given 2.5 mg of enalapril twice daily for 2 to 7 days to be sure they tolerated the drug and to ascertain compliance (6). During this period, 4.2% of patients dropped out, about half because of symptomatic hypotension and about half because of poor compliance. Patients were then given placebo for 14 to 17 days to be sure they could tolerate withdrawal of angiotensin-converting enzyme inhibitor therapy and again to make certain they would be compliant. Another 4.2% of patients dropped out, about half because of clinical deterioration and about half because of poor compliance. Thus, the majority of patients considered eligible could be randomized into SOLVD protocol.

Table 2. Characteristics of Patient Groups

	Placebo Group (n = 1,284)	Enalapril Group (n = 1,285)
Age (yr)	61.0	60.7
Ejection fraction	0.25	0.25
Men (%)	79.8	80.9
NYHA class (%)		
I	10.5	11.4
II	56.6	56.8
III	30.7	30.1
IV	1.9	1.5
Cause of disease (%)		
Ischemic	72.1	70.2
Idiopathic	17.9	18.6
Angina pectoris (%)	38.9	36.1

NYHA class = New York Heart Association functional class.

Cooperative North Scandinavian Survival Study. After the initiation of SOLVD in 1986, the results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial were reported (7). In this trial, 253 patients with advanced heart failure (New York Heart Association class IV) were randomized to enalapril or placebo therapy. After 6 months of therapy, there was a highly significant difference in mortality between the placebo group (44%) and the enalapril group (26%). The results showed conclusively the value of treatment with enalapril in very advanced cardiac failure and provided impetus to continue the SOLVD trial to determine whether mortality could be reduced in patients with mild to moderate heart failure and asymptomatic left ventricular dysfunction.

Results of SOLVD treatment trial. The remainder of this report will deal with the characteristics and results in patients in the treatment trial, which have recently been published (8). Demographic characteristics are shown in Table 2, which also demonstrates that the placebo and enalapril groups were well matched. The all-cause mortality results of the treatment trial are shown in Figure 1, which demonstrates an overall 16% reduction in mortality by log-rank test in the enalapril group compared with the placebo group ($p = 0.0036$). The difference in mortality appeared early in the trial and persisted throughout the study because the mortality curves remain parallel and do not converge. The results for the combined end point of death and hospital admission for congestive failure are shown in Figure 2, which demonstrates a 26% reduction in the enalapril-treated group compared with the placebo group ($p < 0.0001$).

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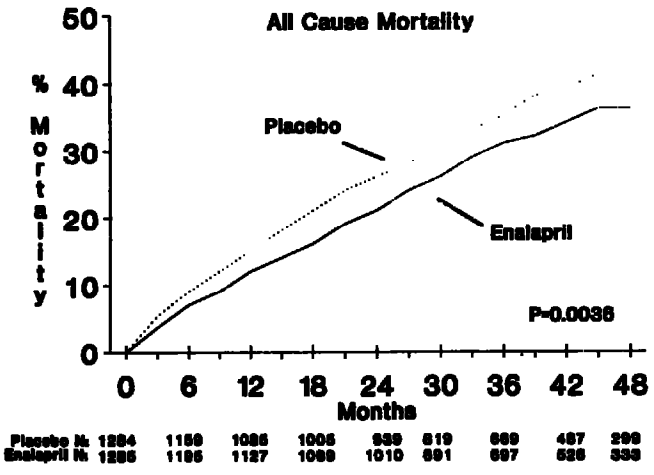
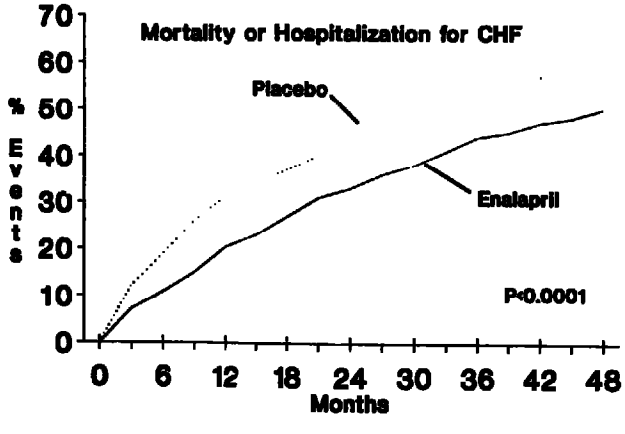


Figure 1. Mortality curves for the placebo- and enalapril-treated groups in the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial. Numbers below the graph show the number of patients in each group at each 6-month study date. Adapted, with permission, from a report by the SOLVD Investigators (8).

The two chief cardiovascular causes of death in the treatment trial were progressive congestive heart failure and sudden death presumably due to arrhythmias. Treatment with enalapril significantly reduced the incidence of death from progressive cardiac failure compared with placebo, but apparently had no effect on sudden death (Fig. 3). A similar result was reported in the CONSENSUS trial (7). However, the second Vasodilator Heart Failure Trial (V-HeFT II), in which outcomes were compared in groups treated with enalapril or with the combination of hydralazine plus isosorbide dinitrate, showed a reduction in mortality in the enalapril group that was due to a lower sudden death rate (9). Because the V-HeFT II study lacked a control group, it is difficult to compare the results directly with those from SOLVD.

The recommended target dose of enalapril was 10 mg twice daily. Among the patients taking study drug at the termination of the protocol, the average daily dose was 16.6 mg for patients taking enalapril and 18 mg for those taking placebo. Of the patients originally assigned to enalapril, 67.5% were still taking the blinded study medication at completion of the study; the corresponding figure for the placebo group was 58.6%. Of the patients originally assigned to enalapril who stopped taking blinded medication, 13.9% had crossed over to open label angiotensin-converting enzyme inhibitors by the end of the 3rd year; the corresponding figure for the placebo group was 23%. These data provide further support for the efficacy of angiotensin-converting enzyme inhibitor therapy. Patients were questioned concerning a large number of possible side effects, and the only effects that were significantly more common in the enalapril-treated than placebo-treated patients were dizziness and fainting (57% vs. 50%) and cough (37% vs. 31%).

Figure 2. Curves for the placebo- and enalapril-treated groups for the combined end point of death plus hospitalization for congestive heart failure (CHF). Adapted, with permission, from a report by the SOLVD Investigators (8).



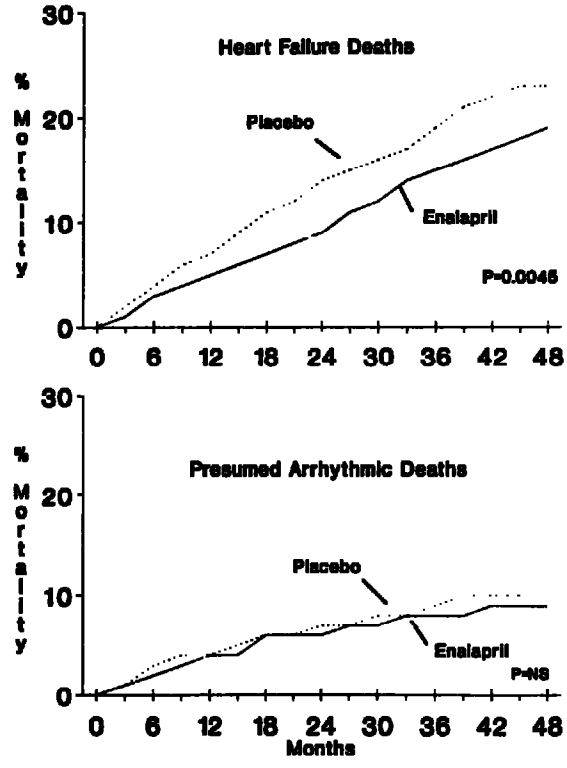


Figure 3. Mortality in the placebo- and enalapril-treated groups due to progressive heart failure (upper panel) and sudden death (lower panel). The difference between the two groups is significant for progressive heart failure but not for sudden death. Adapted, with permission, from a report by the SOLVD Investigators (8).

Conclusions. The results of SOLVD clearly show that morbidity and mortality are reduced by administering the angiotensin-converting enzyme inhibitor enalapril to patients with mild to moderate congestive heart failure. The benefits were sustained over the 4-year study period. However, the mechanism of action of angiotensin-converting enzyme inhibitors is not fully understood. It may depend to some degree on a reduction of myocardial work load, but could also be due in part to changes in neurohormonal systems

other than the renin-angiotensin system, such as the adrenergic system, which is known to be activated in congestive heart failure (10,11). There may also be effects that are related to the actions of angiotensin directly on the myocardium that are not reflected in changes in the levels of circulating neurohumors (12).

References

1. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441–6.
2. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
3. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
4. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 1984;70:271–8.
5. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 1986;314: 1547–52.
6. Studies of Left Ventricular Dysfunction (SOLVD). Rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. Am J Cardiol 1990;66:315–22.
7. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
8. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
9. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
10. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990;82:1724–9.
11. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82:1730–6.
12. Hirsch AT, Talsness CE, Schunkert H, Paul M, Dzau VJ. Tissue-specific activation of cardiac angiotensin converting enzyme in experimental heart failure. Circ Res 1991;69:475–82.