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RESULTS OF THE ATLAS STUDY

High or low doses of ACE inhibitors for heart failure?

ABSTRACT

In a large, randomized study, patients with heart failure who received a large daily dose of an angiotensin-converting inhibitor had a trend toward a lower mortality rate than did patients who received a low daily dose. Moreover, the hospitalization rate was lower in the high-dose group, and the side-effect profile was the same in both groups. Physicians should try to give maximal doses to achieve optimum benefit in this patient population.

IN HEART FAILURE, high doses of angiotensin-converting enzyme (ACE) inhibitors are better than the low doses that many physicians use. This was the principal conclusion of the recently completed ATLAS (Assessment of Treatment with Lisinopril And Survival) study. The results of the ATLAS study were presented at the 47th Annual Session of the American College of Cardiology held in Atlanta, GA, March 29–April 1, 1998 and have been discussed extensively in the medical press. As of this writing, the details of the study have not yet been published in abstract or manuscript form.

The pages that follow review the background, design, and results of the ATLAS trial, and their implications for practicing physicians.

BACKGROUND: ACE INHIBITORS ARE BENEFICIAL—IN HIGH DOSES

A number of placebo-controlled studies showed that ACE inhibitors confer numerous hemodynamic and clinical benefits for patients with symptomatic heart failure.[1–6] When added to a diuretic with or without digoxin, they improve cardiac performance, alleviate symptoms, and increase exercise tolerance.[7–10] Moreover, they are the only agents repeatedly shown to extend survival in heart failure (TABLE 1).[11–15] They also improve electrolyte and neurohormonal measures and quality of life. In view of these benefits, ACE inhibitors are now standard therapy for heart failure.

In most of these trials, the doses of ACE inhibitors used were large. However, in clinical practice, many physicians give smaller doses, believing that higher doses cause a higher incidence of side effects—cough, hypotension, hyperkalemia, azotemia, dysgeusia, drug rash, and agranulocytosis.[16–19]

These smaller doses may not do the job. For example, they may not lower the blood pressure as far, produce the same hemody-

TABLE 1

Clinical trials demonstrating that ACE inhibitors improve survival

TRIAL	PATIENT CHARACTERISTICS
CONSENSUS[11]	Severe heart failure
SOLVD[12]	Mild-to-moderate heart failure
SAVE[13]	Myocardial infarction with low left ventricular ejection fraction
ACE-MI[14]	Acute myocardial infarction
VeHFT II[15]	Chronic heart failure (compared with hydralazine and nitrates)

TABLE 2

ACE inhibitor dosages in heart failure

DRUG	INITIAL DOSAGE	TARGET DOSAGE
Benazepril	5 mg daily	20 mg twice a day
Captopril	6.25–12.5 mg three times a day	50–100 mg three times a day
Enalapril	2.5 mg twice a day	20 mg twice a day
Fosinopril	5 mg daily	20 mg twice a day
Lisinopril	5 mg daily	40 mg daily
Quinapril	5 mg twice a day	20 mg twice a day
Ramipril	2.5 mg daily	10 mg twice a day
Trandolapril	1 mg daily	4 mg daily

namic benefit, or increase exercise tolerance as much as the larger doses used in the controlled trials.[20–21] However, until the results of the ATLAS study were reported, we did not know whether high doses of ACE inhibitors were superior in prolonging life, although several small studies suggested this.

THE ATLAS STUDY DESIGN

Side effects were not more frequent with high doses

The ATLAS trial was designed to determine whether high doses of lisinopril, an ACE inhibitor, would result in lower rates of death and morbidity than would lower doses in patients with chronic heart failure. In all, 287 centers in 19 countries participated in this randomized, double-blind trial.

Patients: Ejection fraction ≤ 30%

All patients had a left ventricular ejection fraction of 30% or less and were in New York Heart Association functional class II, III, or IV. Some had ischemic cardiomyopathy, and some had dilated cardiomyopathy. As an inclusion requirement, all had received diuretics with or without digoxin for 2 months before starting the study. Some were also taking ACE inhibitors, beta-blockers, calcium channel blockers, nitrates, hydralazine, warfarin, or aspirin. Some had received intravenous inotropes, but not within 48 hours of inclusion.

Exclusion criteria included unstable coronary artery disease, unstable ventricular arrhythmias, treatment with antiarrhythmic agents having negative inotropic properties, renal dysfunction (serum creatinine > 2.5 mg/dL), and unstable heart failure.

Treatment: Lisinopril in high vs low doses

For the first 4 weeks, all patients received lisinopril "open-label" to determine if they could tolerate it—2.5 to 5 mg daily for the first 2 weeks, and then 12.5 to 15 mg for the next 2 weeks. Patients who previously had taken an ACE inhibitor received 12.5 to 15 mg for the full 4 weeks.

Then, patients were randomized to receive one of two treatments:

- Low-dose lisinopril (2.5–5 mg daily); or
- High-dose lisinopril (32.5–35 mg daily).

Outcomes measured

The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality, cardiovascular morbidity (nonfatal hospitalization for cardiovascular causes), or combined mortality and cardiovascular morbidity. Patients were followed for an average of 3.5 years.

RESULTS

As noted above, an overview of the ATLAS study results were presented at the 47th Annual Session of the American College of Cardiology held in Atlanta, GA, March 29–April 1, 1998.

In all, more than 3,500 patients were screened, of whom 400 were not taking ACE inhibitors previously. Ninety-five percent of patients tolerated the initial doses of lisinopril and were randomized to receive low doses (n = 1,568) or high doses (n = 1,596). The groups were well matched with respect to all baseline characteristics. Ninety percent of the patients assigned to the high-dose group tolerated the 35-mg dose.

Mortality

According to the investigators, by the end of the study 44.9% of the patients in the low-dose group had died, compared with 42.5% of the patients in the high-dose group. The difference was not statistically significant (P = .128). The rate of cardiovascular mortality was

also lower in the high-dose group, but this difference was also not statistically significant (40.2% vs 37.2%; $P = .073$).

Hospitalizations

Hospitalizations for congestive heart failure were reduced by 24% in the high-dose group ($P = .003$).

Combined endpoint

The combined endpoint of all-cause mortality and cardiovascular morbidity was significantly less in the high-dose group (83.9% vs 79.5%; $P = .002$). This effect was similar across all subgroups of patients.

Side effects

The incidence of side effects did not differ between the two groups. Specifically, there were no differences in light-headedness, hypotension, azotemia, hyperkalemia, or hypokalemia. Patients in the low-dose group had a slightly higher incidence of cough than patients in the high-dose group. Surprisingly, more patients were withdrawn from the low-dose group than from the high-dose group.

Other analyses pending

Other analyses from the trial are pending. Investigators hope to answer several questions:

- Do patients taking low-dose lisinopril require more concomitant medications?
- Are there interactions between the treatment effects of lisinopril and aspirin, beta blockers, diuretics, calcium blockers, and warfarin?
- Are there differences between subgroups on the basis of etiology, New York Heart Association functional class, left ventricular ejection fraction, age, gender, previous use of ACE inhibitors, blood pressure, serum sodium and creatinine levels, and use of hypoglycemic agents or nitrates?

TABLE 3

Guidelines for using ACE inhibitors in heart failure

ACE inhibitors should be used at all levels of left ventricular dysfunction

ACE inhibitors can be started safely on an outpatient basis in most cases

Attempt to titrate ACE inhibitors to the high-dose range over 4–6 weeks; check electrolytes and renal function periodically

Adjust ACE inhibitor dose to lower systolic blood pressure to 100 mm Hg

Asymptomatic hypotension (systolic blood pressure < 100 mm Hg) should not be a limiting factor in dose titration

Abnormal baseline renal function is not a contraindication to the use of ACE inhibitors

If blood pressure remains elevated in symptomatic patients despite maximum doses of ACE inhibitors, add nitrates, then add hydralazine to the regimen

Diuretics may be required, in addition to ACE inhibitors, in 90% of heart failure patients to control fluid retention

Digoxin may be added to ACE inhibitors in symptomatic patients, since digoxin decreases progression of heart failure and prevents recurrent hospitalizations

If patients develop symptomatic hypotension with ACE inhibitor therapy, withhold diuretics and other vasodilators, and then restart these agents at a lower dose

Carvedilol is not a substitute for an ACE inhibitor; it is added to the combination of digoxin, diuretic, and ACE inhibitor therapy

Patients who remain symptomatic with refractory heart failure despite maximally tolerated doses of ACE inhibitors, digoxin, and diuretics should be referred to a heart failure specialist for tailored therapy guided by hemodynamic monitoring

IMPLICATIONS FOR PHYSICIANS

The ATLAS study showed that, compared with low-dose therapy, high-dose ACE inhibitor therapy prevented recurrent hospitalizations and—perhaps—increased the survival rate in patients with symptomatic heart failure. The reductions in risk were approximately half of those observed in the SOLVD trial, when high-dose ACE inhibitors were compared with placebo, indicating that low doses produce 50% of the treatment effect of high doses. The investigators estimate that the widespread use of high-dose ACE inhibitor therapy would prevent 250,000 hospitalizations each year in the United States and 100,000 hospitalizations and deaths.

All patients with symptomatic or asymptomatic left ventricular dysfunction should receive an ACE inhibitor if they can tolerate one. The dose should be increased to the

highest tolerable dose or the maximal recommended dose (TABLE 2). The target dose for lisinopril, enalapril, or quinapril is 40 mg daily. The target dose for captopril is 50 mg three times daily. In the ATLAS study, side effects did not occur more frequently at higher doses.

ACE inhibitors should be the primary therapy for the early stages of heart failure. Digoxin may be used if symptoms persist despite diuretics and an ACE inhibitor. If intolerable ACE inhibitor side effects develop, hydralazine and nitrates have been shown to improve survival, although less effectively than ACE inhibitors, and with more side effects. There is little evidence currently showing that angiotensin II receptor blockers are equivalent to ACE inhibitors, but several clinical trials are attempting to prove this. Carvedilol has never been studied as an alternative to an ACE inhibitor, but has always been added to ACE inhibitor therapy.

In summary, previous clinical trials addressed the issue of when ACE inhibitors should be used in heart failure. The ATLAS study answered the question of how ACE inhibitors should be used, by comparing low doses used in clinical practice vs high doses proven to be of benefit in clinical trials. The ATLAS study showed that high-dose ACE inhibitor therapy was superior in improving survival and preventing recurrent hospitalizations. This study establishes the precedent for titrating ACE inhibitors to the high-dose range for patients with heart failure (TABLE 3).

All heart failure patients should receive an ACE inhibitor, if possible

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