

# High dose lisinopril was more effective than low dose for reducing combined mortality and cardiovascular events in congestive heart failure

*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 admission to hospital rates?

## Design

Randomised (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  $\geq 2$  months, and left ventricular ejection fraction  $\leq 30\%$ . Exclusion criteria were recent revascularisation procedure or ischaemic event, history of ventricular tachycardia, intolerance to angiotensin converting enzyme (ACE) inhibitors, serum creatinine levels  $> 2.5$  mg/dl, or non-cardiac 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/day (n = 1596), or 30 mg/day (n = 1568).

## Main outcome measures

All cause mortality. Secondary endpoints were cardiovascular (CV) mortality and 5 combined endpoints.

## Main results

The groups did not differ for all cause mortality (42.5% for high dose v 44.9% for low dose lisinopril, p = 0.13) or CV mortality (37.2% v 40.2%, p = 0.07). Patients in the high dose group had lower rates of all cause mortality combined with all cause admissions to hospital (p = 0.002), CV admissions to hospital (p = 0.04), or CHF admissions to hospital (p < 0.001) and lower rates of CV mortality plus CV admissions to hospital (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 endpoints of all cause mortality combined with either all admissions to hospital, CV admissions to hospital, or CHF admissions to hospital and CV mortality plus CV admissions to hospital for patients with CHF.

\*See glossary.

## COMMENTARY

Large randomised 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 dose and low dose ACE inhibitor in CHF. The results show a trend toward decreased mortality and a modest reduction in combined endpoints that include admission to hospital 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 dose and high dose ACE inhibitor strategy in CHF was too small and too short to provide clear answers.<sup>1</sup> Although the benefits in the ATLAS study seem relatively modest, morbidity that includes admission to hospital 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? Firstly, the use of ACE inhibitors is well established as firstline treatment in CHF, and every patient with clinical manifestations or with asymptomatic left ventricular systolic dysfunction should be considered for ACE inhibitor treatment. Treatment 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 maximise the ACE inhibitor dose. If side effects develop, however, maintaining patients on a low or intermediate dose is far better than withdrawing treatment.

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.

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

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

Outcomes at 3 years	High dose	Low dose	Hazard ratio (95% CI)	NNT (CI)
Mortality plus admission to hospital	79.7%	83.8%	0.88 (0.82 to 0.96)	26 (16 to 82)
Mortality plus CV admission to hospital	71.1%	74.1%	0.92 (0.84 to 0.99)	34 (17 to 284)
Mortality plus CHF admission to hospital	55.1%	60.4%	0.85 (0.78 to 0.93)	17 (12 to 37)
CV mortality plus CV admission to hospital	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.