Review Article

An overview of survival studies in patients with heart failure

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Summary: Heart failure is associated with poor prognosis, but recent large-scale investigations have generated valuable and practical information to help improve clinical management and patient survival. This review presents an overview of the findings of recent heart failure survival studies and how these may affect therapeutic strategy for patients with this condition.

Introduction

Heart failure is a highly prevalent condition associated with a poor prognosis.¹ It has been estimated that 2.3 million patients in the USA and about 2 million in Germany, France and the United Kingdom are affected at any one time, giving a prevalence in society of approximately 1%.^{2,3} Life expectancy is dramatically shortened in patients with heart failure, and only 50% survive for 5 years after diagnosis.⁴ In addition, more than one-third of patients with heart failure require treatment in a hospital each year.⁵

Recently completed clinical investigations (SOLVD and V-HeFT-II trial)^{6,7} have yielded encouraging evidence that treatment with the long-acting angiotensin converting enzyme (ACE) inhibitor enalapril can reduce mortality and morbidity (hospitalizations) in patients with mild to moderate grades of heart failure. These findings from the SOLVD⁶ and V-HeFT-II⁷ trials extend those of the CONSENSUS study (the Cooperative North Scandinavian Enalapril Survival Study), reported in 1987, which showed clear mortality reductions in enalapril-treated patients compared with placebo therapy in patients with severe heart failure.⁸ This article presents an overview of the findings of the large heart failure survival studies, and how these may affect present and future treatment of heart failure. It also explores reports of differences in the mortality reduction of patients treated with enalapril and captopril, which suggest that the effects of enalapril demonstrated in the SOLVD, V-HeFT-II and CONSENSUS studies are related to some characteristic activity of this agent rather than a class effect of all ACE inhibitors.^{9,10}

Review of recent studies

CONSENSUS

ACE inhibitors had been available for several years before the results of CONSENSUS were reported and had been shown to improve symptoms and exercise capacity in patients with severe heart failure but not necessarily prognosis.^{8,11} Retrospective analyses of placebo-controlled trials suggested, however, that ACE inhibitors might provide beneficial effects on mortality.¹² To examine this possibility, the CONSENSUS trial was designed to study the effect of enalapril compared to placebo on mortality in patients with severe heart failure.

The study randomized 253 patients with severe heart failure to receive either enalapril ($n = 127$) or placebo ($n = 126$) in addition to conventional therapy. Patients recruited were classified as New York Heart Association (NYHA) class IV (symptomatic at rest) despite optimal therapy with diuretics and digoxin. Treatment with non-ACE-inhibiting vasodilators was also permitted. Enalapril-treated patients experienced a 40% reduction in mortality after 6 months and a 27% reduction at the end of the study (Table I). The greatest mortality reduction (a 50% reduction in patients randomized to active treatment) was in deaths caused by progression of heart failure. At the end of the study, NYHA classification had improved in 42% of patients receiving enalapril but in only 22% of those given placebo, a statistically significant difference ($P < 0.001$). The benefits of enalapril treatment in the study were so clear-cut that the Ethical Committee recommended that enrolment and follow-up be discontinued earlier than planned.

Table I Mortality results from CONSENSUS.* (Reproduced with permission from The CONSENSUS Trial Study Group, *N Engl J Med* 1987, 316: 1429–1435)

	<i>Treatment group</i>				<i>Reductions in relative risk %</i>	<i>P value (life-table) analysis</i>
	<i>Placebo (n = 126)</i>		<i>Enalapril (n = 127)</i>			
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>		
Mortality at 6 months (180 days)	55	44	33	26	40	0.002
Mortality at 1 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 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 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.

SOLVD

Although the results of CONSENSUS were dramatic, the study was limited to patients with severe heart failure, and treatment lasted only a few months. The subsequent reports from SOLVD and V-HeFT-II have now furnished information on the use of enalapril over a longer period and in a broader range of patients, including those with mild to moderate heart failure (NYHA class II or III).^{6,7} The treatment arm of SOLVD examined more than 2,500 patients of whom approximately 90% were classified as NYHA class II or III. Because the study was designed as a long-term examination of the effects of treatment on mortality and disease progression, the investigators recruited patients who were in a stable clinical condition and able to tolerate long-term treatment. Before randomization, all patients were initially given 2.5 mg of enalapril twice daily for 2–7 days to identify those unable to comply with the regimen or to tolerate active drug.⁶ After this initial phase, patients were given matching placebo for 14–17 days to allow identification and exclusion of those whose clinical condition worsened on withdrawal of the drug. Following randomization, patients received double-blind treatment with either placebo (*n* = 1284) or enalapril (*n* = 1285). Double-blind treatment was given in addition to conventional therapy for heart failure, which generally consisted of diuretics, digoxin and vasodilators (but not other ACE inhibitors).

Enalapril treatment was initiated at a dosage of 2.5 mg or 5.0 mg twice daily based on the investigators' assessment of the patients' clinical condition. The dosage was titrated to 10 mg twice daily in patients with stable renal function who did not develop symptomatic hypotension. If symptoms of

heart failure did not resolve with this regimen, increased doses of diuretics or digoxin were recommended as the first step. If maximal therapy with these agents was considered ineffective, open-label treatment with an ACE inhibitor was allowed and double-blind therapy was discontinued. The primary aim of the trial was to assess the effect of study treatment on mortality, although an important additional endpoint was hospitalization for heart failure.

Following completion of the study, the average follow-up period was 41.4 months (range 22–55 months). A reduction in mortality and hospitalization due to heart failure was evident in the enalapril group after 3 months of randomization (Table II) and continued throughout treatment. The difference in mortality appeared to be most marked in the first 24 months after randomization.

At the end of the scheduled follow-up, 452 patients in the active-treatment group and 510 patients in the placebo group had died. This outcome represents a risk reduction of 16% (*P* < 0.0036). The largest mortality reduction was for deaths attributed to progression of heart failure (risk reduction 22%, *P* < 0.0045), although death due to other causes also declined (Table III).

A significant reduction in the combined endpoint of death or hospitalization for congestive heart failure was also observed in enalapril-treated patients (Table II). The overall risk reduction was 26% (*P* < 0.0001). Overall, 971 hospitalizations were required in the placebo group, compared to 683 in the enalapril-treatment group. The total number of patients requiring hospitalization was 470 in the placebo group and 332 in the active-treatment group. Interestingly, the difference in mortality was observed only among patients hospitalized at least once during the trial. Based on

Table II Effect of treatment on mortality and hospitalization for heart failure in the SOLVD treatment arm. (Adapted with permission from The SOLVD Investigators, *N Engl J Med* 1991, **325**: 293–302)

Months of follow-up	Mortality			Death or hospitalization for heart failure		
	Placebo Number	Enalapril Number	Risk reduction %	Placebo Number	Enalapril Number	Risk reduction %
3	69	47	33	164	92	46
6	126	91	29	259	150	45
12	201	159	23	401	262	40
24	344	277	23	559	434	30
36	450	396	16	680	555	28
48	504	443	17	731	607	27
Overall	510	452	16	736	613	26
	<i>P</i> = 0.0036			<i>P</i> < 0.0001		

Table III Number of deaths, causes of death, and number of patients who died or were hospitalized for congestive heart failure (CHF), according to treatment in SOLVD. (Adapted with permission from The SOLVD Investigators, *N Engl J Med* 1991, **325**: 293–302)

Variable	Placebo No. (%)	Enalapril (%)	Risk reduction (%)	<i>P</i> value
Randomized patients	1284 (100.0)	1285 (100.0)	–	–
Deaths	510 (39.7)	452 (35.2)	16	< 0.0036
Deaths or hospitalizations for CHF	736 (57.3)	613 (47.7)	26	< 0.0001
Cardiovascular deaths	461 (35.9)	399 (31.1)	18	< 0.002
Cardiac	441 (34.3)	376 (29.3)	19	< 0.0015
Arrhythmia without worsening CHF	113 (8.8)	105 (8.2)	10	–
Heart failure or arrhythmia with CHF	251 (19.5)	209 (16.3)	22	< 0.0045
Myocardial infarction	53 (4.1)	40 (3.1)	28	< 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)	–	–

these observations, the investigators hypothesized that prevention of hospitalization for heart failure could be an effect of enalapril that is linked to the ability to reduce mortality.

More patients taking placebo than taking enalapril received other vasodilators during the trial to treat worsening heart failure. Therefore, the investigators reported that the risk reductions of 16% for mortality and 26% for the combined outcome of mortality or hospitalization for heart failure determined by intention-to-treat analysis over the course of the trial probably underestimate the actual benefits of the drug.

The effects of active treatment were consistent among most of the subgroups in the study, based on serum sodium concentration, cause of heart

failure, or severity of heart failure. In subgroups based on ejection fraction at baseline, the effects of enalapril on mortality and hospitalizations appeared to be greatest in patients in the two tertiles with lowest ejection fraction. In the tertile with least depressed ejection fraction, a trend toward fewer hospitalizations was observed in patients alive at the end of the study, and the 95% confidence intervals included the possibility of a 20% risk reduction for mortality or hospitalization as a result of worsening heart failure.

V-HeFT-II

V-HeFT-II compared the effects on mortality of enalapril with those of the vasodilator combination

of hydralazine and isosorbide dinitrate.⁷ The majority of patients in this study had heart failure classified as NYHA class II or III. Following randomization, 403 patients received double-blind treatment with enalapril, and 401 received the vasodilator combination. Because this trial compared enalapril treatment with a treatment regimen already proven to reduce mortality,¹³ V-HeFT-II also included comparisons of the effects of treatment on physiological endpoints (peak oxygen consumption during exercise and left ventricular ejection fraction) in addition to mortality.

The mortality curves of the two treatment arms separated early after randomization, and the relative reduction in mortality for patients treated with enalapril continued for up to 4 years of the study. Mortality after 2 years (a major predetermined endpoint of the study) was significantly lower in the enalapril group (18%) than in the hydralazine/isosorbide dinitrate treated group (25%), a risk reduction of 28% ($P = 0.016$).

Because V-HeFT-II was a comparison of two active treatments added to conventional therapy, the authors drew particular attention to the magnitude of the mortality-reducing effect by comparing the results with those of V-HeFT-I, a placebo-controlled study. Because the patient populations in both trials were homogenous and the mortality curves for patients randomized to receive hydralazine/isosorbide dinitrate were reproducible in both trials (Table IV), the authors compared mortality results of the two studies and found that adding enalapril to conventional treatment reduced mortality after 1 year to 9% from a historic value of 20% with placebo in V-HeFT-I.

In V-HeFT-II, the nonspecific vasodilator combination produced significantly more improvement in exercise performance and left ventricular ejection fraction, indicating more effective vasodilatation than with enalapril, despite the clearly greater reduction in mortality in patients receiving enalapril. The authors suggest that this observation may mean that not all therapeutic endpoints assessed in trials of heart failure treatment are affected in the

same way and that the beneficial effect of enalapril on mortality may be a result of a specific non-vasodilator mechanism.

Other studies

There is further interesting evidence to suggest that the degree of ACE inhibition produced by enalapril may be linked to the mortality-reducing effect.^{9,10,14} One report, from a retrospective analysis of baseline therapy in the Xamoterol in Severe Heart Failure Study, reported a greater probability of survival for patients taking enalapril than for those taking captopril.⁹ The excess mortality in captopril-treated patients could not be related to factors considered indices of heart failure severity. After examining the dosage schedules for the two ACE inhibitors, the authors proposed that, in general, patients on captopril may have been taking an insufficient dose or receiving an insufficient number of daily doses. Because enalapril has greater potency and longer duration of action as an inhibitor of ACE, differences in mortality may be attributable to differences in the blockade of the renin-angiotensin system.

Differences in mortality have also been reported when low and high doses of enalapril have been compared in patients with severe heart failure.¹⁴ Fewer patients died or required hospital treatment for heart failure while taking higher doses that would be expected to inhibit ACE to a greater extent. Moreover, ACE inhibitors have characteristic profiles of activity with respect to inhibition of tissue and circulatory renin-angiotensin systems.¹⁵ Because the mortality reductions seen with enalapril may be related to the extent of inhibition of ACE, these properties should not be considered a class effect common to all ACE inhibitors unless clinical evidence becomes available to support this view.¹⁰

Table IV Cumulative mortality for V-HeFT-I and V-HeFT-II. (Reproduced with permission from Cohn *et al.*, *N Engl J Med* 1991, **325**: 303–310)

Study group	No. of patients	Cumulative mortality			
		1 year	2 years	3 years	4 years
(%)					
V-HeFT-I					
Placebo	273	20	34	47	54
Hydralazine isosorbide dinitrate	186	12	26	36	50
V-HeFT-II					
Hydralazine isosorbide dinitrate	401	13	25	36	47
Enalapril	403	9	18	31	42

Conclusion

The consistency of the effect seen with enalapril in these independent, well-conducted survival studies provides good evidence that this agent should be regarded as a new cornerstone in the treatment of heart failure. Addition of enalapril to conventional therapy with diuretics and digoxin has been clearly shown to improve the prognosis of patients with

heart failure of all grades. Medical practitioners now have firm clinical evidence on which to base choices of treatment for heart failure. The results of the SOLVD trial suggest that 3 years of enalapril treatment in 1,000 heart failure patients similar to those enrolled in SOLVD might prevent about 50 premature deaths and an additional 350 hospitalizations.⁶

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