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Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

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Background—Angiotensin-converting enzyme (ACE) inhibitors are generally prescribed by physicians in doses lower than the large doses that have been shown to reduce morbidity and mortality in patients with heart failure. It is unclear, however, if low doses and high doses of ACE inhibitors have similar benefits.

Methods and Results—We randomly assigned 3164 patients with New York Heart Association class II to IV heart failure and an ejection fraction $\leq 30\%$ to double-blind treatment with either low doses (2.5 to 5.0 mg daily, $n=1596$) or high doses (32.5 to 35 mg daily, $n=1568$) of the ACE inhibitor, lisinopril, for 39 to 58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death ($P=0.128$) but a significant 12% lower risk of death or hospitalization for any reason ($P=0.002$) and 24% fewer hospitalizations for heart failure ($P=0.002$). Dizziness and renal insufficiency was observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.

Conclusions—These findings indicate that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small. (*Circulation*. 1999;100:2312-2318.)

Key Words: heart failure ■ drugs ■ mortality ■ morbidity ■ trials

Several treatment guidelines have made a strong recommendation to physicians that angiotensin-converting enzyme (ACE) inhibitors be used in all patients with heart failure resulting from left ventricular systolic dysfunction who can tolerate treatment with these drugs.^{1,2} Despite this guidance, a large proportion of patients with heart failure are not receiving ACE inhibitors,^{3,4} and when used, the doses prescribed are substantially smaller than the target doses used in the large-scale studies that established the utility of these drugs.⁵ This practice persists although there is little information about the efficacy of low doses of ACE inhibitors in the treatment of chronic heart failure.

The preference of physicians for low doses of ACE inhibitors may reflect the perception that low doses are as effective as high doses and are associated with a significantly lower risk of important side effects.⁵ Yet, the validity of these 2 assumptions has never been adequately tested in a con-

trolled clinical trial, because most studies have been performed to determine if, not how, ACE inhibitors should be used in the treatment of heart failure. The few studies that have compared low and high doses of ACE inhibitors in heart failure have focused on their physiological and symptomatic effects⁶⁻¹⁰ and thus were too small to evaluate possible differences between low and high doses on the risk of major clinical events.

We conducted the Assessment of Treatment with Lisinopril and Survival (ATLAS) study to compare the efficacy and safety of low and high doses of ACE inhibition on the risk of death and hospitalization in chronic heart failure.

Methods

Patients were recruited into the ATLAS study if they had New York Heart Association (NYHA) class II, III, or IV symptoms of heart failure associated with a left ventricular ejection fraction $\leq 30\%$

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*A list of the ATLAS Study Investigators and Coordinators appears in the Appendix.

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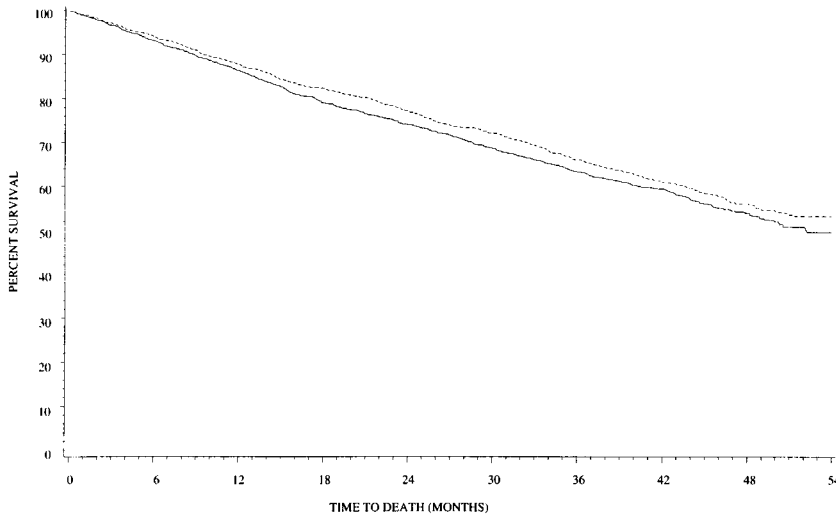


Figure 1. Kaplan-Meier analysis showing time to death in the low-dose and high-dose lisinopril groups. Solid line indicates low-dose group; dotted line, high-dose group. Compared with low-dose group, patients in high-dose group had an 8% lower risk, $P=0.128$.

despite treatment with diuretics for ≥ 2 months. Patients with class II symptoms were required to have received treatment for heart failure in an emergency room or hospital within 6 months. Prior use of digitalis, ACE inhibitors, or vasodilators was allowed but not mandated. Patients were excluded if they had had an acute coronary ischemic event or revascularization procedure within 2 months, had a history of sustained or symptomatic ventricular tachycardia, were known to be intolerant of ACE inhibitors, had a serum creatinine >2.5 mg/dL, or had any noncardiac disorder that could limit survival. The trial was conducted in accordance with the Declaration of Helsinki; the protocol was approved by the institutional review boards of all 287 participating hospitals in all 19 countries; written informed consent was obtained from all patients.

Study Design

Following an initial evaluation, all patients received open-label lisinopril for 4 weeks to assess their ability to tolerate the drug, as described previously.¹¹ Those who could tolerate 12.5 to 15 mg daily for ≥ 2 weeks were randomly assigned (double-blind, 1:1 ratio) to either a low-dose or high-dose ACE inhibitor strategy. The target dose of lisinopril was 2.5 to 5.0 mg daily in the low-dose group and 32.5 to 35 mg daily in the high-dose group. These doses were selected on the basis of data indicating that doses of 2.5 to 5.0 mg of lisinopril daily had favorable hemodynamic effects^{5,8} and that doses of 20 to 40 mg daily were comparable to the doses of ACE inhibitors used in clinical trials that demonstrated a reduction in morbidity and mortality.¹²⁻¹⁴ To achieve these targets, after randomization all patients received a 2.5- or 5.0-mg tablet of open-label lisinopril once daily (dose was selected by the investigator); in addition, patients received up to three 10-mg tablets of double-blind lisinopril (high-dose strategy) or matching placebo (low-dose strategy). The study medications were continued at the highest tolerated doses (along with the patient's usual medications for heart failure) for the remainder of the trial. Changes in NYHA class and laboratory tests were evaluated every 3 to 6 months. If the patient's condition deteriorated, physicians could prescribe open-label therapy with an ACE inhibitor, after which dosing with the study medication could be maintained, reduced, or discontinued at the discretion of the investigator. The study was to be completed when the last patient randomized into the study had been followed for a minimum of 3 years or until 1600 patients had died.

End Points

The primary end point was all-cause mortality, and the 4 secondary end points specified in the original protocol were cardiovascular mortality, cardiovascular hospitalizations, all-cause mortality combined with cardiovascular hospitalizations, and cardiovascular mortality combined with cardiovascular hospitalizations. While the study was in progress, and without knowledge of any interim results or

treatment assignments, the Steering Committee recognized that hospitalization for any reason (rather than for a cardiovascular reason) represented a less biased approach to the analysis of morbidity and accordingly added (in March 1997) the combined risk of all-cause mortality and hospitalization for any reason to the list of end points. Because of concerns that the overall mortality rate in the study was lower than expected, the Steering Committee considered designating this new end point as the primary end point but instead chose to designate it as a secondary end point with priority over all others. The combined risk of fatal and nonfatal myocardial infarction plus hospitalization for unstable angina was also added as a prespecified analysis. All end points were adjudicated according to prespecified criteria by an End Points Committee blinded to the treatment assignment.

Statistical Analysis

A sample size of 3000 patients was selected on the basis of the following assumptions: recruitment would be completed in 18 months with the last patient followed for 36 months, the 1-year mortality rate in the high-dose group would be 19%, and the study would have 90% power to detect a 15% relative difference in mortality between the treatment groups ($\alpha=0.05$, 2-tailed). Because the use of high doses of ACE inhibitors had been reported to reduce mortality by 16% when compared with placebo,¹³ the protocol assumed that low doses of ACE inhibitors would have little effect on

TABLE 1. Pretreatment Characteristics of Patients in the Study

	Low-Dose (n=1596)	High-Dose (n=1568)
Age, y	63.6±10.3	63.6±10.5
Sex, M/F	1265/331	1251/317
NYHA class		
II	231	262
III	1252	1194
IV	113	112
Cause of heart failure		
Coronary artery disease, %	65	64
Left ventricular ejection fraction	0.23±0.06	0.23±0.06
Systolic blood pressure, mm Hg	126±20	125±19
Heart rate, beats/min	80±15	80±14
Previous use of ACE inhibitor, %	89	89

Data are mean+SD except where indicated.

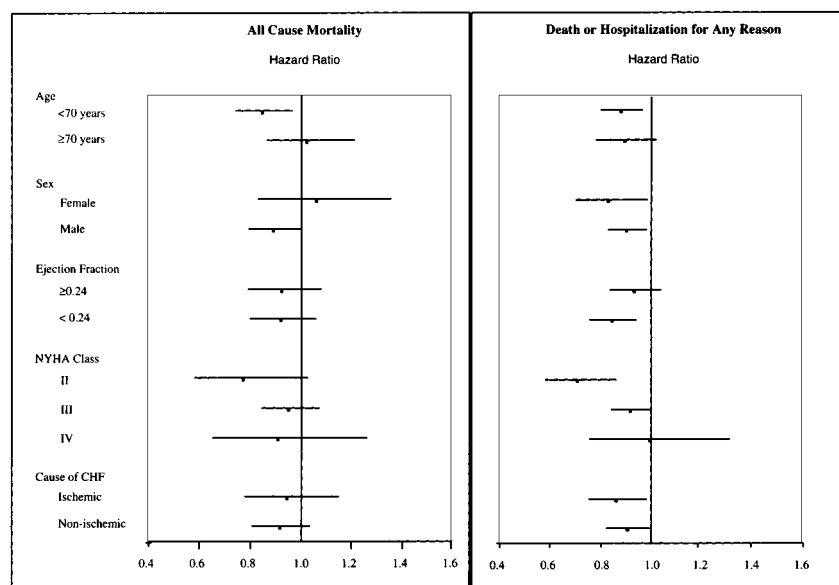


Figure 2. High-dose:low-dose hazard ratios for all-cause mortality (left) and for death or hospitalization for any reason (right) in patient subgroups defined by 5 pretreatment characteristics. Point estimates are shown as small squares, and lines to the left and right of the squares represent the 95% CIs. Points to the left of unity indicate an advantage of high doses over low doses. The effect in each subgroup was not different from the effect seen in the complementary group.

the risk of death. No allowance was made for the possibility that patients might stop taking the double-blind study medication or commence open-label therapy with an ACE inhibitor.

An independent Data and Safety Monitoring Board was prospectively constituted at the start of the study, periodically reviewed the blinded results, and was empowered to recommend early termination of the study if it observed a treatment effect that exceeded the prespecified boundaries. To protect against increasing a false-positive error rate due to repeated interim analyses, the Lan-DeMets procedure¹⁵ using an O'Brien-Fleming type boundary¹⁶ was used. Using this procedure, comparisons of the 2 treatments for all-cause mortality at the scheduled end of the trial were considered significant if $P < 0.0394$ was attained; thus, 96.1% CIs were used for the hazard ratio for the primary end point. In contrast, secondary end points were assessed at the 0.05 level of significance, and 95% CIs were used to describe their hazard ratios.

Cumulative survival curves were constructed as time-to-first-event plots by Kaplan-Meier survivorship methods, and differences between the curves were tested for significance by both the log-rank statistic and a Cox proportional hazard regression model, adjusted (as protocol-specified) for NYHA class and ejection fraction. The analyses included all randomized patients, and all events were assigned to the patient's randomized treatment group (according to the intention-to-treat principle). According to the original protocol, the occurrence of cardiac transplantation was classified as a cardiovascular death. Between-group differences in postrandomization events were analyzed by the Wilcoxon rank sum test, and between-

group differences in laboratory values were evaluated by ANCOVA using baseline values as the covariate.

Results

The ATLAS Trial began on October 13, 1992 and completed follow-up of all patients at midnight on September 14, 1997. Of the 3793 patients who entered the initial open-label tolerability phase, 629 were not deemed eligible for randomization: 55 patients died or had worsening heart failure, 176 patients were withdrawn for possible side effects when the dose of lisinopril was increased toward 12.5 to 15 mg, and 398 patients did not fulfill the criteria for participation in the study or did not participate for administrative or other reasons. The remaining 3164 patients were randomized to double-blind therapy: 1596 to the low-dose strategy and 1568 to the high-dose strategy.

The 2 groups were similar with respect to all pretreatment characteristics (Table 1).¹¹ After randomization, target doses were achieved in 92.7% of the patients in the low-dose group and 91.3% of the patients in the high-dose group. At the end of dose titration following randomization, patients received an average of 4.5 ± 1.1 mg daily of lisinopril in the low-dose group and 33.2 ± 5.4 mg daily of lisinopril in the high-dose

TABLE 2. Effect of Treatment on Major Clinical Events

	Low-Dose	High-Dose	Hazard Ratio	<i>P</i>
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
All-cause mortality+hospitalization for cardiovascular reason	1182 (74.1)	1115 (71.1)	0.92 (0.84–0.99)	0.036
All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Values in parentheses indicate percentage or range. *P* values determined by log-rank test. Hazard ratios represent 95% CI, except for all-cause mortality, shown as 96.1% CI.

*Analysis not specified in protocol before breaking the blind.

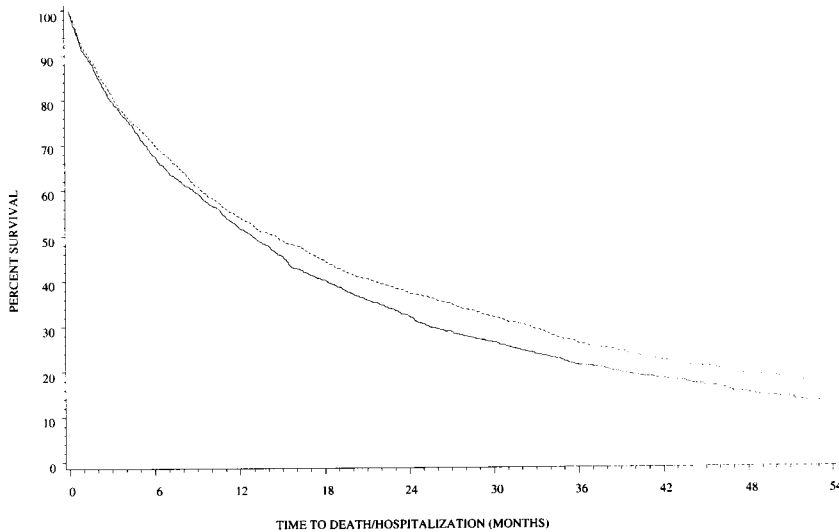


Figure 3. Kaplan-Meier analysis showing time to death or hospitalization for any reason in the low-dose and high-dose groups. Solid line indicates low-dose group; dotted line, high-dose group. Compared with the low-dose group, patients in the high-dose group had a 12% lower risk of death or hospitalization, $P=0.002$.

group. During the course of the study, 30.6% of the patients in the low-dose group and 27.2% of the patients in the high-dose group stopped taking the study medications. Moreover, 22.1% of the patients in the low-dose group and 18.3% of the patients in the high-dose group were started on open-label therapy with an ACE inhibitor other than the study drug. The duration of follow-up in surviving patients ranged from 39 to 58 months (median 45.7). No patient was lost to follow-up with respect to vital status.

Effect on Mortality

Patients in the high-dose group had an 8% lower risk of all-cause mortality ($P=0.128$; Figure 1) and a 10% lower risk of cardiovascular mortality ($P=0.073$) than those in the low-dose group; neither difference was statistically significant. The number of cardiac transplants was small and similar in the 2 groups (20 in the low-dose group and 19 in the high-dose group); inclusion or exclusion of the transplants did not affect the results. The effect on mortality in subgroups was not different from the overall effect (Figure 2).

Effect on the Risk of Death and Hospitalization and on Total Hospitalizations

The combined risk of morbidity and mortality was significantly lower in the high-dose group than in the low-dose group regardless of whether a comprehensive or cause-specific definition was used. For the prioritized analysis of death or hospitalization for any reason, patients in the high-dose group had a 12% lower risk than those in the

low-dose group, $P=0.002$ (Table 2 and Figure 3). The reduction in risk was similar regardless of age, sex, cause of heart failure, ejection fraction, or NYHA class (Figure 2). A significant reduction in the combined risk of death and hospitalization also was observed in the high-dose group in all combined analyses of morbidity and mortality that used a cause-specific definition of death or hospitalization (Table 2). However, the 8% lower risk of fatal and nonfatal myocardial infarction and hospitalization for unstable angina in the high-dose group was not statistically significant.

When the total number of hospitalizations was analyzed (including first and recurrent), the high-dose group experienced 13% fewer hospitalizations for any reason ($P=0.021$), 16% fewer hospitalizations for a cardiovascular reason ($P=0.05$), and 24% fewer hospitalizations for heart failure ($P=0.002$), Table 3. There were no differences in NYHA functional class between the 2 treatment groups at any time during the study.

Safety

Of the 3793 patients who received open-label therapy with lisinopril, 176 patients experienced adverse effects or were found to have laboratory abnormalities (at a dose of ≤ 15 mg daily) that prevented their randomization to double-blind therapy. These included cough in 13 patients, hypotension/dizziness in 43 patients, renal insufficiency in 68 patients, and abnormal values for serum potassium in 6 patients.

Three months after randomization, systolic blood pressure had decreased 4.4 ± 0.6 mm Hg more and diastolic blood

TABLE 3. Effect of Treatment on Number of Hospitalizations

	Low-Dose	High-Dose	Percent Reduction in High-Dose Group	P
Hospitalizations for any reason	4397	3819	13	0.021
Hospitalizations for cardiovascular reason	2923	2456	16	0.050
Hospitalization for heart failure	1576	1199	24	0.002
Hospitalization for ischemic events	543	432	20	0.085

P values are derived from the Wilcoxon rank sum test for between-group comparisons of the number of hospitalizations per patient.

TABLE 4. Selected Adverse Experiences

	Patients With Adverse Experience		Patients Requiring Withdrawal of Study Drug	
	Low-Dose (n=1596)	High-Dose (n=1568)	Low-Dose (n=1596)	High-Dose (n=1568)
Worsening heart failure	709 (44)	594 (38)	76 (4.8)	62 (4.0)
Dizziness	193 (12)	297 (19)	0 (0.0)	5 (0.3)
Hypotension	107 (7)	169 (11)	10 (0.6)	13 (0.8)
Worsening renal function	112 (7)	155 (10)	6 (0.4)	5 (0.3)
Cough	211 (13)	166 (11)	14 (0.9)	14 (0.9)
Hyperkalemia	56 (4)	100 (6)	1 (0.1)	6 (0.4)
Hypokalemia	53 (3)	22 (1)	0 (0.0)	0 (0.0)

Values in parentheses indicate percentage.

pressure had declined 2.3 ± 0.4 mm Hg more in the high-dose group compared with the low-dose group ($P < 0.001$), but the 2 groups showed little change in heart rate. At 3 months, the increase in serum creatinine in the high-dose group was slightly greater than in the low-dose group ($P < 0.001$), but the number of patients with major increases in serum creatinine (>1 mg/dL) was not different.

As expected, patients in the high-dose group experienced dizziness, hypotension, worsening renal function, more frequent hyperkalemia, and less frequent hypokalemia than those in the low-dose group (Table 4). However, these side effects did not lead patients to stop the study medication more frequently in the high-dose group than in the low-dose group (17.0% versus 18.0%). Compared with the low-dose group, fewer patients in the high-dose group experienced cough or reported worsening heart failure as an adverse reaction.

Discussion

The results of the ATLAS study indicate that the use of high doses instead of low doses of the ACE inhibitor lisinopril reduces the risk of major clinical events in patients with chronic heart failure. This finding is consistent with earlier clinical studies, which suggested that high doses of ACE inhibitors produce greater hemodynamic and symptomatic benefits than low doses,^{9,10} and experimental studies, which indicated that high doses produce a larger reduction in mortality than low doses.¹⁷ Although high doses of enalapril were not superior to low doses in an earlier multicenter trial in heart failure,¹⁸ that study treated patients for only 6 months and recorded only 53 deaths and 90 hospitalizations for heart failure. In contrast, the ATLAS trial recorded nearly 1400 deaths and >8200 hospitalizations during a treatment period up to 5 years, and thus had sufficient power to detect small but meaningful differences in long-term outcome.

Nevertheless, the present study did not observe a significant difference between the 2 treatment groups in the risk of death, the primary end point of the study. This observation may represent the lack of a true difference or a smaller than anticipated treatment effect. When the protocol was first developed in 1992, we assumed that low doses of lisinopril would not decrease mortality rates. Hence, in calculating the sample size, we presumed that the difference in mortality risk

between high doses and low doses in this study would be nearly identical to the observed difference in mortality risk between high doses of ACE inhibitors and placebo in the SOLVD trial,¹³ which enrolled similar types of patients. Yet, low doses of ACE inhibitors might favorably affect survival. In addition, the original calculations of sample size assumed that the annual mortality rate would be 19%, and they made no allowances for the possibility that patients randomized to high doses of ACE inhibitors might stop taking their study medication or that patients randomized to low doses of ACE inhibitors might start taking high doses of these drugs. Yet the observed annual mortality rate in the trial was only 15%, and many patients were not maintained on their assigned study medications.

It is noteworthy that patients receiving high doses did not experience a greater improvement in NYHA class than those who received low doses. The lack of a difference suggests that changes in symptoms cannot be used as a guide to the selection of a dose of an ACE inhibitor for clinical use, because an increase in dose may reduce the risk of death and hospitalization even if there is no improvement in functional status.⁵

As expected, adverse effects characteristic of ACE inhibitors were seen more frequently in the high-dose than in the low-dose group. More patients assigned to high doses experienced dizziness, hypotension, worsening renal function, and hyperkalemia, compared with those assigned to low doses. However, these adverse reactions could generally be managed by changes in the dose of lisinopril or concomitant medications, so that the number of patients who discontinued double-blind therapy because of these adverse reactions was small. Furthermore, consistent with the observed reduction in the frequency of hospitalizations, patients assigned to high doses reported fewer episodes of heart failure. Lessening of pulmonary congestion could also explain the lower incidence of cough observed in the high-dose group, even though cough is a side effect commonly associated with ACE inhibition. All of these observations should be viewed in the context that most patients (nearly 90%) had tolerated some dose of an ACE inhibitor before entering the study, and 4% of patients were excluded from participation because they could not tolerate intermediate doses of the drug.

Although we observed that high doses were more effective than low doses of ACE inhibitors in reducing the risk of death and hospitalization, our results cannot predict what we might have observed if low doses of ACE inhibitors had been compared with placebo or if high doses of ACE inhibitors had been compared with intermediate doses of these drugs. However, it is noteworthy that when compared with the low-dose group, the high-dose group had an 8% lower risk of death (rather than the 16% lower risk seen when high doses were compared with placebo in the SOLVD study)¹³ and a 15% lower risk of death or hospitalization for heart failure (compared with the 26% lower risk seen when high doses were compared with placebo in the SOLVD study).¹³ These observations suggest that low doses of ACE inhibitors may provide approximately half of the benefits associated with the use of high doses of these drugs. In the absence of an unusual dose-response relation, we would anticipate that differences in efficacy between high doses and intermediate doses would be even smaller than the small differences in efficacy between high doses and low doses observed in the present trial.

Our observations suggest that patients with heart failure should not be maintained on very low doses of an ACE inhibitor unless these are the only doses that can be tolerated. It is less clear, however, if patients should be titrated to the high doses used in the present study. Although the ATLAS trial did not compare the efficacy and safety of intermediate and high doses of an ACE inhibitor, it is likely that differences between such doses (if any) are very small.

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Appendix

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