## ACE Inhibitors in high doses superior to low doses for chronic heart failure (American College of Cardiology - 1998)

**In the 1990s, numerous randomized clinical trials have conclusively demonstrated significant benefits of angiotensin-converting enzyme inhibitors (ACEIs) in patients with depressed left ventricular ejection fractions (LVEF). However, only 30% to 40% of suitable patients with reduced systolic function in fact receive these life-saving agents in clinical practice. Moreover, of those patients with congestive heart failure (CHF) who do receive ACEIs, the doses given in the community are 4 to 6 times lower than those used in the randomized clinical trials.**

The preference for low doses is based on the belief that low and high doses exert similar benefits, but that the latter produce more adverse effects. The **Assessment of Treatment with Lisinopril and Survival (ATLAS)** trial was designed to address the question of whether ACEIs in general practice should be given at the current low doses or at the high doses used in the clinical trials, comparing the survival of patients with depressed LVEFs receiving these 2 dosing regimens.

### ATLAS Study Design

This double-blind, randomized trial enrolled **3164 patients** from 287 centers in 19 countries. Inclusion criteria required patients to have **NYHA Class II-IV CHF, LVEF =30%, and standard treatment with digoxin, diuretic, and/or ACEI**. All patients underwent a 2-week open label treatment period with 12.5 to 15mg/day of lisinopril. Patients who tolerated this run-in phase were randomized to receive either **low-dose (2.5 to 5mg/day; 1568 patients)** or **high-dose (32.5 to 35mg/day; 1596 patients)** lisinopril. The primary endpoint was all-cause mortality. The a priori chief secondary endpoint was the composite all-cause mortality and hospitalization for any reason.

### High-Dose Lisinopril Superior

Overall survival of the study group was a median of 54 months with a total of 1383 deaths (43.7%). Follow-up was a median of 46 months. Thirty percent of the study cohort stopped the study medication, and 17% started open label ACEI therapy, resulting in a 19mg difference in lisinopril dose at the end of the trial between the low and high-dose groups. There were no significant differences between the study groups with respect to age, NYHA class, LVEF, or previous ACEI use.

There was a **nonstatistically significant 8% risk reduction** in **all-cause mortality** in patients treated with high-dose as opposed to low-dose lisinopril (44.9% total mortality in low-dose group versus 42.5% in high-dose, P=0.128). **Cardiovascular mortality** decreased by 10% in patients randomized to the high-dose group (40.2% versus 37.2%, P=0.073). The composite endpoint of **death or hospitalization** for any reason was **decreased 12**% (83.9% versus 79.8%, P=0.002). This finding remained statistically significant after controlling for age, sex, LVEF, etiology of CHF, and NYHA class. **Patients assigned to the high-dose lisinopril group also had a 14% reduction in the composite endpoint of death or CHF hospitalization, and a 24% reduction in CHF hospitalizations compared to the low-dose cohort (P=0.002).** In addition, the frequency of hospital admissions was decreased in patients assigned to the high-dose lisinopril group. The frequency of hospitalization for patients in the high-dose group for any reason, for cardiovascular events, and for CHF decreased by 13%, 16%, and 24%, respectively, compared to patients receiving low-dose therapy (P&it0.05).

### High-Dose Lisinopril Well-Tolerated

The frequency of adverse effects was not significantly increased in patients treated with high-dose lisinopril compared to those randomized to the low-dose group. Specifically, the rates of hypotension (7% for low-dose group compared to 11% for high-dose group), renal dysfunction (11% versus 16%), and cough (13% versus 11%) were not clinically significantly different between the treatment groups. The rate of CHF was somewhat higher (44%) in the low-dose group compared to the high-dose lisinopril cohort (38%).

### Conclusion

**The results of the ATLAS trial strongly support the use of the high-doses of ACEIs employed in the randomized CHF trials as opposed to the current low-doses used in general clinical practice. High-dose lisinopril resulted in a statistically significant 12% reduction in deathan 8% reduction in total mortality (P=0.13), a 14% reduction in death or CHF hospitalization (P=0.002), and a 24% reduction in CHF hospitalization (P=0.002) without significant increases in the rate of adverse events.**

These findings have profound implications for the management of patients with CHF. If all patients in the US with depressed left ventricular systolic function and Class II-IV CHF were treated with high-dose ACEIs, there would be 100,000 fewer deaths annually. The adoption of these practice recommendations would also decrease hospitalizations for CHF by and 250,000 fewer admissions for CHF, leading to a potential leading to a cumulative savings of 2 billion dollars annually.

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**Statement of Relevance from the ACC**

The ATLAS trial was designed to address whether low-dose therapy is as efficacious as high-dose treatment with lisinopril. The 8% reduction in the primary endpoint of all-cause mortality seen in the high-dose arm was not statistically significant. However, there was a significant 12% reduction in the predefined secondary endpoint of all-cause mortality and hospitalization for any reason, as well as a significant 24% reduction in hospitalizations due to CHF in the high-dose ACE inhibition therapy group. This would translate to the annual prevention of 100,000 deaths and 250,000 hospitalizations due to CHF, with the potential of $2 billion saved in healthcare cost per year.

Suggested Reading

Packer M: Do angiotensin-converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? Journal of the American College of Cardiology 28(5):1323-7, 1996 Nov 1.
Goa KL, Balfour JA, Zuanetti G: Lisinopril. A review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. Drugs 52(4):564-88, 1996 Oct.
Barcina Sanchez C, Martin Cortes M, Fernandez Fernandez A: Lisinopril in the treatment of heart insufficiency. Anales de Medicina Interna 12(5):246-53, 1995 May.

Do Angiotensin-Converting Enzyme Inhibitors Prolong Life in Patients with Heart Failure Treated in Clinical Practice?
Packer M
Journal of the American College of Cardiology 28(5):1323-7, 1996 Nov 1

Angiotensin converting enzyme (ACE) inhibitors have emerged as a significant advance in the treatment of heart failure; yet only a minority (i.e., 30% to 40%) of eligible patients are being treated with these drugs, and even among treated patients, the doses used in clinical practice are substantially lower than those used in the clinical trials that established the efficacy and safety of these agents. The preference for low doses is based on the belief that low and high doses exert similar benefits but that high doses produce more side effects. Yet, most studies indicate that large doses of ACE inhibitors produce greater hemodynamic and clinical effects than small doses, with no additional toxicity. However, it is uncertain whether the survival effects of these drugs are also related to dose. To address this question, a large multinational, double-blind clinical trial (Assessment of Treatment With Lisinopril and Survival [ATLAS]) was launched to compare the effects of low and high doses of the ACE inhibitor lisinopril on the survival of patients with heart failure. If the study demonstrates that large doses are needed to produce optimal effects on mortality, then the low dose strategies that are now widely used in clinical practice may be inadvertently nullifying the enormous potential benefits that ACE inhibitors might otherwise have on public health.

Lisinopril. A Review of its Pharmacology and Clinical Efficacy in the Early Management of Acute Myocardial Infarction.
Goa KL, Balfour JA, Zuanetti G
Drugs 52(4):564-88, 1996 Oct

Following establishment of its efficacy in hypertension and congestive heart failure, the ACE inhibitor lisinopril has now been shown to reduce mortality and cardiovascular morbidity in patients with myocardial infarction when administered as early treatment. The ability of lisinopril to attenuate the detrimental effects of left ventricular remodelling is a key mechanism; however, additional cardioprotective and vasculoprotective actions are postulated to play a role in mediating the early benefit. The GISSI-3 trial in > 19 000 patients has demonstrated that, when given orally within 24 hours of symptom onset and continued for 6 weeks, lisinopril (with or without nitrates) produces measurable survival benefits within 1 to 2 days of starting treatment. Compared with no lisinopril treatment, reductions of 11% in risk of mortality and 7.7% in a combined end-point (death plus severe left ventricular dysfunction) were evident at 6 weeks. Advantages were apparent in all types of patients. Thus, those at high risk-women, the elderly, patients with diabetes mellitus and those with anterior infarct and/or Killip class > 1 -also benefited. These gains in combined end-point events persisted in the longer term, despite treatment withdrawal after 6 weeks in most patients. At 6 months, the incidence rate for the combined end-point remained lower than with control (a 6.2% reduction). The GISSI-3 results concur with those from recent large investigations (ISIS-4, CCS-1, SMILE) of other ACE inhibitors as early management in myocardial infarction. However, the results of the CONSENSUS II trial (using intravenous enalaprilat then oral enalapril) were unfavourable in some patients. These findings, together with the development of persistent hypotension and, to a lesser extent, renal dysfunction among patients in the GISSI-3 trial, have prompted considerable debate over optimum treatment strategies. Present opinion generally holds that therapy with lisinopril or other ACE inhibitors shown to be beneficial may be started within 24 hours in haemodynamically stable patients with no other contraindications; current labelling in the US and other countries reflects this position. There is virtually unanimous agreement that such therapy is indicated in high-risk patients, particularly those with left ventricular dysfunction. The choice of ACE inhibitor appears less important than the decision to treat; it seems likely that these benefits are a class effect. Lisinopril has a tolerability profile resembling that of other ACE inhibitors, can be given once daily and may be less costly than other members of its class. However, present cost analyses are flawed and this latter points remains to be proven in formal cost-effectiveness analyses. In conclusion, early treatment with lisinopril (within 24 hours of symptom onset) for 6 weeks improves survival and reduces cardiovascular morbidity in patients with myocardial infarction, and confers ongoing benefit after drug withdrawal. While patients with symptoms of left ventricular dysfunction are prime candidates for treatment, all those who are haemodynamically stable with no other contraindications are also eligible to receive therapy. **Lisinopril and other ACE inhibitors shown to be beneficial should therefore be considered an integral part of the early management of myocardial infarction in suitable patients**.

The prognosis in patients with heart failure (HF) is poor. The angiotensin converting enzyme (ACE) inhibitors are among the most promising of current options, with benefits not only in terms of haemodynamic and clinical improvement but also in mortality. Data are reviewed comparing the once-daily ACE inhibitor lisinopril with captopril or enalapril in patients already receiving digoxin and/or diuretics for heart failure. Data are also reviewed which compare lisinopril with digoxin in patients already receiving diuretics alone for heart failure. Lisinopril is more effective than placebo and at least as effective as captopril or enalapril in these comparative studies on the basis of haemodynamics, exercise test results and clinical signs and symptoms of heart failure. Lisinopril may also be a suitable alternative, as well as being an adjunct, to digoxin in patients already receiving diuretics alone. Lisinopril is usually well tolerated in patients with heart failure. The mechanism of benefit of ACE inhibitors in heart failure is not clear, but apart from blockade of the renin-angiotensin-aldosterone system (RAAS), may also involve modulation of sympathetic stimulation, cardioreparation and regulation of potassium balance. The new ATLAS study (Assessment of Treatment with Lisinopril And Survival) is being conducted to address the question of whether ACE inhibitors in general practice should be given at the current low doses, or at the higher doses used in large survival studies

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## ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction

V. Rationale and Approach to Pharmacotherapy (cont.)

Angiotensin Converting Enzyme Inhibitors: Recommendations

Class I - 1. Patients within the first 24 hours of a suspected acute MI with ST-segment elevation in two or more anterior precordial leads or with clinical heart failure in the absence of significant hypotension or known contraindications to use of ACE inhibitors. 2. Patients with MI and LV ejection fraction less than 40% or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from acute MI.

Class IIa - 1. All other patients within the first 24 hours of a suspected or established acute MI, provided significant hypotension or other clear-cut contraindications are absent.

2. Asymptomatic patients with mildly impaired LV function (ejection fraction 40% to 50%) and a history of old MI.

Class IIb - 1. Patients who have recently recovered from MI but have normal or mildly abnormal global LV function.

A number of large, randomized clinical trials have assessed the role of ACE inhibitors early in the course of acute MI. All trials in which only oral ACE inhibitors were used demonstrated a benefit in mortality. The only trial not showing benefit using ACE inhibitors was the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II, in which patients were randomly assigned within the first day to receive either intravenous enalaprilat or placebo followed by increasing oral dosages of either enalapril or placebo. This trial was terminated early by the Safety Committee because of the high probability that a significant beneficial effect of enalapril over placebo was unlikely to be demonstrated with continuation of the trial, as well as a concern over an adverse effect among elderly patients experiencing an early hypotensive reaction.[527] The 95% confidence limits ranged from showing a 7% benefit to 29% harm.

Clarification of the role of ACE inhibitors early in the course of MI has more recently resulted from large-scale clinical trials in which oral ACE inhibitors were used. In the ISIS-4 trial 58 000 patients with suspected acute MI were randomly assigned within the first 24 hours (median 8 hours) to receive either oral captopril or placebo; a significant 7% proportional reduction was observed in 5-week mortality among those randomly assigned to captopril.[421] The largest benefit was among those with an anterior infarction.[528] Among the 143 fewer deaths in the group allocated captopril, 44 occurred in days 0 through 1 and 37 in days 2 through 7,[529] demonstrating that early therapy is important. The GISSI-3 trial used oral lisinopril in over 19 000 patients with either ST-segment elevation or depression who were randomly assigned to it or open control.[420] There was a significant reduction in 6-week mortality (odds ratio 0.88; 95% CI, 0.79 to 0.99); 60% of the lives were saved during the first 5 days of treatment. The SMILE (Survival of Myocardial Infarction: Long-Term Evaluation) study involved 1556 patients randomly assigned within 24 hours to receive either placebo or zofenopril.[530] The patient population was restricted to those with anterior MI who had not received thrombolytic therapy. Use of an early ACE inhibitor in this trial suggested a strong trend of more lives saved in the first 6 weeks (RR 25%, P=.19). A Chinese captopril pilot study involving more than 13 600 patients with suspected acute MI also revealed an approximate 0.5% absolute mortality benefit among those who were randomly assigned to the ACE inhibitor compared with the control population.[531] A meta-analysis of these major trials along with 11 smaller trials that involve more than 100 000 patients reveals a 6.5% overall odds reduction (2P=.006) with an absolute benefit of 4.6 fewer deaths per 1000 patients treated among those who received the ACE inhibitor.[529] These data suggest that ACE inhibitors have a role in early management as well as in the convalescent phase of acute MI.

Although detailed subgroup analysis of the ISIS-4 and GISSI-3 trials awaits further publication, it would appear that the benefits of ACE inhibitors are greater among those with an anterior infarct or who have evidence of previous infarction, heart failure, and tachycardia, ie, those at highest risk. Nevertheless, all trials with oral ACE inhibitors have shown benefit from its early use, including those in which entry criteria included all suspected acute infarctions. Data from these trials indicate that ACE inhibitors should generally be started within the first 24 hours, ideally, after thrombolytic therapy has been completed and blood pressure has stabilized. When there are no patient complications and no evidence of symptomatic or asymptomatic LV dysfunction by 4 to 6 weeks, ACE inhibitors can be stopped. ACE inhibitors should not be used if systolic blood pressure is less than 100 mm Hg, if clinically relevant renal failure is present, if there is a history of bilateral stenosis of the renal arteries, or if there is known allergy to ACE inhibitors. ACE inhibitor therapy should start with low-dose oral administration and increase steadily to achieve a full dose within 24 to 48 hours. For example, in ISIS-4 an initial 6.25 mg dose of captopril was given, followed by 12.5 mg 2 hours later, 25 mg 10 to 12 hours later, and then 50 mg twice a day. GISSI patients received 5 mg oral lisinopril at the time of randomization, 5 mg after 24 hours, 10 mg after 48 hours, then 10 mg daily for 6 weeks or open control. Similar graded-dose schedules should be used with other ACE inhibitors, such as ramipril, zofenopril, enalapril, or quinapril. Intravenous enalaprilat should be avoided.