

VIEWPOINT

Angiotensin converting enzyme inhibitors in heart failure: how good are they?

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The natural history of heart failure is one of relentless deterioration to an early death. Despite giving symptomatic relief, diuretics and digoxin have not been shown to affect the progressive nature of the syndrome. Three large independent trials showed that the addition of an angiotensin converting enzyme (ACE) inhibitor to the therapeutic regimen reduced mortality in patients with moderate or severe heart failure.¹⁻³ Several studies have also showed that ACE inhibitors improve symptoms and exercise tolerance.⁴⁻¹³ As a result ACE inhibitors have become a routine part of the treatment of heart failure, indeed it is now widely considered unethical to perform placebo controlled studies of these agents. However, it is difficult to extrapolate information gained from clinical trials to individual patients. Close scrutiny of the data reveals more modest benefits than are apparent from the "headline" results.

Mortality

The CONSENSUS study showed that treatment with enalapril caused a 40% reduction in mortality at six months, from 44% in the placebo group to 26% in the treatment group in a population of 253 patients with New York Heart Association (NYHA) class IV symptoms.¹ The patient group was elderly (mean age over 70 years) and was on established treatment with large doses of diuretics. By the end of the study (mean period of follow up patients assigned to enalapril only 215 days) 50 (39%) of the initial 127 patients treated with enalapril had died. No information has been published subsequently on the longer term results of this trial. Looking at the average increase in life expectancy given to a patient in class IV heart failure by the addition of enalapril is salutary—the interval between the two mortality curves suggests a figure of approximately 20 weeks. Patients with NYHA class IV symptoms have such a poor quality of life that it may be argued that unless symptoms improve considerably, the addition of a few months to life expectancy is no great gain unless it is as a bridge to cardiac transplantation. Symptomatic status was measured in the CONSENSUS study as physician determined changes in NYHA functional class, a rather crude and subjective assessment. There was a significant difference

in favour of enalapril: 54 (42%) of 127 of patients on active treatment improved their NYHA classification compared with 27 (22%) of 126 of those on placebo. However, over half (56%) of the patients treated with enalapril did not improve: they died or continued in NYHA functional class IV.

In the Studies of Left Ventricular Dysfunction (SOLVD) treatment study the risk of death was reduced by 16% after a mean treatment period of 41 months in 2569 patients with mainly moderate heart failure (over 90% were in NYHA class II and III).² In the treatment group 452 (35.2%) out of 1285 patients died during follow up compared with 510 (39.7%) out of 1284 patients assigned to placebo. Although at first sight the figures seem less impressive than those of the CONSENSUS study, the mean increase in life expectancy for a patient treated with enalapril was six to eight months compared with about five months in the CONSENSUS study. Because most patients seen in everyday clinical practice are in class II and III heart failure the SOLVD data may be of more direct clinical relevance. Nevertheless, several criticisms may be made of the study. Only 6.4% of nearly 40 000 patients with ejection fractions of less than 35% were included in the treatment study, raising doubts about the applicability of these data to the patients seen in everyday practice. In particular 12% of patients were excluded because of "cardiovascular" problems and a total of 38% were excluded for reasons of "administration", coexistent disease, and "other" problems. Patients unable to tolerate the drug or its withdrawal were excluded in a run-in phase, which may have affected the results in either direction. By the end of the study over 30% of the patients treated with enalapril and over 40% of those taking placebo had stopped taking blinded medication while the use of open label ACE inhibitors was quite common (23% and 14% in the placebo and enalapril groups respectively at three years). Also about 50% of the patients were taking vasodilators (mainly nitrates) other than ACE inhibitors throughout the trial period.

The second Vasodilator Heart Failure Trial (V-HeFT II) study compared direct-acting vasodilators (a combination of hydralazine and isosorbide dinitrate in high doses) with enalapril in a group of 804 men with heart

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Controlled trials examining the effect of ACE inhibitors on exercise capacity*

Study	Agent	NYHA functional class	Number of patients	Baseline exercise capacity (s)	Increase in exercise capacity after ACE inhibitor (s)
Captopril multicenter research group 1983 ⁴	Captopril	II & III	92	495	119
Cleland <i>et al</i> , 1984 ⁷	Captopril	III & IV	14	336	210
Kramer <i>et al</i> , 1984 ⁶	Captopril	II, III & IV	16	540	162
Sharpe <i>et al</i> , 1984 ⁷	Enalapril	II & III	36	558	498
McGrath <i>et al</i> , 1985 ⁸	Enalapril	II & III	25	577	No significant increase in exercise duration
Captopril-digoxin Multicenter Research Group, 1989 ⁹	Captopril	Mainly II & III	164	572	81
Quinapril, research group, 1988 ¹⁰	Quinapril	II & III	225	267	54
Cleland <i>et al</i> , 1985 ¹¹	Enalapril	II, III & IV	20	390	252
Cowley <i>et al</i> , 1986 ¹²	Captopril	? II & III (not specified)	10	708	126
Franciosa <i>et al</i> , 1985 ¹³	Enalapril	II, III & IV	17	546	174
V-HeFT II, 1991 ¹	Enalapril	Mainly II & III	804	No increase in peak oxygen consumption	

*This is not an exhaustive list.

failure (predominantly NYHA class II and III).³ Overall mortality (mean duration of follow up 2.5 years, range 6 months to 5.7 years) was not significantly different in the two groups, with 132 deaths in the 403 patients assigned to enalapril and 153 deaths in those patients receiving the hydralazine/nitrate combination. Cumulative mortality at two years was significantly lower in the enalapril group than in the hydralazine/nitrate group (18% *v* 25% respectively). By four years, however, the cumulative mortality of the patients assigned to enalapril was 42%. No women were included in the study and only half the patients had heart failure caused by coronary artery disease. This unusually low proportion with coronary artery disease may have tended to reduce overall mortality because this aetiology is said to carry an adverse prognosis in patients with heart failure.¹⁴ Over a third of patients were said at baseline to use alcohol excessively with no comment made on its subsequent use or discontinuation.

Thus the 16–31% reduction in one year mortality (depending on functional class) with ACE inhibitors represents a slowing rather than a halting of disease progression. The life expectancy of patients with heart failure remains considerably shortened. It is perhaps of much more importance therefore, to determine whether these agents improve the quality of remaining life. Surrogates for clinical improvement such as exercise tolerance have been looked at in numerous, but usually small, controlled trials.

Quality of life

Although many of the results do show statistically significant increases in exercise tolerance the figures are very variable and the absolute increases are often small (see table). The captopril multicentre research group report⁴ is perhaps representative, with a 24% improvement in treadmill exercise tolerance actually reflecting a 2 minute increase in exercise time to a mean maximum value of only 614

seconds. Such figures are heavily dependent on the exercise protocol chosen and it is difficult to extrapolate improvements in incremental exercise protocols to everyday activity. Although it was only a secondary end point in the V-HeFT II trial, exercise capacity was measured by determining peak oxygen consumption during incremental bicycle ergometry. This represents the largest single study of the effect of an ACE inhibitor on exercise capacity. In contrast to the hydralazine-nitrate combination which produced a small (<1 ml/kg/min) increase in peak oxygen consumption, enalapril did not increase peak oxygen consumption at any of the time points examined during follow up. Other reports on the effect of ACE inhibitors on oxygen uptake during exercise, a more objective and reproducible index of exercise tolerance than simple exercise duration,¹⁵ have given variable results. Franciosa *et al*¹³ found both oxygen consumption and treadmill exercise tolerance were increased significantly by enalapril in comparison to placebo while Cowley *et al*¹² showed that although treadmill exercise duration was significantly increased by captopril there was no change in oxygen consumption.

The need for hospital admission can also be used as an index of the quality of life of chronically sick patients. Once again the results are disappointing. Although significantly reduced compared with placebo (47.7 *v* 57.3% over a study period of almost four years) the rates of hospital admission during treatment with ACE inhibitors in the SOLVD study are depressingly high. During the study 613 of 1285 patients treated with enalapril required 971 hospital admissions for congestive heart failure.

Functional status and quality of life were examined as part of the SOLVD treatment study and the preliminary results were reported recently.¹⁶ The NYHA functional class determined by a physician at one year remained unchanged or improved in slightly but significantly more (74%) of the patients given enalapril than those given placebo (66%). A self administered questionnaire, however,

showed that patients perceived improvements only in "social functioning" at six weeks and one year and in "general health" at six weeks only. There were no significant differences between the two groups with respect to heart failure symptoms, activities of daily living, depression, and general life satisfaction at any point during follow up. The results of a more detailed study of a sample group of the SOLVD population are awaited.

Angiotensin converting enzyme inhibitors in combination with diuretic treatment are the best available medical treatment for heart failure. In all the trials described patients were on established diuretic treatment. Single agent treatment of heart failure with ACE inhibitors is ineffective¹⁷ and it cannot be excluded that much of the beneficial effect of ACE inhibitors in heart failure may be the result of a reduction of the adverse haemodynamic and neuro-hormonal effects of diuretic therapy. Direct acting vasodilators in high dose are a more cumbersome and less well tolerated regimen but may be superior in their capacity to improve exercise tolerance. Neither ACE inhibitors nor any other medical treatment come close to the prognostic and symptomatic improvement that can be gained by cardiac transplantation.¹⁸ Organ availability unfortunately precludes more widespread use of this highly successful treatment. ACE inhibitors are undoubtedly an advance and their modest efficacy contrasts with the disappointing results obtained from trials of inotropes (both β agonists and phosphodiesterase inhibitors,^{19,20}) calcium antagonists,²¹ and vasodilators such as hydralazine,²² and prazosin.²³ However, they are a limited advance and other treatments, both pharmacological and perhaps biomechanical, are needed to improve significantly the lot of patients with this disabling and progressive condition.

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