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Delayed effects of one-year treatment with low-dose as compared with high-dose enalapril on morbidity and mortality of patients with severe heart failure

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Uptitrating severe heart failure patients from a conventional low dose of enalapril to a high dose yields more favourable clinical results in severe heart failure patients treated with high dose than with low dose. To investigate subsequent effects on morbidity and mortality of high dose enalapril, an open two-year extension study was performed with all patients receiving the high dose. Of 83 New York Heart Association class III–IV patients (83 % male, aged 27–74 years; mean 55), 43 patients had completed the one year basic study. 41 patients (18 patients in the low-dose extension group and 23 patients in the high-dose extension group) entered extension and received 40 mg enalapril per day. Clinical status, exercise capacity and kidney function were assessed at months 15, 18, 24, 30 and 36 and survival rates were evaluated at month 36 after randomisation. At month 15 the change in New York Heart Association score was similar in both treatment groups, but at month 18 New York Heart Association score decreased more in the high-dose extension group than in the low-dose extension group (-0.8 vs -0.5 , $p < 0.05$) with no further difference between the groups up to 36 months. At month 24 exercise capacity increased more in the high-dose extension group than in the low-dose extension group ($p < 0.05$), whereas heart rate and peripheral blood pressure at maximal exercise were similar in both groups. Except for a larger drop in systolic ($p < 0.05$) and diastolic ($p < 0.05$) resting blood pressure in the high-dose extension group, both groups had a similar safety profile, including kidney function. Three patients in the low-dose extension group and 13 patients in the high-dose extension group completed the open extension study. At the end of the study at month 36 there were 12 heart transplants (7 in the low dose extension group versus 5 in the high-dose extension group) and 22 deaths (15 in the low dose extension group versus 7 in the high-dose extension group) resulting in a significant improvement in survival ($p < 0.05$). The present data suggest a marked clinical benefit from maximising ACE-inhibitor doses in patients with severe heart failure. While symptomatic improvement may appear as the first response secondary to uptitrating enalapril to a more vigorous dose, enhanced exercise tolerance seems to warrant prolonged high enalapril treatment and may finally translate into a survival benefit. *J Clin Bas Cardiol 1998; 1: 19–24.*

Key words: Severe heart failure, high dose enalapril, exercise tolerance, survival

Despite the survival benefit shown with ACE-inhibitors the doses used in clinical practice unfortunately tend to be much lower than those used in the clinical trials. However, low doses of ACE inhibitors may not completely suppress angiotensin II and may be insufficient to promote effects through bradykinin and prostaglandin stimulation on the other [1]. Recent dose-effect considerations are based on the understanding that improvement induced by interfering with the converting enzyme is not limited to the haemodynamic effects but that a structural component might be involved, which results from inhibiting neurohumorally-mediated proliferation of the vascular tissue [2]. To treat this component with ACE-inhibitors has added a further target in heart failure therapy. The upper end of the therapeutic dose-response relation with ACE inhibitors has not been fully explored so far. However, with the potential extension of standard heart failure therapy to β -blockers, angiotensin receptor antagonists, calcium channel blockers, or phosphodiesterase inhibitors, establishing the appropriate dose of ACE inhibitors has become critical.

Recently, we reported the results obtained with low and high captopril dosages in a retrospective study of severe heart failure patients [3]. We observed a greater improvement in symptoms in the patients receiving over 75 mg captopril daily. Since the study was not randomised, it could not be ruled out, however, that patients who could tolerate higher captopril dosages were less compromised. Therefore, we performed a *prospective* study to find out whether an increase in dose (40 mg per day) of a long-acting ACE-inhibitor, enalapril, would result in a greater improvement in a population of severe heart failure patients than a low, more widely used dose (10 mg per day).

After one year the high dose resulted in a significantly more pronounced improvement in symptoms than the low dose, but without jeopardising kidney function [4]. As a consequence, all patients completing the study were switched to the higher enalapril dose. This report describes the results of this open extension study during two additional years of treatment.

Methods

Study design (Fig. 1)

The study is an extension of our basic study [4], which was a 48-week, double-blind, randomised, controlled, parallel-study comparing safety and tolerability of two different dose regimens of enalapril in 83 patients with severe heart failure. Clinical status, effort capacity, haemodynamics and neurohumoral activity were assessed for both regimens. All patients who entered in the extension study were treated with enalapril 40 mg/day (2 x 20 mg/day). The objectives of the extension study were to prove the tolerability of 40 mg enalapril per day (2 x 20 mg/day), to observe delayed effects on morbidity and mortality of a switch from 10 to 40 mg/day in the previous study using a homogenous patients population of severe heart failure over a three year period. Patients in the two treatment groups – 42 in the low-dose (LD) extension group (enalapril 10 mg for 12 months followed by enalapril 40 mg up to 36 months) and 41 patients in the high-dose (HD) extension group (enalapril 40 mg for 12 months followed by enalapril 40 mg up to 36 months) were separately analysed. The patient's clinical condition was assessed and exercise capacity and

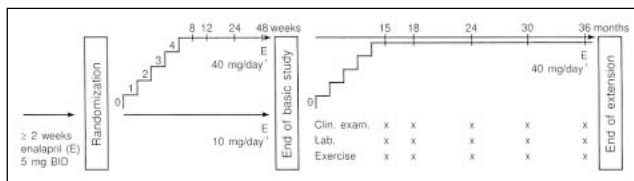


Figure 1: Flow chart. E, enalapril; BID, twice daily doses; Clin. exam., clinical examination; Lab., routine laboratory.

laboratory values were determined at each clinical visit as given in the flow chart. The protocol was approved by the local ethical committee and included written consent of the patients.

Patients (Table 1)

Eighty-three patients with heart failure in NYHA functional class III–IV while receiving digitalis, diuretics and low dose ACE inhibitor therapy (enalapril ≤ 10 mg/day or captopril ≤ 50 mg/day) through at least three months were entered in the basic study. The clinical diagnosis of heart failure was confirmed by at least one of the following parameters: left atrial mean pressure > 10 mmHg or pulmonary artery mean pressure > 35 mmHg or cardiac index < 2.5 litres/min per m^2 at haemodynamic evaluation performed after a 2-week-run-in when previous ACE inhibitor regimens were withdrawn and patients received enalapril 5 mg b.i.d. in an open fashion.

Statistical methods

Continuous variables are expressed as means \pm SEM. Patient characteristics were compared using the Fisher's exact test for dichotomous variables or the Wilcoxon rank-sum test for ordered categorical data. The comparability for the treatment groups at baseline was assessed by the McCullagh's method with treatment as factor for the New York Heart Association score and by ANOVA with treatment as factor effect for diastolic and systolic blood pressure and exercise performance. The efficacy analyses were performed using an intention to

treat approach; that is, all patients with efficacy data both at baseline and on treatment were analysed including protocol violators or drop-outs. If in the intention to treat approach a patient's data were missing at months 15, 18, 24, 30 and 36, respectively, the last observation prior to that month was carried forward and used in the analyses. Patients who died during the study or within 14 days after the end of the study for a reason other than congestive heart failure worsening, were assigned the New York Heart Association score for their previous visit while patients who died because of worsening of congestive heart failure were put in the worst category. Patients who underwent heart transplantation were given the score of their previous visit since they were already a candidate for heart transplant at the start of the study. The comparison between the two groups was made using McCullagh's method (for ordered categorical variables) with baseline and treatment as model effects and with ANOVA on the ranks with treatment as model effect. Within group comparisons, to assess the significance of the change from baseline in the two treatment groups separately, were made using the Wilcoxon signed-rank test and paired t-test. Efficacy ordered categorical variables were analysed by McCullagh's method. Treatment groups were compared with regard to the incidence of clinical and laboratory adverse effects by means of Fisher's exact test. Kaplan Meier survival estimates and the log-rank test were used to compare survival between groups. A $p < 0.05$ was considered significant in all analyses.

Results

Patient characteristics and comparability (Table 1)

Table 1 summarises demographic and clinical characteristics of 83 patients who entered the run-in stabilisation period of the basic study. Forty-two were randomized to the low-dose group and 41 patients to the high-dose group. The treatment groups were similar with respect to key demographic and clinical signs of congestive heart failure as well as concerning concomitant treatments with digitalis, diuretics, nitrates and aspirin, but there was a significant difference with respect to aetiology of congestive heart failure ($p = 0.04$).

Table 1: Baseline demographic and clinical variables in 83 patients

	Low-dose extension n = 42	High-dose extension n = 41
Male/Female	34/8	35/6
Age (years)	56 \pm 1.7	56 \pm 1.4
NYHA Status		
Class II	1	1
Class III	37	29
Class IV	4	11
Etiology of heart failure*		
Idiopath. Cardiomyopathy	33 (79)	27 (66)
Coronary Heart Disease	9 (21)	14 (34)
Heart transplant candidates	24 (57)	25 (61)
Treatment		
ACE-inhibitors	42 (100)	41 (100)
Digitalis	42 (100)	41 (100)
Nitrates	21 (50)	30 (73)
Diuretics		
Furosemide (mg/d)	81 \pm 13	90 \pm 13
Spironolactone	1 (2)	1 (2)
Ethacrynic acid	6 (14)	10 (24)

ACE, angiotensin converting enzyme; NYHA, New York Heart Association. Data given as mean \pm SEM or as absolute numbers with percentages in parentheses. *Significant difference ($p = 0.04$) between the two groups with respect to aetiology; more patients in the low dose group had idiopathic cardiomyopathy and more patients in the high dose group had ischemic heart disease. No other significant differences between groups.

Functional assessments (New York Heart Association class) (Fig. 2)

Due to two drop-outs, the low-dose extension group comprised 41 patients and the high-dose extension group comprised 40 patients for analysis of NYHA score. Both groups were comparable with regard to mean NYHA score at baseline.

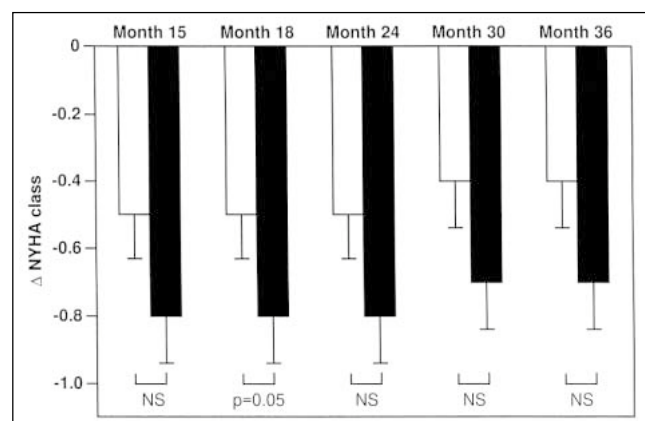


Figure 2: Mean changes \pm SEM in NYHA functional class from baseline to months 15, 18, 24, 30 and 36 in the low-dose extension group (open bars, n = 41) and in the high-dose extension group (black bars, n = 40).

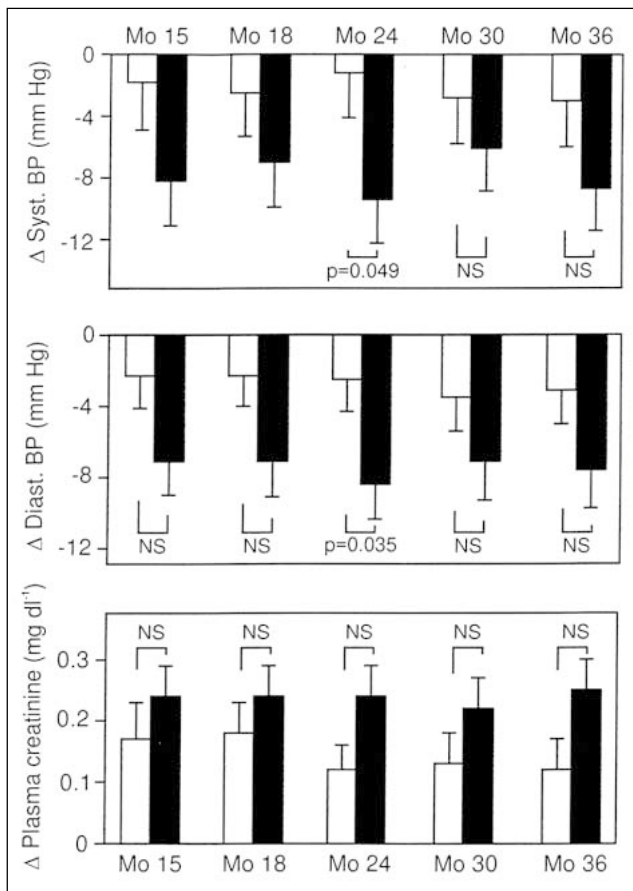


Figure 3: Mean changes \pm SEM in systolic and diastolic blood pressure and in plasma creatinine from baseline to months 15, 18, 24, 30 and 36 in the low-dose extension group (open bars, $n = 41$) and in the high-dose extension group (black bars, $n = 39$). Mean changes \pm SEM in plasma creatinine from baseline to months 15, 18, 24, 30 and 36 in the low-dose extension group (open bars, $n = 38$) and in the high-dose extension group (black bars, $n = 34$).

At months 15, 18, 24, 30 and 36 NYHA class decreased from baseline in the low-dose extension group as well as in the high-dose extension group, and the decrease in NYHA score from baseline was significant in the two treatment groups at all months ($p < 0.01$ for both groups at all times). However, the magnitude of change from baseline was similar in both treatments except for month 18, when the improvement in NYHA class was larger in the high-dose extension group than in the low-dose extension group.

Systolic and diastolic blood pressure and kidney function (Fig. 3)

Both groups were comparable with regard to systolic and diastolic blood pressure at baseline. Systolic blood pressure decreased in the high-dose extension group only, ($p < 0.01$ at months 15, 24 and 36 and $p < 0.05$ at months 18 and 30, respectively) and the change from baseline was significantly more pronounced in the high-dose extension group than in the low-dose extension group at month 24 ($p < 0.05$). Diastolic blood pressure also decreased in the high-dose extension group only ($p < 0.01$ at all months) and the magnitude of change from baseline was also significantly different between both treatments at month 24 ($P < 0.05$). There were small, but significant increases over baseline in the plasma levels of creatinine in the low-dose extension group ($p < 0.01$ at all months) as well as in the high-dose extension group ($p < 0.01$ at month 15 and 18 and $p < 0.001$ at month 24, 30 and

Table 2: Maximal exercise response in the low-dose extension group and in the high dose extension group

Variable	Low-dose extension ($n = 28$)	High-dose extension ($n = 30$)	p-value ⁺
Workload (w)			
Baseline	66 ± 4.0	66 ± 4.2	ns
24 months	69 ± 6.2	$82 \pm 5.5^{***}$	0.019
30 months	67 ± 5.9	$74 \pm 4.7^*$	ns
36 months	69 ± 6.4	$73 \pm 4.7^*$	ns
HR (bpm)			
Baseline	136 ± 4.3	135 ± 4.2	ns
24 months	140 ± 4.7	131 ± 4.2	ns
30 months	140 ± 4.5	130 ± 4.2	ns
36 months	138 ± 4.5	129 ± 4.4	ns
Syst.BP (mmHg)			
Baseline	152 ± 4.5	162 ± 4.4	ns
24 months	146 ± 5.3	163 ± 5.3	ns
30 months	145 ± 5.1	160 ± 4.4	ns
36 months	$142 \pm 5.1^*$	158 ± 5.3	ns
Diast. BP (mmHg)			
Baseline	93 ± 2.3	97 ± 2.4	ns
24 months	$86 \pm 2.3^{**}$	92 ± 2.4	ns
30 months	$85 \pm 2.3^{**}$	92 ± 2.6	ns
36 months	$85 \pm 2.3^{**}$	92 ± 2.7	ns

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline within the low-dose extension group and within the high-dose extension group; ⁺ between groups.

36, respectively). The changes in plasma creatinine levels were, however, similar for both treatments. The plasma levels of potassium did not change on average.

Maximal exercise response (Table 2)

In 28 patients in the low-dose extension group and in 30 patients in the high-dose extension-group maximal exercise response was established at baseline and at months 24, 30 and 36, respectively. Both groups were comparable with regard to maximal workload, heart rate, systolic and diastolic blood pressure during maximal exercise at baseline. At month 24, 30 and 36 maximal workload increased over baseline in the high-dose extension group only ($p < 0.001$ at month 24 and $p < 0.05$ at months 30 and 36, respectively) and the change from baseline was significantly different between the high-dose extension group and the low-dose extension group at month 24 ($p < 0.05$). Maximal systolic blood pressure decreased at month 36 ($p < 0.05$) and maximal diastolic blood pressure decreased at months 24, 30 and 36 ($p < 0.01$ at all months) in the low-dose extension group only, but the change from baseline was not significantly different between the two treatment groups.

Drop-outs and clinical adverse events (Table 3)

The original double-blind study was completed by 19 of 42 (45%) patients in the low-dose extension group and by 24 of 41 (58%) patients in the high-dose extension group. Due to two drop-outs, 41 patients entered open extension, 18 patients in the low-dose extension group and 23 patients in the high-dose extension group. The first extension was completed at 24 months by 8 patients in the low-dose extension group and by 17 patients in the high-dose extension group. Due to 4 drop-outs, 21 patients entered the second extension, 5 patients in the low-dose extension group and 16 patients in the high-dose extension group. The second extension was completed at 36 months by 17 patients (4 patients in the low-dose extension group and 13 patients in the high-dose extension group). There were 10 drop-outs during first extension and 1 drop-out during second extension in the low-dose extension group

Table 3: Reason for drop-out and discontinuation of treatment during first and second open extension

Reason for discontinuation	Low-dose extension n = 18	High-dose extension n = 23
No. of patients not entering 2 nd extension	3	1
Non-compliance	0	1
Protocol violation	2	3
Adverse clinical experience*	6	3
Heart transplant**	3	2
Total drop-outs	14	10

*including worsening heart failure and death; **all heart transplants occurred during the first 24 months so none occurred during the second year extension.

and 6 drop-outs during first extension and 3 drop-outs during second extension in the high-dose extension group. Four additional patients are missing, who completed first extension, but who did not consent to enter second extension (Fig. 4). No patients were withdrawn from therapy because of laboratory adverse experiences. A total of 52 patients had at least one clinical adverse experience (death and heart transplant included) during the 36 month active treatment phase or within 14 days after end of therapy, 28 (67 %) in the low-dose extension group and 24 (59 %) in the high-dose extension group. A summary of the clinical adverse events counted by body system is provided in Table 3. The proportion of patients with clinical adverse experiences was similar in both treatment groups.

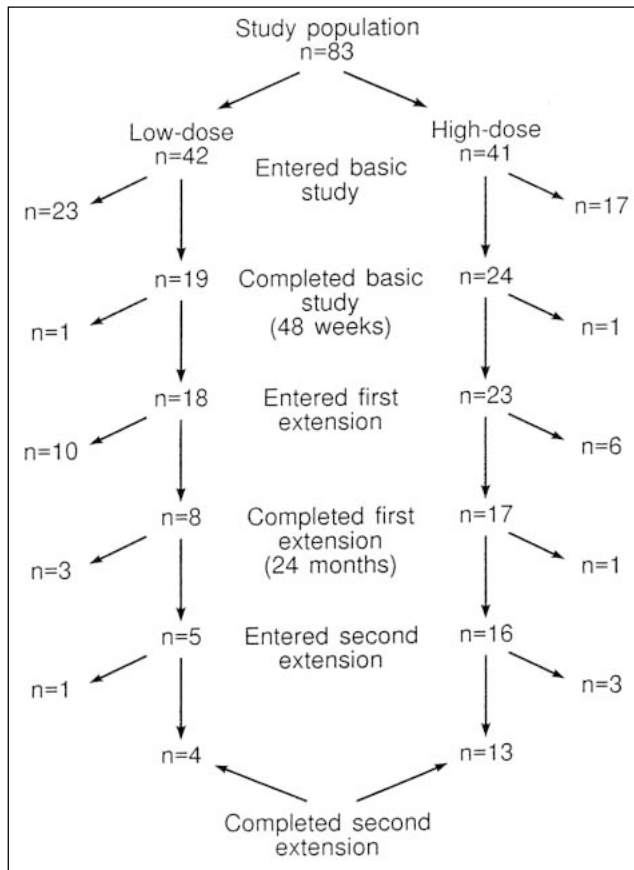


Figure 4: Number of all randomized patients (all patients-treated-cohort and study completing cohort) and number of drop outs at month 0, 15, 18, 24, 30 and 36, as allocated to the low-dose extension group and to the high-dose extension group.

Table 4: Clinical adverse event in the low-dose extension group and in the high-dose extension group (excluding worsening congestive heart failure and sudden death)

Adverse events	Low-dose extension (n = 42)	High-dose extension (n = 41)
Cardiovascular		
Coronary, acute MI, shock	4 (9.5 %)	3 (7.3 %)
Arrhythmia, PM	8 (19 %)	9 (22 %)
CV accident, syncope	3 (7.1 %)	1 (2.4 %)
Arterial occlusion	1 (2.4 %)	1 (2.4 %)
Pulmonary embolism	0	2 (4.9 %)
Respiratory	5 (12 %)	3 (7.3 %)
Metabolic/endocrine	3 (7.1 %)	5 (12 %)
Digestive	2 (4.8 %)	6 (15 %)
Urogenital	1 (2.4 %)	0
Nervous/psychiatric	3 (7.1 %)	5 (12 %)
Infection	2 (4.8 %)	0

Table 5: Mortality within 2 weeks after study completion at 36 months

Causes of death	Low-dose extension (n = 42)	High-dose extension (n = 41)
Cardiovascular		
Progressive heart failure	4 (9.5 %)	2 (4.9 %)
Sudden	9 (21 %)	2 (4.9 %)
MI	0	1 (2.4 %)
Stroke	1 (2.4 %)	1 (2.4 %)
Other: Sepsis, CA	1 (2.4 %)	1 (2.4 %)
Total deaths	15 (36 %)	7 (17 %)

MI, myocardial infarction; CV, cerebrovascular

Clinical outcome (Table 4, Fig. 5)

The cause of a patient's death was classified on the basis of the blinded review of the circumstances surrounding the death, as obtained from the hospital chart or from interviews with relatives. Kaplan Meier survival curves in both treatment groups were compared 3 years after patients entered the double blind phase of the study. During this period there were 22 deaths, 15 in the low-dose extension group and 7 in the high-dose extension group (Table 4) resulting in a significant difference ($p < 0.05$ log rank) among the study groups.

Discussion

Heart failure treatment is aimed to improve symptoms and to prolong life. ACE-inhibitors have been shown to be extremely successful therapy in both respects. This evidence of benefit would be expected to impact greatly on clinical practice, but, nevertheless, most physicians use doses of ACE inhibitors that are far below the doses that showed the prognostic benefits of these drugs. In clinical practice many physicians may hesitate to use a high enalapril dose because of potential side effects such as hypotension or an increase in plasma creatinine levels. But, proof that enalapril or any other longacting ACE inhibiting agent used in the treatment of heart failure is clearly dangerous in terms of progressive renal insufficiency was never really obtained. Not unexpectedly, after long-term treatment with high-dose enalapril, serum creatinine levels increased slightly in our patients. However, no patient taking 20 mg enalapril twice daily dropped out because of clinically relevant deterioration in kidney function.

Changes in kidney function were observed with ACE inhibitors by most investigators, and appeared not to be generally related to prolonged hypotensive periods during enalapril treatment [5]. It is important to note that – in contrast

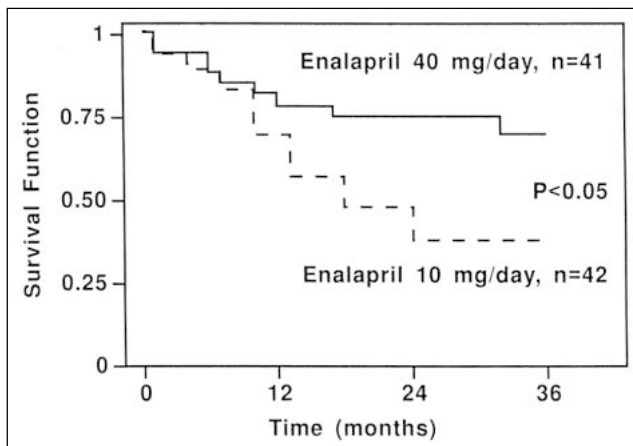


Figure 5: Kaplan Meier survival curves in 42 patients allocated to the low-dose extension group and in 41 patients allocated to the high-dose extension group.

with diastolic blood pressure – creatinine levels did not change differently between groups in our study. Thus, previous safety concerns based on a comparison between a dose of 150 mg per day of the short-acting ACE-inhibitor captopril and 40 mg per day of the long-acting ACE-inhibitor enalapril were not corroborated [6, 7].

Although never proven in controlled trials, it was frequently suspected that the *a priori* ability of patients to tolerate high doses of enalapril might indicate intrinsically better results. In our basic study, that provided first evidence of the advantage of treating severe heart failure patients with 40 mg enalapril per day over the treatment with 10 mg enalapril per day, we took this possibility into account and allocated the patients to up-titration to high-dose or to ongoing low-dose in a random fashion. Thus, our finding of a dose-dependent improvement in symptomatology appears to be valid [4]. Moreover, even though based on an open design only, this extension study suggests that the improvement in clinical status achieved with this approach is well sustained and that high dose ACE-inhibitors may be effective therapy for severe heart failure patients to enhance exercise performance (by an average of 23 %) provided they are treated for long enough. In fact, the majority of the improvement in exercise capacity demonstrated to occur after vasodilator therapy in various studies, has been shown to occur during long-term therapy [8, 9], because prolonged improvement of nutritive flow may be required to allow recovery of impaired skeletal muscle metabolism [10, 11]. Early improvement in exercise capacity has also been shown after treatment with the ACE-inhibitor, captopril, in patients with less severe heart failure [12]. However, a dose-dependence of the improvement in exercise capacity was demonstrated in one study with quinapril [13] and also cilacapril, which did not increase exercise capacity in low-dose ranges [14] was shown to be effective in improving exercise capacity and oxygen utilisation by peripheral musculature when administered at a higher dose [15]. Of importance, the increase in exercise tolerance was not associated with an increase in peak heart rate suggesting an increase in peak stroke volume after long-term high-dose enalapril treatment. Moreover, only in patients who had been treated with high doses of enalapril throughout was a drop in resting blood pressure observed, reflecting a more pronounced peripheral vasodilatation after two years compared with one year of treatment with 40 mg enalapril. This sustained effect on the peripheral vasculature may have supported the ability to increase maximal effort capacity.

If symptoms are already well controlled and exercise tolerance is improved, however, prognostic benefit is the next reason for considering treating a patient with a high ACE inhibitor dose. To support this goal, no adequate comparisons of the of low versus high doses of ACE inhibitors yet exist. The NETWORK study randomly allocated patients to enalapril 2.5 mg, 5 mg or 10 mg twice daily for six months. However the study was unable to detect a difference between the highest and lowest dose in the combined end-point of death, admission to hospital for heart failure, and worsening heart failure [personal communication]. The ATLAS study allocated patients to receive lisinopril at low or high dose with a minimum follow-up time of two years and the results are promising. A further study (ACHIEVE), currently underway compares different dosages of quinapril. Hopefully one of these large studies will establish the usefulness of high ACE inhibitor dosages in the treatment of heart failure. With respect to a potential survival benefit by high dose enalapril in the present study, one must suspect that in patients with NYHA class IV heart failure the prognosis will remain poor even if treated with ACE inhibitors in doses used in the clinical trials [16] unless the chance of a heart transplant is given. In our study a similar number of heart transplants were performed in both treatment groups as all transplanted patients had been candidates before inclusion. Nevertheless we found that in the group which received 40 mg enalapril per day for three years more patients were better off than in the other group who had received the high dose only for two years (because they were in the low-dose group during the one-year-double blind phase of the study).

Therefore, in particular, when treating severe heart failure patients on the transplant list, up-titration of the dose against symptoms may be optimal to delay further irreversible worsening, may delay the need for a transplant.

We conclude from our findings that in severe, advanced heart failure the improvement in functional capacity by both clinical symptoms and effort capacity, as well as a potential survival benefit were related to the dose and the duration of enalapril treatment. While haemodynamic derangements may be partially equalised at any time by aggressive therapy which also effects in some improvement of symptoms, patients who are treated with high enalapril dosages from the beginning may gain a greater and longlasting benefit from this treatment which finally may translate into prolongation of life. However, this issue awaits the outcome of large prospective dose finding studies.

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