EDITORIAL COMMENT

Is the Optimal Dose of Angiotensin-Converting Enzyme Inhibitors in Patients With Congestive Heart Failure Definitely Established?*

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The publication of the trial by Nanas et al. (1) in this issue of the Journal, comparing two doses of enalapril in patients with congestive heart failure (CHF), is timely. First, with the results of the CONSENSUS (2), SOLVD (3,4) and V-HeFT II (5) trials, we had a clear demonstration of the benefits of angiotensin-converting enzyme (ACE) inhibitors in patients with CHF. Then, there were the NETWORK (6) and ATLAS (7) trials, testing whether a “high” dose of ACE inhibitors did better than a low dose. In fact, what was really compared was a standard dose and a low dose. Now, there is a trial comparing a standard dose and a really high dose of enalapril.

ACE INHIBITORS ARE EFFICACIOUS IN PATIENTS WITH CHF (DUE TO SYSTOLIC DYSFUNCTION)

Thirteen years ago, a major advance occurred in the treatment of CHF with the publication of the CONSENSUS trial results (2). Enalapril was tested in New York Heart Association (NYHA) class IV patients. The trial was stopped much earlier than scheduled (inclusion of 253 patients, 400 planned) because of the major difference in mortality between the two groups: at six months the mortality rate was as high as 44% in the placebo group; it was 26% in the enalapril group (reduction in relative risk, 40%). There was also a nice functional improvement. The planned dose in the enalapril group was 40 mg/d (20 mg twice daily). However, only 28% of the patients tolerated this dosage; the mean dose was 18 mg/d.

The population that could benefit from ACE inhibitors was broadened when the SOLVD trials results were published. In the so-called “SOLVD-treatment trial,” in patients with left ventricular ejection fraction (LVEF) ≤35%, patients had to be in NYHA class II to IV (3). They were mainly in class II or III (class I—not to be included, 10.5%; class IV, only 1.9%). After a mean follow-up of 41 months, the mortality rate was 39.7% in the placebo group and 35.2% in the enalapril group (reduction in relative risk: 16%). The target dose of enalapril was 20 mg/d (10 mg twice daily), but only half of the patients received it, and the mean dose received by the patients actually taking the drug was 17 mg/d.

In the “SOLVD-prevention trial,” also in patients with LVEF ≤35%, the patients had to be asymptomatic (however, 33% were in NYHA class II) (4). There was no significant effect of enalapril on mortality, but fewer enalapril-treated patients developed CHF: 20.7% vs. 30.2%, after a mean follow-up of 37 months. As in the previous trial, the target dose was 20 mg/d, but only half of the patients received it, and the mean dose received by the patients actually taking the drug was 17 mg/d.

The V-HeFT II trial was not placebo-controlled (5). It compared enalapril with hydralazine-isosorbide dinitrate, which had been proven superior to placebo in a previous V-HeFT trial (8). In V-HeFT II, patients were mainly in NYHA class II (51%) or III (43%). At two years, mortality was 25% in the hydralazine-isosorbide dinitrate group and 18% in the enalapril group (reduction in relative risk, 28%). Overall (including patients who stopped taking the drug), the average daily dose of enalapril was 15 mg.

We therefore had clear evidence of the beneficial effects of enalapril on mortality, hospitalizations and functional class in patients with CHF. The next question was: what is the optimal dose (9,10)? Very often patients do not receive the target dose proven efficacious in the clinical trials, and in those receiving ACE inhibitors, the dosage is much lower than the dose tested in the clinical trials (11–14).

ARE THE STANDARD DOSES MORE EFFICACIOUS THAN LOW DOSES?

The NETWORK (6) and ATLAS (7) trials, published in 1998 and 1999, respectively, intended to investigate the dose-response relationship of ACE inhibitors in patients with CHF. In NETWORK, 1,532 patients were randomized to receive enalapril 5, 10 or 20 mg/d (drug given twice daily) (6). Two thirds of the patients were in NYHA class II, the other third was class III or IV. All patients took the prescribed dose in the low dose group: 96% did so in the medium dose group, and 85% did so in the “high” dose group. After a follow-up of 5.5 months, the rate of worsening of heart failure was exactly the same in the three groups (7.8%). Heart failure–related hospitalizations were not less frequent in higher dose groups (low dose, 5.1%; medium dose, 5.5%; high dose, 7.9%). There was a trend toward a lower death rate with increasing dose, 4.2%, 3.3% and 2.9%, respectively, but this was not significant. The
changes in functional class were similar in the three groups. Treatment withdrawals were more frequent in the 20-mg/d group (27%) than in the two other groups (19% each). Thus, do these results imply that 5 mg of enalapril per day is sufficient (as efficacious on hard end points as higher doses and better tolerated)?

This may be so, but the ATLAS trial results suggest that high doses bring more benefit than lower doses (7). The 3,164 patients were randomized to receive 2.5 to 5.0 mg or 32.5 to 35 mg of lisinopril per day. They all had a LVEF ≤30%. The NYHA class was mainly III (77%, II: 16%, IV: 7%). After a median follow-up of 46 months, the mortality rate was 44.9% in the low dose group and 42.5% in the high dose group, a nonsignificant difference. However, the number of hospitalizations was lower in the high dose group—3,819 vs. 4,397 (p = 0.02); the difference was larger for hospitalizations for heart failure—1,199 vs. 1,576 (p = 0.002). There was no difference in the evolution of the NYHA class between the two groups.

What is called “high” doses should more adequately be called “standard” doses. The authors say that “doses of 20 to 40 mg (of lisinopril) daily were comparable to the doses of ACE inhibitors used in clinical trials that demonstrated a reduction in morbidity and mortality.” The references are the CONSENSUS trial (2), the SOLVD trial (3) and another trial (15); but these trials did not compare the effect of different ACE inhibitors on mortality, and we thus do not know the comparable doses of different ACE inhibitors.

All together, standard doses look superior to lower doses. However, we still did not know whether standard doses were the optimal ones. This is why the present trial (1) is timely.

ARE HIGH DOSES MORE EFFICACIOUS THAN STANDARD DOSES?

In this randomized trial, 248 patients received either 10 mg or 30 mg of enalapril twice daily. Left ventricular ejection fraction had to be ≤35%; the mean was 19%. The NYHA class was II in 42% of the patients, III in 44% and IV in the remaining. This population resembles that of the SOLVD treatment trial (3). The mean daily dose of enalapril was 18 mg in the 20-mg dose group and 42 mg in the 60-mg dose group. At one year, the target dose was achieved in 80% of the 20-mg dose patients but in only 45% of the 60-mg dose patients. Nevertheless, even if the target doses were not often achieved, this trial did compare standard doses (the ones achieved in the CONSENSUS, SOLVD and V-HeFT II trials) and high doses.

The mortality rate was exactly the same in both groups: 18% at one year. There was no difference in survival between the two groups in subgroup analyses according to age, etiology of heart failure, blood pressure, heart rate or ejection fraction. Similarly, there was no difference in terms of hospitalizations, of ejection fraction changes (nice improvement, from 20% to 30% in both groups) and functional status changes (from NYHA class 2.6 to 1.9 in both groups).

All trials put together, the conclusion is that doses of enalapril >20 mg/d are not more efficacious than standard doses, but that we should always try to reach a dose of 20 mg/d (10 mg twice daily) of enalapril in patients with CHF due to systolic dysfunction.

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