Long-Term Survival of Non-Elderly Patients With Severe Heart Failure Treated With Angiotensin-Converting Enzyme Inhibitors

— Assessment of Treatment With Captopril and Enalapril Survival Study (ACCESS) —

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The present study examined the effect of treatment with angiotensin-converting enzyme inhibitors (ACEIs) on the long-term prognosis in 119 patients with dilated cardiomyopathy (DCM). Conventional therapy was used in 29 patients and 90 patients were treated with ACEIs: 50 were taking captopril and 40 were taking enalapril; 24 were taking ≥ 75 mg captopril or ≥ 20 mg enalapril daily (high-dose group) and 66 patients received smaller doses (low-dose group). No significant differences between groups were detected with respect to demographics and clinical signs of congestive heart failure (CHF). During follow-up, 65 patients survived and 54 patients died: 34 patients were in group 1 and 20 patients were in the placebo group. Patients treated with ACEIs had a significantly better survival during the first to third year, but the difference was not significant between the high- and low-dose groups. Comparison of the cumulative probability of death in the enalapril and captopril groups showed a trend of significant reduction of mortality by 13% in the enalapril group ($p < 0.10$). These data indicate that ACEIs have a beneficial effect on prolonging the short- and long-term survival in DCM patients, so it is strongly recommended that all patients with DCM should be treated with ACEIs unless contraindicated. In this study, lower doses of ACEI seemed prognostically equivalent to higher doses, and enalapril appeared to be preferable to captopril in the treatment of severe CHF. Additional prospective large studies are necessary to verify the relationship observed here between the optimal dosage as well as the duration of action of different ACEIs and their outcomes. (*Circ J* 2002; 66: 886–890)

Key Words: ACE inhibitors; Congestive heart failure; Prognosis

Patients with severe cardiac failure have associated high rates of morbidity and mortality, usually because of the progressive deterioration of hemodynamics and symptoms, which leads to death even with intensive medical treatment or mechanical support. Chronic therapy with angiotensin-converting enzyme inhibitors (ACEI) has been proven to effectively improve left ventricular function,^{1,2} improve exercise performance incrementally, reduce hospitalization^{3,4} and, most importantly, prolong life in congestive heart failure (CHF).^{5,6} However, there are few studies comparing low vs high doses of ACEI on survival in a patient population with dilated cardiomyopathy (DCM).^{7–9} Direct comparisons of long-term outcome among severe heart failure patients treated with short-acting vs long-acting ACE inhibitors have been conducted in only one study,¹⁰ so it is still uncertain whether the survival effects of these drugs are related to dose or duration of action.

Moreover, some physicians may avoid using these drugs

in patients with the following conditions: (1) low pretreatment blood pressure or at risk of hypotension; (2) relative contraindication because of side effects or previous intolerance to ACEI; (3) preexisting renal failure or deterioration in kidney function after treatment; and (4) clinical manifestations considered not severe enough for ACEI treatment. Previous surveys indicate that only a minority (<40%) of eligible patients are being treated with these drugs^{6,11} and underutilization of ACEI in many patients with CHF continues to be a common problem observed in clinical practice.⁷

The primary purpose of the present study was to evaluate specifically in the DCM patient population the long-term outcome of ACEI therapy vs conventional therapy. Second, we wanted to determine whether higher or lower doses of ACEI are superior in the treatment of patients with severe CHF defined by a left ventricular ejection fraction (LVEF) <30%. Finally, we evaluated the prognostic role of a short-acting (captopril) inhibitor vs a long-acting inhibitor (enalapril).

Methods

Study Design and Patient Definition

This was a 6-year retrospective study of 119 patients (95 men, 24 women) with New York Heart Association (NYHA) class III–IV heart failure and an LVEF <30%

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treated with or without ACEI. They were referred to Cheng-Hsin Medical Center between May 1995 and January 1999, and reviewed to assess whether treatment with ACEI affected the long-term survival. Age at onset was 48 ± 13 years (range, 9–65) and the mean interval from the onset of symptoms of cardiac failure (NYHA class III–IV dyspnea) to initial assessment was 30 ± 31 months. The mean LVEF was $18 \pm 8\%$ ($\pm$ SD) (range, 4–29%) and the mean time of follow-up was 24 ± 21 months (range, 0.1–64). All patients underwent 2-dimensional, M-mode and color echocardiography and cardiac catheterization after rigorously tailored therapy with or without inotropic agents. At assessment, all patients were receiving furosemide in a mean daily dose of 64 ± 48 mg/day and 80% were taking digitalis. Intravenous inotropic drugs (dopamine, dobutamine and isoproterenol) were needed by 58% of patients. Informed consent was obtained from all patients with DCM participating in this study according to a protocol that was approved by the Institutional Review Board.

All patients had DCM diagnosed on the basis of 4 presentations: (1) symptoms and signs of left or biventricular failure, (2) global left ventricular hypokinesis with prominent left ventricular dilatation on echocardiography, (3) angiographic or radionuclide ventriculography and/or echocardiography revealed LVEF $<30\%$ and (4) at least one of the following parameters: (i) an elevated right atrial mean pressure (≥ 10 mmHg), (ii) pulmonary artery mean pressure (≥ 35 mmHg), (iii) pulmonary capillary mean pressure (≥ 20 mmHg) or (iv) peak exercise oxygen capacity (PEOC) ≤ 14 ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$.

Exclusion criteria included age greater than 65 years, transplant recipients during the time of the study (56 patients), acute myocarditis proved by endomyocardial biopsy, valvular heart disease requiring surgery, active infection, irreversible renal dysfunction, severe chronic obstructive airway disease, and coexisting systemic disease with poor prognosis. The criteria for heart transplant were defined according to Huang et al.¹²

Cardiac Catheterization and Endomyocardial Biopsy

Right- and left-sided cardiac catheterization was performed in all patients on medical treatment. Right- and left-sided heart pressures were measured before bilateral coronary angiography through a 7 or 6F catheter placed in the cardiac chambers by the femoral or radial approach combined with the jugular technique.¹³ Cardiac output was determined by the Fick method, and the cardiac index was then derived.

Endomyocardial biopsy was performed in all of the studied patients showing normal coronary angiographic results that excluded myocarditis or specific heart muscle disease. In each patient at least 3 samples were taken from the right ventricle.

Study Groups

Patients were divided into 2 groups according to treatment with or without ACEI: 90 patients (group 1: ACEI group) were treated with ACEI (50 were taking captopril in a mean daily dose of 45 ± 20 mg (range, 12.5–100), 40 were taking enalapril in a mean daily dose of 15 ± 10 mg (range, 2.5–40)); conventional therapy (group 2: placebo) was used in the remaining 29 patients.

Retrospective assignment to high-dose or low-dose ACEI treatment was performed according to the time of inclusion: 12 patients each were taking enalapril ≥ 20 mg or

Table 1 Characteristics of The Study Groups

	Group 1 (n=90)	Group 2 (n=29)	p value
<i>Clinical data</i>			
Age (years)	49 ± 13	53 ± 14	ns
M/F	74/16	24/5	ns
BSA (m ²)	1.7 ± 0.2	1.6 ± 0.2	ns
BP (mmHg)	118 ± 25	113 ± 24	ns
Symptom history (months)*	28 ± 30	35 ± 34	ns
NYHA functional class	3.2 ± 0.3	3.1 ± 0.4	ns
LVEF (%)	19 ± 8	17 ± 7	ns
Heart rate (beats/min)	91 ± 19	92 ± 15	ns
Atrial fibrillation (%)	21	17	ns
Ventricular tachycardia (%)	51	59	ns
LBBB (%)	21	24	ns
<i>Medication</i>			
Digitalis (%)	78	83	ns
Furosemide (mg/day)	66 ± 40	58 ± 35	ns
Nitrates (%)	63	51	ns
Cordarone (%)	45	42	ns
Carvedilol (%)	18	34	ns
Inotropic agents (%)	59	58	ns
<i>Echocardiographic data</i>			
LVEDD (mm)	68 ± 9	70 ± 10	ns
LVESD (mm)	59 ± 9	61 ± 11	ns
FS (%)	14 ± 6	12 ± 4	ns
MR (0–4)	2 ± 1	2 ± 1	ns
<i>Hemodynamic data</i>			
MBP (mmHg)	95 ± 18	90 ± 13	ns
SPAP (mmHg)	49 ± 17	46 ± 14	ns
MPAP (mmHg)	35 ± 12	32 ± 10	ns
PCWP (mmHg)	23 ± 10	21 ± 10	ns
RAP (mmHg)	11 ± 7	9 ± 6	ns
PVR (Wood Units)	3 ± 3	3 ± 2	ns
TPR (Wood Units)	10 ± 6	10 ± 6	ns
SVR (Wood Units)	22 ± 7	23 ± 9	ns
CI (L $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$)	2.3 ± 0.8	2.5 ± 0.7	ns

Values presented are mean $\pm$ SD or number (%) of patients. LVEF, left ventricular ejection fraction; LBBB, left ventricular bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MBP, mean blood pressure; SPAP, systolic pulmonary artery pressure; PCWP, pulmonary artery wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; TPR, total pulmonary vascular resistance; SVR, systemic vascular resistance; CI, cardiac index; FS, fractional shortening; MR, mitral regurgitation; *interval from onset of heart disease; NYHA, New York Heart Association.

≥ 75 mg captopril daily ('high-dose' group; n=24), and 66 patients received smaller doses ('low-dose' group).

Statistical Analysis

End points for follow-up were cardiac death, non-cardiac death or study closure. The main clinical, hemodynamic and color echocardiographic variables were prospectively recorded in all patients. Continuous data are expressed as means $\pm$ SD. Patient characteristics were compared using the Fisher's exact test. Unpaired t testing compared differences in variances between group means. Differences among patient groups were compared by analysis of variance or chi-square analysis. Differences in mortality rates among the treatment and non-treatment groups were analyzed by the Kaplan-Meier product limit survival method with log-rank testing to examine the difference between curves. Differences were considered significant for p values <0.05 .

Follow-up

At the end of the observation period of 1 month after

Fig 1. Kaplan Meier survival curves estimates in severe heart failure patients receiving ACE inhibitors or placebo.

Fig 2. Kaplan Meier survival curves estimates in severe heart failure patients receiving high dose or low dose ACE inhibitors.

Fig 3. Kaplan Meier survival curves estimates in severe heart failure patients receiving enalapril or placebo.

Fig 4. Kaplan Meier survival curves estimates in severe heart failure patients receiving captopril or placebo.

initial assessment, there was no further modification in ACEI therapy in any patient. None of the patients on captopril or enalapril therapy had to discontinue their therapy because of serious side effects during the monthly follow-up.

Results

Patient's Characteristics and Compatibility (Table 1)

There were no significant differences between the 2 groups in age at onset, left ventricular shortening fraction, left ventricular end-diastolic and end-systolic diameters, cardiac indexes, mean blood pressure, mean pulmonary capillary wedge pressure, or mean pulmonary artery pressure. The treatment groups were similar with respect to key demographic and clinical signs of CHF as well as concomitant treatments with digitalis, diuretics, nitrate, carvedilol and cordarone.

Clinical Outcome

During follow-up, 65 patients survived and 54 died: 34 patients (enalapril (14), captopril (20); high-dose (8), low-dose (26)) were in group 1 and 20 were in the placebo group. The Kaplan-Meier curves are depicted in Fig 1. The overall mortality at 12 months was 59% (17/29 patients) in the placebo group and 29% (26/90 patients) in the ACEI group (a risk reduction of 51%) ($p=0.008$). The overall

mortality at 36 months was 69% (20/29 patients) in the placebo group and 38% (34/90 patients) in the ACEI group ($p=0.003$). Patients treated with ACEI had a significantly better survival during the first to the third year, and the average risk reduction over the duration of the trial was 45% (95% confidence interval: 11–65%).

The overall mortality rates among the high-dose patient population were 25% and 33% at 1 and 3 years, respectively, and for the low-dose patient population they were 32% and 39%, respectively. The data demonstrated a reduction of mortality by 15% in the high-dose group, but the difference was not significant between the groups. The Kaplan-Meier curves are shown in Fig 2.

Fig 3 and 4 illustrates the cumulative probability of death in the placebo, enalapril and captopril groups. In comparison of the outcomes in patients with severe heart failure treated with enalapril or captopril to placebo, the overall mortality at 12 months was 25% (10/40 patients) in the enalapril group (a risk reduction of 58%, $p=0.002$) and 32% (16/50 patients) in the captopril group (a risk reduction of 46%, $p=0.05$); the overall mortality at 36 months was 35% (14/40 patients) in the enalapril group (a risk reduction of 49%, $p=0.002$) and 40% (20/50 patients) in the captopril group (a risk reduction of 42%, $p<0.05$).

Fig 5 illustrates the cumulative probability of death in the enalapril and captopril groups. The overall mortality at 36 months was 35% (14/40 patients) in the enalapril group

Fig 5. Kaplan Meier survival curves estimates in severe heart failure patients receiving enalapril or captopril.

and 40% (20/50 patients) in the captopril group. The data demonstrated a trend of a significant reduction of mortality by 13% in the enalapril group ($p < 0.10$).

Causes of Death (Table 2)

Of the 54 patients who died, 15 (28%) died of sudden death and 35 (65%) died of progressive heart failure. In group 1, deaths were sudden in 10 (26%), attributed to progressive heart failure in 21 (62%) and caused by pulmonary emboli in 1, septic shock in 1 and fatal stroke in 1 patients. In group 2, deaths were sudden in 5 (25%) and attributed to progressive heart failure in 14 (70%) and septic shock in 1 (5%) patients. There was no significant difference in the incidence of sudden cardiac death between the treatment and placebo groups; however, there was a 52% reduction in mortality from progression of heart failure in the ACEI group ($p < 0.05$) (95% confidence interval: 4–76%).

Discussion

Congestive heart failure is a serious condition with a high mortality rate, as demonstrated by our placebo group. The 1- and 3-year mortality rates calculated from the life table were 59% and 69%, respectively. This study clearly demonstrates a relationship between the intensity of ACEI therapy and the outcomes of 119 Chinese patients with advanced heart failure. At the end of the present study, patients treated with ACEI had a significantly better survival time than the placebo group during the first year, with continuation of this trend throughout the third year. Our data strongly support the beneficial effects of ACEI on long-term survival reported previously^{5,6,14,15} although in those studies a variety of ACEI were used at different dosages, for varying durations and timing of treatment, at various levels of systemic blood pressure and stages of heart failure, and with various study end-points^{3,9,11,16–18}

Several previous studies have demonstrated that large doses of cilacipril (2.5 mg daily);⁴ lisinopril (35 mg daily);¹⁸ quinapril (40 mg daily);³ enalapril (40 mg daily);^{8,19} or captopril (≥ 75 mg daily)²⁰ produce greater hemodynamic and clinical effects (ie, improving exercise tolerance and lowering the need for hospitalization) than small doses. Those findings indicate the beneficial effects of ACEI treatment through the amelioration of the negative effects and vicious cycle of neurohormone activation on the preload,

Table 2 Survival Time and Cause of Death

	Group 1 (N=90)	Group 2 (N=29)	p value
Survival time (days)	949	555	<0.001
Deaths (n)	34	20	<0.005
Cause			
Any cardiac death			
Progression of heart failure	21	14	<0.05
Sudden cardiac death	10	5	ns
Stroke	1	0	ns
Pulmonary embolism	1	0	ns
Sepsis	1	1	ns

afterload and cardiac pumping activity in patients with severe heart failure.¹² It has also been demonstrated in an experimental model of heart failure that a higher dose of lisinopril more successfully reduced mortality than did a lower dose.²¹ Other studies have demonstrated that high doses of ACEI had a similar frequency of side effects to low doses in heart failure.^{3,9,19} In contrast to those findings, it has been suggested that low doses of ACEI might be as effective as high doses,^{8,16,17,20} but produce fewer side effects, especially the serious hypotensive effects^{6,21–23} that can compromise cerebral and renal function.

In the NETWORK trial assessing the dose-response effects of ACEI in heart failure,²⁴ the data showed no significant difference in mortality between those patients receiving low (5 mg daily), moderate (10 mg daily) and high (20 mg daily) doses of enalapril. Furthermore, among 3,164 heart failure participants with a LVEF less than 30% in the ATLAS trial, the data showed high-dose lisinopril (35 mg) reduced all-cause mortality by 8%, but the difference was insignificant.¹⁸ On the other hand, the present data show a reduction of mortality by 15% in the high-dose group, but the difference was not significant as well. In addition, none of the patients on captopril or enalapril therapy had to discontinue it because of side effects during the follow-up. Taking all the data together, we consider that low doses of ACEI might be prognostically equivalent to high doses. Thus, the clinical benefit of dosage optimization on survival is still controversial. Overall, ACEI therapy still reduces mortality by decreasing the rate of progression of heart failure, but on the basis of the evidence so far, we think that the mechanisms by which the various doses of ACEI affect clinical symptoms and survival may be different. Thus, evidence-based medicine may be the best approach for the treatment of heart failure.

Up to now, there has only been one study conducting a direct comparison of ACEI in heart failure, but it was of short duration and did not evaluate clinical outcome.¹⁰ Hence, the relationship between duration of action by the different ACEI and clinical outcomes in the treatment of patients with severe CHF remains to be determined. Importantly, the present study showed a reduction in mortality by 13% in the enalapril group as compared with the captopril group. Although both groups were significantly better than placebo, enalapril seems marginally preferable to captopril in the treatment of chronic heart failure in non-elderly (age ≤ 65 years) patients. Our data are in accordance with a previous trial that assessed the effects of xamoterol in addition to ACEI therapy in severe heart failure. In that trial, patients on enalapril had a lower mortality than those on captopril treatment.²⁵ On the basis of these findings, we suggest that when ACEI are used in

the treatment of patients with severe chronic heart failure, long-acting agents might reduce mortality more successfully than short-acting agents.²³ Notably, it remains to be evaluated why enalapril was superior to captopril, but factors such as ACEI lipophilicity and tissue converting enzyme inhibition;^{26,27} rather than merely dose effect, may be important.

Study Limitations

The limitations of this study imposed by its retrospective nature, small sample and some variables such as norepinephrine, tumor-necrotizing factor, endothelin-1 and plasma atrial natriuretic peptide were not examined. Additional prospective large randomized studies are necessary to verify the relationship observed here between dose effect as well as duration of action of ACEI and outcomes.

Conclusions

The present data suggest that captopril and enalapril have a beneficial effect on the long-term clinical outcomes of non-elderly (age ≤ 65 years) patients with DCM. After a treatment period of 1 year, ACEI were shown to be effective and the effect was sustained throughout the third year. Overall, ACEI therapy reduced mortality by decreasing the rate of progression of heart failure. In this study, lower doses of ACEI seemed prognostically equivalent to higher doses, and enalapril preferable to captopril in the treatment of severe heart failure. Our findings suggest that ACEI should be prescribed to all heart failure patients, if not contraindicated, irrespective of systolic function, age or gender.

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