Outcome of Patients With Congestive Heart Failure Treated With Standard Versus High Doses of Enalapril: A Multicenter Study

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We sought to prospectively and randomly compare survival with clinical and hemodynamic variables in patients with congestive heart failure (CHF) treated with standard versus high doses of enalapril.

Angiotensin-converting enzyme (ACE) inhibitors produce hemodynamic and symptomatic benefits in patients with CHF, but there is still controversy about the optimal dose in this clinical setting.

Two hundred and forty-eight patients with advanced CHF (age 56.3 ± 12 years) were randomized to receive a maximal tolerated dose of enalapril, up to 20 mg/day in group 1 (mean dose achieved 17.9 ± 4.3 mg/day, n = 122) and 60 mg/day in group 2 (mean dose achieved 42 ± 19.3 mg/day, n = 126).

At enrollment, patients in group 1 were in New York Heart Association (NYHA) functional class 2.6 ± 0.7 and had a mean systolic blood pressure (SBP) of 117 ± 18 mm Hg, a mean heart rate (HR) of 85 ± 16 beats/min and a left ventricular ejection fraction (LVEF) of 20.0 ± 9.8%. In group 2, patients were in NYHA class 2.6 ± 0.7, their SBP was 118 ± 17 mm Hg, HR 83 ± 15 beats/min and LVEF 18.8 ± 8.1%. There were no significant differences in these characteristics between the two groups of patients at enrollment. After 12 months of follow-up, 22 (18%) of 122 patients in group 1 and 23 (18%) of 126 patients in group 2 had died (p = 0.99, with 80% power of the study to detect a delta difference of 13%).

The NYHA class was the same (1.9 ± 0.7) in both groups; SBP was 111 ± 16 and 111 ± 17 mm Hg, HR 77 ± 12 and 79 ± 13 beats/min and LVEF 31 ± 19% and 30 ± 12% in groups 1 and 2, respectively. These differences were not statistically significant. The study had a power of 80% to detect (p = 0.05) the following changes: 13% in death rate, 0.25 units in NYHA class, 6 mm Hg in SBP, 5 beats/min in HR and 6% in LVEF.

No significant differences were found in survival and hemodynamic variables between patients receiving standard and those receiving high doses of enalapril. (J Am Coll Cardiol 2000;36:2090–5) © 2000 by the American College of Cardiology

Angiotensin-converting enzyme (ACE) inhibitors produce hemodynamic and symptomatic benefits in patients with congestive heart failure (CHF) beyond those which can be achieved with conventional drugs (1–6). The COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS) (7) and Studies Of Left Ventricular Dysfunction (SOLVD) (8) have shown that enalapril significantly reduces mortality in patients with CHF. An overview of the randomized trials examining the effect of ACE inhibitors on mortality and morbidity in patients with heart failure identified 34 completed trials of ACE inhibitors compared with placebo (9). A meta-analysis of these data showed that ACE inhibitors significantly reduce total mortality and hospital stays due to CHF decompensation, with consistent effects in a broad range of patients. The beneficial effect of ACE inhibitors appears to be a class effect. However, nearly half of the patients included in these 34 studies were treated with enalapril.

In the large enalapril trials (7,8,10,11)—CONSENSUS, SOLVD (Treatment), SOLVD (Prevention) and Veterans Administration Vasodilator Heart Failure Trial (V-Heft II)—the final mean dose of enalapril was 15 to 18.4 mg/day; the intended dose was 40 mg/day for CONSENSUS and 20 mg/day for the other trials. Small-scale studies have shown that large doses of ACE inhibitors produce greater hemodynamic (12,13) and clinical improvement (14–16) compared with customary doses.

This trial was designed to evaluate the effects of high dose enalapril compared with standard dose enalapril on the mortality, morbidity and clinical status of patients with CHF.
METHODS

This was a prospective, randomized trial that was open-label for the treatment and functional status evaluation and blinded for the laboratory evaluation of patients with moderate to severe CHF.

All patients in the study had symptoms of heart failure for at least three months and had left ventricular ejection fractions (LVEFs) ≤ 0.35. Patients were randomized to receive the maximal tolerated dose of enalapril, up to 20 mg/day (10 mg twice daily) in group 1 and up to 60 mg/day (30 mg twice daily) in group 2. All patients in the trial initially received standard therapy with digoxin, nitrates and diuretics, as needed. Treatment was started on an outpatient basis, at a dose of 2.5 mg twice daily. The dosage of enalapril was titrated at weekly intervals and reached the target dose on the fifth week in group 1 (20 mg/day) and on the ninth week in group 2 (60 mg/day). Enalapril was not increased further if the systolic blood pressure (SBP) dropped to <90 mm Hg or if the drug induced symptoms of hypotension. The patients were clinically evaluated every week until enalapril dose maximization and on the third, sixth and twelfth month of follow-up thereafter.

In addition, all patients underwent a blinded evaluation of their left ventricular function by radionuclide ventriculography before randomization and at one-year follow-up. Patients were excluded if any of the following was present: acute pulmonary edema within the previous 15 days, hemodynamically important aortic or mitral valve stenosis, myocardial infarction or open heart surgery within the previous three months, unstable angina, anticipated cardiac surgery, right heart failure due to pulmonary disease, serum creatinine concentration >3 mg/dl, hypertrophic or restrictive cardiomyopathy or pericardial disease. The principal end points of the trial were the one-year mortality rate and cause of death. Sudden death was defined as death within 1 h of the onset of new symptoms (17). In addition, the major secondary objective was the evaluation of the effect of high dose enalapril on cardiovascular morbidity, defined as hospital admission for heart failure or other cardiovascular causes, and on the patients’ clinical status and left ventricular function.

The study was approved by the hospitals’ Review Committees, and informed consent was obtained from each patient.

Statistical analysis. The power of the study was estimated for the 248 recruited patients. This sample size provides the ability to detect, with a power of 80% and p = 0.05, the following changes: 13% in death rate, 0.25 units in New York Heart Association (NYHA) functional class, 6 mm Hg in SBP, 5 beats/min in heart rate (HR) and 6% in LVEF. These are relatively small changes for each clinical variable.

The baseline characteristics of the two treatment groups were compared by using the t test and the chi-square test. Cumulative survival curves were constructed as time to first event plots by Kaplan-Meier survivorship methods, and the differences between the curves were tested for significance by the log-rank statistics, with the use of the Cox proportional hazards regression model (which included the protocol and other variables as covariates), for the determination of hazard ratios. For continuous variables, the median value was used as a cut-off level. The analyses included all randomized patients, and all events were assigned to the patients’ original treatment group (on the intention-to-treat principle). In the analysis of mortality, patients were censored at the time of death or cardiac transplantation.

Changes over time in clinical status (NYHA), ejection fraction, blood pressure and HR were analyzed by the paired t test. The unpaired t test was used for comparisons between the two groups. All data are presented as the mean value ± SD.

RESULTS

Recruitment of patients began in July 1993 and ended in December 1997. Patients were enrolled in the trial and randomly assigned to the standard target dose of enalapril, 10 mg twice daily (group 1, n = 122), or to the high target dose of enalapril, 30 mg twice daily (group 2, n = 126).

No patient was lost in follow-up. The baseline characteristics of the randomized patients in group 1 (n = 122) and in group 2 (n = 126) were similar (Table 1).

Although LVEF ≤ 35% was sufficient to qualify for entry into the study, the mean ejection fraction of the patients in this study was very low—20.0 ± 9.8% in group 1 and 18.8 ± 8.1% in group 2 (p = 0.424). The dose titration of enalapril reached a mean total daily dose of 17.9 ± 4.4 mg for group 1 and 42.5 ± 19.4 mg for group 2 (p = 0.000). In groups 1 and 2, respectively, 72.5% and 32.5% of the patients reached their target enalapril doses by the end of three months of follow-up, and 79.6% and 45.5%, respectively, by the end of the first year.

Concomitant therapy. There were no differences between the two groups with respect to concomitant treatment during the follow-up period. At the end of the study, 95%
of the patients in group 1 were treated with digoxin (mean dose 0.197 ± 0.0646 mg/day) versus 90% of the patients in group 2 (mean dose 0.199 ± 0.068 mg/day) (p = 0.849).

All patients were treated with furosemide (105.98 ± 97.00 and 115.47 ± 123.00 mg/day in groups 1 and 2, respectively) (p = 0.655).

Effect of different enalapril dosages on survival. By intention-to-treat analysis, there were 22 deaths (18.03%) in group 1 and 23 deaths (18.25%) in group 2 (p = 0.995) (Fig. 1). When the protocol (high vs. standard dose) was used as a covariate in the Cox regression model, with death at one year as an end point, the hazards ratio was 0.998 (confidence interval [CI] 0.556 to 1.790).

No statistically significant differences in survival were observed in subgroup analyses in terms of age, etiology of heart failure, SBP, ejection fraction and HR when using high dose enalapril as a covariant for each subgroup (Table 2).

A stratified analysis was also performed within each study group to assess the potential different effects of the treatment on patient subgroups (Tables 3, 4).

In group 1, cause of heart failure, SBP and LVEF appeared to have no prognostic significance. In contrast, in group 2, ischemic cardiomyopathy, SBP, 120 mm Hg and LVEF, 19% were predictors of poor prognosis, with hazards ratios of 2.92 (CI 1.13 to 7.53, p = 0.026), 2.99 (CI 1.16 to 7.72, p = 0.023) and 4.09 (CI 1.37 to 12.19, p = 0.012), respectively.

Data from the patients’ hospital admissions in both study groups are summarized in Table 5. No statistically signifi-
no difference was found when death and hospital admission were used as a composite end point for statistical analysis (p = 0.645, log-rank test) (Fig. 2).

At the 12-month evaluation, LVEF had increased from 20.0 ± 9.8% to 31.5 ± 19.2% (p = 0.000) in group 1 and from 18.8 ± 8.1% to 30.1 ± 12.3% (p = 0.000) in group 2. The patients’ functional status (NYHA) improved from 2.6 ± 0.7 to 1.9 ± 0.7 (p = 0.000) in group 1 and from 2.6 ± 0.7 to 1.9 ± 0.7 (p = 0.000) in group 2. However, SBP and HR did not change significantly from baseline levels in either group.

There was no significant difference in LVEF and NYHA functional class between groups 1 and 2 at baseline and at one-year follow-up. Furthermore, no significant difference in the percent change in LVEF (p = 0.535) and NYHA class (p = 0.329) was observed between the groups at baseline and at one year. This study had more than adequate power to detect clinically significant changes in the major relevant variables (death rate, NYHA class, blood pressure, HR and LVEF).

### DISCUSSION

In this prospective, randomized study, the effects of high dose enalapril on mortality and morbidity were compared with those of standard dose enalapril. Both dosages improved the patients’ clinical condition over the first three months of treatment, without further significant improvement during the rest of the follow-up period. There were no differences in mortality or morbidity between the two groups.

Our data showed a difference in the prognostic significance of the etiology of heart failure (ischemic vs. other), SBP (<120 vs. ≥120) and ejection fraction (<19% vs. ≥19%) between the two study groups. The significance of this observation remains to be established. It may be due to a deleterious effect of high dose enalapril in patients with ischemic cardiomyopathy, or to a salutary effect in patients with dilated cardiomyopathy. No similar observations have been made in previous large-scale trials of ACE inhibitors (8,18,19), although conflicting results have been reported with regard to the relative effectiveness of ACE inhibitors in ischemic versus nonischemic heart disease (20,21).

In the three large survival studies—CONSENSUS (7), SOLVD (8) and V-HeFT II (11)—enalapril was adminis-

### Table 3. Prognostic Significance of Different Patient Characteristics in Group 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;57 years</td>
<td>0.77</td>
<td>0.33–1.78</td>
<td>0.542</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.15</td>
<td>0.27–4.92</td>
<td>0.849</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;120 mm Hg</td>
<td>1.13</td>
<td>0.49–2.62</td>
<td>0.766</td>
</tr>
<tr>
<td>Heart rate ≥80 beats/min</td>
<td>0.52</td>
<td>0.21–1.32</td>
<td>0.170</td>
</tr>
<tr>
<td>Cause of heart failure (ischemic vs. other)</td>
<td>1.71</td>
<td>0.72–4.08</td>
<td>0.224</td>
</tr>
<tr>
<td>NYHA class III and IV vs. class I and II</td>
<td>3.6</td>
<td>1.25–10.90</td>
<td>0.018</td>
</tr>
<tr>
<td>Ejection fraction &lt;20%</td>
<td>1.93</td>
<td>0.70–5.28</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Continuous variables were treated the same as categoric variables, with the median value as a cut-off level.

NYHA = New York Heart Association.

### Table 4. Prognostic Significance of Different Patient Characteristics in Group 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;57 years</td>
<td>1.05</td>
<td>0.45–2.48</td>
<td>0.904</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.77</td>
<td>0.52–5.96</td>
<td>0.355</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;118 mm Hg</td>
<td>2.99</td>
<td>1.16–7.72</td>
<td>0.023</td>
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<tr>
<td>Heart rate ≥80 beats/min</td>
<td>1.03</td>
<td>0.42–2.48</td>
<td>0.951</td>
</tr>
<tr>
<td>Cause of heart failure (ischemic vs. other)</td>
<td>2.92</td>
<td>1.13–7.53</td>
<td>0.026</td>
</tr>
<tr>
<td>NYHA class III and IV vs. class I and II</td>
<td>3.02</td>
<td>1.10–8.24</td>
<td>0.031</td>
</tr>
<tr>
<td>Ejection fraction &lt;19%</td>
<td>4.09</td>
<td>1.37–12.19</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Continuous variables were treated the same as categoric variables, with the median value as a cut-off level.

NYHA = New York Heart Association.
Dose response trials of ACE inhibitors. The results of the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, a large-scale clinical study comparing two different doses of lisinopril in patients with CHF, have recently been reported (22). The high dose group had a nonsignificant 8% lower risk of death (p = 0.128), but a significant 12% lower risk of death or hospital admission for any reason (p = 0.002). However, there were major differences between the ATLAS trial and ours. First, the low dose group received a very low dose of lisinopril (2.5 to 5 mg/day). Second, the high dose group received doses comparable to those of our standard dose group (group 1) and to those used in the clinical trials that demonstrated a reduction in morbidity and mortality (7,8).

In addition, the results of another large, multicenter, randomized clinical trial—the NETWORK of general practitioners and hospital physicians involved in the study of low versus high doses of enalapril in patients with heart failure—which compared the effect of low versus high doses of enalapril on mortality in patients with CHF, were recently reported. There were no differences between the three different regimens tested, neither in the combined end point (death, hospital admission and worsening of heart failure) nor in mortality alone, at the completion of six months follow-up. The results of this study are not comparable to ours, mainly because the doses of enalapril, in all three groups of the trial, were lower (2.5 mg × 2, 5 mg × 2 and 10 mg × 2), whereas in our study, the effect of a substantially larger dose (30 mg × 2) was compared with that of the usual dose (10 mg × 2), which was identical to the higher dose used in NETWORK. In addition, in the NETWORK trial, patients with less severe heart failure were enrolled (65% in NYHA class II and 35% in NYHA class III), and the follow-up period was shorter (six months). This might explain the low mortality rate observed in the study in question (23).

Enalapril trials. The mean achieved enalapril dose of 17.9 mg/day in our standard dose group was comparable to that achieved in CONSENSUS (18.4 mg/day), SOLVD (16.6 mg/day) and V-HeFT II (15 mg/day). To the best of our knowledge, ours is the first comparative study of enalapril, using the standard dose of the large survival trials (7–10) as low dose, and as high dose, a target of 60 mg/day, resulting in an actually administered mean dose of 42.5 mg, the highest ever reported.

The higher overall mortality (18.1%) in our study, in comparison to 12.4% in SOLVD and 9.0% in V-HeFT II, may be explained by the lower mean LVEF of our patients (19.4% in our study vs. 24.8% in SOLVD vs. 28.6% in V-HeFT II), the lower mean SBP (117.2 mm Hg in our study vs. 125.3 mm Hg in SOLVD vs. 125.5 mm Hg in V-HeFT II) and the lower NYHA functional class (10.7% for patients in class IV in our study vs. 1.5% in SOLVD vs. 2% in V-HeFT II). In contrast, the mortality rate in our study was lower than that observed in the CONSENSUS study (36%), most likely because the patients included in that study were in worse overall clinical conditions (10.7% for patients in class IV in our study vs. 100% in CONSENSUS), and because relatively fewer patients had coronary artery disease in our study (50.2%) than in CONSENSUS (72%). Measurements of LVEF were not reported in CONSENSUS.

The relatively low mortality rate in our study, despite the severely depressed LVEF, poor clinical status and low SBP, may be attributable not only to enalapril treatment, but also to overall advances in the treatment of cardiovascular diseases made in the last decade, offering a comprehensive management of advanced heart failure (24).

Clinical significance. The results of our study and previous experimental data (25–27) suggest that inhibition of circulating ACE to reduce plasma angiotensin II is probably not the sole important action of ACE inhibitors. This hypothesis is supported by small clinical studies that have shown that high doses of ACE inhibitors produce hemodynamic effects comparable to those of low doses (1,16,28–30).

On the basis of the findings of our study and previous comparative studies (16), as well as large survival trials (7–9) of enalapril, the dose of 20 mg/day seems to be optimal to improve hemodynamic and clinical status, and probably for life prolongation in patients with CHF. Data are insufficient to assess the effect of lower doses than the ones used in the large survival trials (31–33).

Study limitations. The present study was not blinded with regard to the patients’ treatment. Therefore, a bias of physicians and patients in favor of the standard dosage cannot be excluded, because high doses may produce more side effects. However, the significant difference in the achieved doses between groups 1 and 2 argues against this bias. In addition, the study was blinded with regard to the laboratory evaluations. Regarding a stratified survival analysis, the number of patients in each subgroup was too small for valid comparisons.

Conclusions. Doses of enalapril higher than those used in the large clinical trials of ACE inhibitors as treatment for patients with CHF do not appear to improve the survival of these patients. However, larger scale trials may be warranted to determine whether selected patient subgroups might benefit from higher doses.
REFERENCES


