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EDITORIAL REVIEW

Do Angiotensin-Converting Enzyme Inhibitors Prolong Life in Patients With Heart Failure Treated in Clinical Practice?

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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.

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The most important advance in the management of chronic heart failure during the past decade has been the development of agents that inhibit the angiotensin-converting enzyme (ACE). This class of drugs has produced hemodynamic, symptomatic and prognostic benefits in patients with left ventricular dysfunction beyond that which can be achieved with the use of conventional drugs. Numerous trials have demonstrated that ACE inhibition can relieve the symptoms and enhance the exercise capacity of patients with heart failure while producing few adverse reactions (1–4). In addition, in large-scale studies, ACE inhibitors have reduced morbidity and mortality, regardless of the severity of symptoms, even in patients with an acute myocardial injury but without symptoms of heart failure (5–11). These observations, taken together, provide a compelling argument that ACE inhibitors should be given to *all* patients with left ventricular systolic dysfunction, with or without symptoms of heart failure, as long as the drugs are well tolerated. If this recommendation were followed, this class of drugs would prevent at least 60,000 deaths and 100,000 hospital admissions in the United States each year (6).

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Factors That Might Limit the Impact of ACE Inhibitors

Will the use of ACE inhibitors for heart failure have such an important impact on public health? Present surveys indicate that only a minority (i.e., 30% to 40%) of eligible patients in the United States are being treated with these drugs. Some physicians have yet to accept the benefits of ACE inhibitors, whereas others routinely avoid the use of these drugs in specific types of patients (e.g., those with low pretreatment blood pressure or mildly impaired renal function) who are believed to be at high risk of experiencing side effects with treatment. Still others readily discontinue the use of ACE inhibitors after a modest and asymptomatic decline in blood pressure or renal function. Yet, the available data indicate that such patients derive as much benefit from the use of ACE inhibitors as low risk patients. In controlled trials, patients with low baseline blood pressures and those who experienced further decreases in blood pressure responded symptomatically to ACE inhibition as well as those in whom blood pressure was not a concern (12). Similarly, patients with renal insufficiency before treatment or who had worsening renal function during treatment showed as great a reduction in mortality with ACE inhibition as those in whom renal function remained within normal limits before or during treatment (13,14). Hence, strategies that avoid the use of ACE inhibitors in selected groups may deprive many patients of the advantages of these drugs.

Yet, even if physicians prescribed ACE inhibitors to all patients who might benefit from these drugs, such use may still not result in a significant decline in the risk of morbidity and

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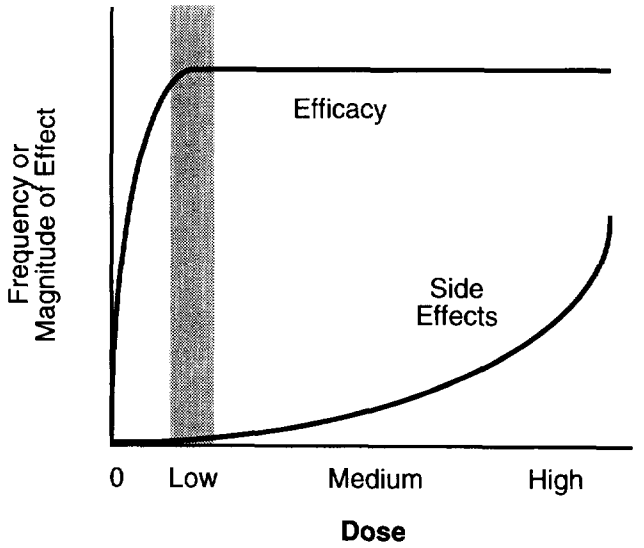

Figure 1. This graph (and those shown in Fig. 2 to 4) depicts hypothetical dose–response relations governing the use of angiotensin-converting enzyme inhibitors in heart failure. Here, the relation between dose and efficacy is assumed to be flat (low doses are as effective as high doses), whereas the relation between dose and safety is assumed to be curvilinear (the frequency of side effects is dependent on dose). If this were true, physicians would use low doses (as shown in the **shaded area**) because such doses produce all the therapeutic benefits at minimal risk.

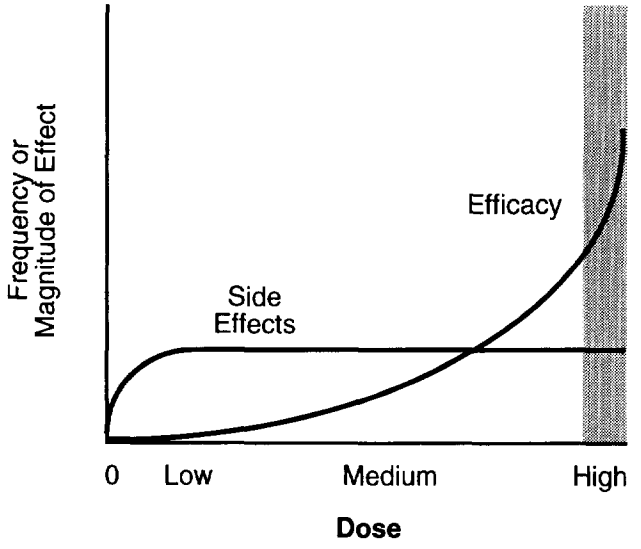

Figure 2. The relation between dose and efficacy is assumed to be curvilinear (high doses are more effective than low doses), whereas the relation between dose and safety is assumed to be flat (low and high doses have a similar safety profile). Under these circumstances, patients would benefit only if they were treated with large doses of an angiotensin-converting enzyme inhibitor (**shaded area**).

mortality in heart failure because the doses used in clinical practice are far lower than those used in clinical trials. The doses of captopril used in controlled studies were 150 to 300 mg daily (1,9), but the drug is usually prescribed in clinical practice at a daily dose of 25 to 50 mg. Similarly, the doses of enalapril used in large-scale trials were 20 to 40 mg daily (5–8); yet the drug is most commonly prescribed by physicians at a dose of 2.5 to 5.0 mg daily. In general, the most common dose of an ACE inhibitor utilized in clinical practice is similar to that recommended for the initiation, rather than the maintenance, of therapy.

Reasons for Using Low Doses of ACE Inhibitors in Heart Failure

Why are physicians using doses of ACE inhibitors that are only 10% to 25% of those used in clinical trials? Physician surveys indicate that this pattern of use is based on two principal assumptions:

Assumption 1. Low doses are as effective as high doses but produce fewer side effects. Many physicians state that their 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 than low doses. This relation between dose and effect is illustrated in Figure 1. Figure 1 assumes that the dose–response relation for the favorable effects of the ACE inhibitors is flat, whereas the dose–response relation for the adverse effects of these drugs is steep. Because low doses provide the largest difference between the drug's favorable and toxic effects, low doses would be preferred.

Is there evidence to support this assumption? In early studies, low doses of an ACE inhibitor produced hemodynamic effects similar to high doses (15,16), and in clinical practice, low doses produce symptomatic improvement in many patients with few side effects. However, most observations indicate that large doses of ACE inhibitors produce greater hemodynamic (17,18) and clinical (19–22) effects than small doses. In one retrospective open-label study with captopril (19), high doses (>75 mg daily) produced a more favorable effect on functional capacity than low doses (<75 mg daily). In a double-blind study with quinapril (20), exercise capacity improved more in patients assigned to 40 mg daily than in patients treated with 10 mg daily. In one double-blind study with enalapril (21), patients allocated to 15 mg twice daily experienced fewer cardiovascular events than those assigned to 2.5 mg twice daily. In a second double-blind study with enalapril (22), patients assigned to high doses (20 mg twice daily) showed greater hemodynamic, neurohormonal and symptomatic benefits than those assigned to low doses (5 mg twice daily). Of note, in all four studies, the frequency of side effects with low doses was similar to that seen with high doses. Finally, in an experimental model of heart failure, high doses of lisinopril were superior to low doses of lisinopril in prolonging life (23). Taken collectively, these observations suggest that the dose–response relations for the benefits and risks of ACE inhibitors in heart failure resemble those depicted in Figure 2 rather than Figure 1; the dose–response relation for the favorable effects is steep, whereas that for the adverse effects of these drugs is flat. Yet, Figure 2 indicates that the use of low doses of an ACE

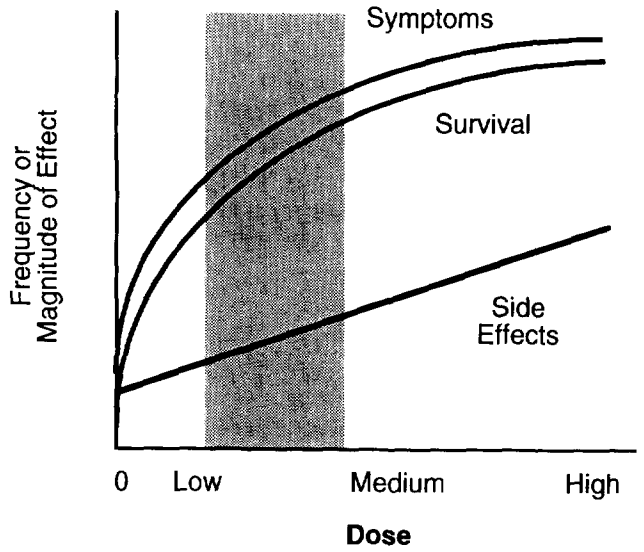

Figure 3. The relation between dose and symptoms is parallel to the relation between dose and survival. Note that in this graph (as well as that shown in Fig. 4), the y intercept for symptoms and side effects is not zero because placebo therapy is associated with symptomatic improvement and side effects in some patients. Under these circumstances, physicians should use low doses **(shaded area)**, which would maximize the risk/benefit relation.

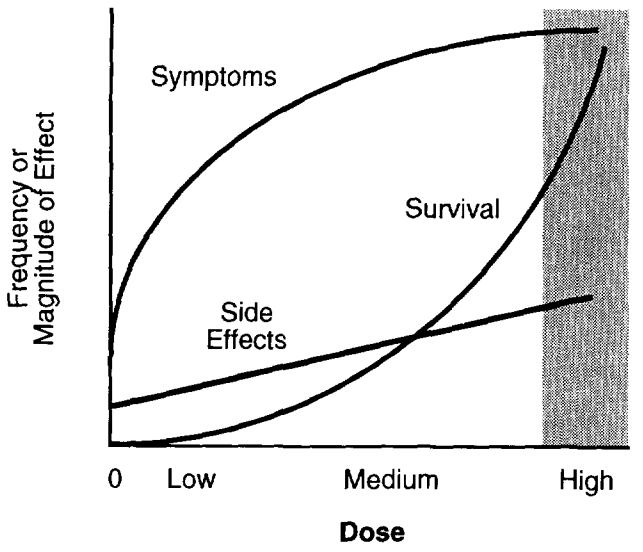

Figure 4. The relation between dose and survival is not parallel to the relation between dose and symptoms. Under these circumstances, physicians should use large doses **(shaded area)** despite their increased side effects because only large doses produce favorable effects on survival.

inhibitor exposes patients with heart failure to all of the risks but provides them with few of the benefits of these drugs.

Assumption 2. A physician can assess the effect of an ACE inhibitor on the survival of an individual patient by evaluating the drug's effect on symptoms or blood pressure. Recognizing that Figures 1 and 2 may represent extreme points of view, many physicians would suggest that both the efficacy and the safety of ACE inhibitors are dependent on dose (i.e., high doses are more effective and more toxic than low doses). As a result, many clinicians would adopt an intermediate approach to the use of ACE inhibitors; specifically, they would initiate therapy with low doses in all patients and increase the dose only if patients fail to respond favorably to treatment. Accordingly, patients would be exposed to high doses (and their attendant risks) only if they had tolerated but had failed to improve with low doses.

Yet, such an approach assumes that we know when we have reached an effective dose of an ACE inhibitor by simply asking the patient if his or her symptoms have improved; this would be true if the only reason for prescribing these drugs was to relieve symptoms. However, ACE inhibitors are used in the treatment of heart failure to reduce mortality as well as disability, and we do not know whether the effect of these drugs on survival occurs simultaneously with their effect on symptoms. Many physicians believe that the dose–response relations for symptoms and survival are precisely parallel to each other (as depicted in Fig. 3), and thus, symptoms could be used as an end point to titrate the effect on survival. However, it is possible that the shapes of the dose–response curves for symptoms and for survival are substantially different, such that survival is prolonged only with the use of large doses (as depicted in Fig. 4)—doses far greater than those needed to produce an optimal effect on symptoms.

Why should the dose–response relation for symptoms be different than that for survival? There are two possibilities: 1) The mechanisms by which ACE inhibitors affect symptoms and survival may be different. Symptoms may be primarily influenced by a drug's hemodynamic effects (which are apparent at low doses), whereas survival may be principally mediated by a drug's effects on neurohormonal systems (which are most markedly affected at large doses) (13,19,21–24). 2) Symptoms are highly subjective and can be influenced by factors that have little to do with the pharmacologic effects of the drug, whereas survival is not subject to interpretative biases. For example, in controlled trials, 25% to 35% of patients assigned to placebo therapy (i.e., 0 mg of an ACE inhibitor) show a significant reduction in the symptoms of heart failure (25); yet, placebo therapy does not provide adequate effects on survival.

Alternatively, instead of using symptoms, some physicians would use a physiologic measure (e.g., blood pressure) as an end point for the titration of therapy, that is, they would initiate treatment with low doses in all patients and increase the dose until blood pressure (or some other variable) changes by a predetermined value. Such an approach assumes (without supporting evidence) that there is a relation between the hypotensive actions of the drug and its effects on mortality. Furthermore, because blood pressure-based titration was not used in any clinical trial, it is not clear that such an approach would achieve the same survival benefits as the use of fixed doses. Why, then, would physicians substitute a physiologic measure (blood pressure) for a definitive clinical end point (mortality)? Such a substitution primarily occurs because physicians cannot measure the effect of a drug on mortality in

an individual patient, but they can measure the drug's effect on blood pressure. To many physicians, the ability to measure *any* effect is more appealing than the blind acceptance of the empiric results of a clinical trial. They would say, "By measuring blood pressure, I know that the drug is doing *something*. How does a physician using fixed high doses know that the drug is prolonging life in the specific patient he is treating?" Although such a response ignores the fundamental fact that survival benefits are seen in populations, not in individuals, this point of view is held by many clinicians.

What Dose of an ACE Inhibitor Should Physicians Use?

Thus, even after many years of development, there remains an important unresolved issue concerning the use of ACE inhibitors in patients with heart failure. We know a great deal about *whether* patients should receive ACE inhibitors, but we know little about *how* patients should receive them. What is the most appropriate dosing regimen? Are the low doses used in clinical practice as effective as the high doses used in clinical trials?

To address these questions, a large multinational, double-blind, randomized controlled clinical trial was launched to evaluate the efficacy and safety of two different dosing regimens of an ACE inhibitor (lisinopril) in patients with heart failure. The trial is known by the acronym ATLAS (Assessment of Treatment With Lisinopril and Survival). The objective of the study is to compare the effects of two doses of lisinopril—low doses (2.5 to 5.0 mg once daily) and high doses (32.5 to 35.0 mg once daily)—on the morbidity and mortality of patients with heart failure. Begun in 1993, the study has enrolled >3,000 patients with New York Heart Association functional class II or IV heart failure and a left ventricular ejection fraction ≤30% at 288 sites in 18 countries; all patients will be followed up for 3 to 4.5 years. The primary end point in the study is all-cause mortality, and the study is intended to have a 90% power to detect a 15% difference between the two treatment groups at the end of the follow-up period. The study will also compare the effect of high and low doses of lisinopril on nonfatal end points (e.g., development of progressive heart failure) as well as on measures of safety. The results of the study will be available in late 1997.

What should physicians do until the results of the ATLAS study are available? Most studies suggest that physicians should prescribe the doses of ACE inhibitors used in clinical trials; to do otherwise is to assume—in the absence of supporting data—that low doses are prognostically equivalent to high doses. Nevertheless, it seems likely that most physicians will continue to use doses that are lower than those that have been utilized in controlled clinical trials on the basis of the belief that such doses are sufficient to prolong life. Yet, the margin for error for selecting a dose to relieve symptoms is not the same as the margin of error for selecting a dose to extend life. When treating symptoms, there is room for error because if the patient remains symptomatic despite the use of low doses, the patient returns to the physician who now has the opportunity to increase the dose until symptoms are relieved. However, such a margin for error does not exist when ACE inhibitors are used to reduce mortality because physicians cannot increase a subtherapeutic dose of a drug into the therapeutic range in a patient who has died. If low doses do not prolong life, then the dosing strategies that are now used widely in clinical practice would effectively nullify the enormous potential benefits that ACE inhibitors would otherwise have on public health. Until the results of the ATLAS trial are available, is this a risk that physicians should be willing to take?

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