High-dose lisinopril was more effective than low-dose for reducing combined mortality and cardiovascular events in CHF

Packer M, Poole-Wilson PA, Armstrong PW, et al., on behalf of the ATLAS Study Group. **Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure.** Circulation. 1999 Dec 7;100:2312-8.

QUESTION

In patients with congestive heart failure (CHF), is high-dose lisinopril more effective than low-dose lisinopril for reducing mortality and hospitalization rates?

DESIGN

Randomized (allocation concealment unclear*), blinded (patients, investigators, and outcome assessors),* controlled trial with 3-year follow-up.

SETTING

287 hospitals in 19 countries.

PATIENTS

3793 patients were screened, and 3164 (mean age 63.6 y, 80% men) were studied. Inclusion criteria were New York Heart Association class II, III, or IV CHF, despite use of diuretics for ≥ 2 months, and left ventricular ejection fraction ≤ 30%. Exclusion criteria were recent revascularization procedure or ischemic event, history of ventricular tachycardia, intolerance to angiotensin-converting enzyme (ACE) inhibitors, serum creatinine levels > 2.5 mg/dL, or noncardiac disorders that could limit survival. Follow-up was 100%.

INTERVENTION

Patients received their usual CHF medications and were allocated to lisinopril, 2.5 or 5.0 mg/d (n = 1596), or 30 mg/d (n = 1568).

MAIN OUTCOME MEASURES

All-cause mortality. Secondary end points were cardiovascular (CV) mortality and 5 combined end points.

MAIN RESULTS

The groups did not differ for all-cause mortality (42.5% for high-dose vs 44.9% for low-dose lisinopril, P = 0.13) or CV mortality (37.2% vs 40.2%, P = 0.07). Patients in the high-dose group had lower rates of all-cause mortality combined with all-cause hospitalization (P = 0.002), CV hospitalization (P = 0.04), or CHF hospitalization (P < 0.001) and lower rates of CV mortality plus CV hospitalization (P = 0.03) (Table) than did patients in the low-dose lisinopril group.

CONCLUSION

High-dose lisinopril was more effective than low-dose lisinopril for reducing the combined end points of all-cause mortality combined with either all hospitalization, CV hospitalization, or CHF hospitalization and CV mortality plus CV hospitalization for patients with CHF.

Source of funding: Zeneca Pharmaceuticals.

For correspondence: Dr. M. Packer, Division of Circulatory Physiology, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA. FAX 212-305-7439.

*See Glossary.

High-dose vs low-dose lisinopril for congestive heart failure (CHF)†

Outcomes at 3 y	High-dose	Low-dose	Hazard ratio (95% CI)	NNT (CI)
Mortality plus hospitalization	79.7%	83.8%	0.88 (0.82 to 0.96)	26 (16 to 82)
Mortality plus CV hospitalization	71.1%	74.1%	0.92 (0.84 to 0.99)	34 (17 to 284)
Mortality plus CHF hospitalization	55.1%	60.4%	0.85 (0.78 to 0.93)	17 (12 to 37)
CV mortality plus CV hospitalization	69.4%	72.7%	0.91 (0.84 to 0.99)	30 (16 to 281)

†CV = cardiovascular. Other abbreviations defined in Glossary; NNT and its CI calculated by using hazard ratios provided in article.

COMMENTARY

Large randomized controlled trials (RCTs) have shown that high-dose ACE inhibitors are generally safe in CHF. Many clinicians remain concerned, however, about safety issues and resort to the use of low-dose ACE inhibitors. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial is the largest RCT comparing a high- and low-dose ACE inhibitor in CHF. The results show a trend toward decreased mortality and a modest reduction in combined end points that include hospitalization and mortality. This finding is somewhat surprising because a larger benefit with high-dose ACE inhibitors was anticipated. The only other RCT that evaluated a low- and high-dose ACE-inhibitor strategy in CHF was too small and too short to provide clear answers (1). Although the benefits in the ATLAS study seem relatively modest, morbidity that includes hospitalization is a major consideration in CHF, both from the patient's and the clinician's perspective.

How are clinicians to interpret the results of the ATLAS trial? First, the use of ACE inhibitors is well established as first-line therapy in CHF, and every patient with clinical manifestations or with asymptomatic left ventricular systolic dysfunction should be considered for ACE-inhibitor therapy. Therapy should be initiated with caution, however, especially in elderly patients and in those with renal dysfunction or low blood pressure. Patients should be followed with careful and gradual increases in dose. If the drug is tolerated, an attempt should be made to maximize the ACE inhibitor dose. If side effects develop, however, maintaining patients on a low or intermediate dose is far better than withdrawing therapy.

In addition, as suggested by the ATLAS study and many previous investigations, such symptoms as cough, hypotension, dizziness, and renal dysfunction are not always related to ACE inhibitor use and may be caused by CHF, concomitant illnesses, or other medications. Permanent withdrawal of ACE inhibitors should be a last resort and considered only in patients who clearly cannot tolerate this lifesaving intervention.

Eva Lonn, MD
Hamilton General Hospital McMaster Clinic
Hamilton, Ontario, Canada

Reference

1. **The NETWORK Investigators.** Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. Eur Heart J. 1998; 19:481-9.