

High- Versus Low-dose Angiotensin Converting Enzyme Inhibitor Therapy in the Treatment of Heart Failure: An Economic Analysis of the Assessment of Treatment With Lisinopril and Survival (ATLAS) Trial

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Background: Angiotensin-converting enzyme (ACE) inhibitors reduce heart failure death and hospitalization. Prescribed doses often are lower than randomized clinical trial (RCT) targets and practice guideline recommendations.

Objective: To assess the cost-effectiveness of high- versus low-dose ACE inhibitor therapy in the ATLAS trial.

Study Design: A 19-nation RCT of high-dose (32.5-35.0 mg/day) versus low-dose (2.5-5.0 mg/day) lisinopril in 3164 patients with class II-IV heart failure and left ventricular ejection fraction $\leq 30\%$.

Methods: Data on clinical outcomes and major cost events (hospitalizations and drug utilization) were collected prospectively. Hospital costs were estimated using Medicare and representative managed care diagnosis-related group reimbursement rates. ACE inhibitor drug costs were estimated using US average wholesale prices. Costs were discounted at 3% annually.

Results: Patients in the high-dose lisinopril group had fewer hospitalizations (1.98 vs 2.22, $P = .014$) and hospital days (18.28 vs 22.22, $P = .002$), especially heart failure hospitalizations (0.64 vs 0.80, $P = .006$) and heart failure hospital days (6.02 vs 7.45, $P = .028$) compared with the low-dose group. The high-dose lisinopril group also had lower heart failure hospital costs (\$5114 vs \$6361, $P = .006$) but higher ACE inhibitor drug costs (\$1368 vs \$855, $P = .0001$). Total hospital and drug costs were similar between high- and low-dose lisinopril groups (mean difference $-\$875$, 95% CI $-\$2613$ to $\$884$). Sensitivity analyses confirmed these findings.

Conclusions: Cost savings from fewer heart failure hospitalizations offset higher ACE inhibitor costs in the high-dose group. The improved clinical outcomes were achieved without increased treatment costs.

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patients with left ventricular systolic dysfunction and without a contraindication to ACE inhibitor therapy.³⁻⁶ However, ACE inhibitors are not prescribed for many patients with heart failure and, when prescribed, often are used at lower doses than those demonstrated effective in randomized clinical trials (RCTs) and recommended by treatment guidelines.⁷⁻¹⁰

The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared the effect of high-versus low-dose lisinopril therapy on death and hospitalization in New York Heart Association (NYHA) class II-IV heart failure patients with left ventricular ejection fraction (LVEF) $\leq 30\%$.¹¹ Excluded from ATLAS were patients with myocardial infarction, unstable angina, or coronary revascularization within the preceding 2 months; current symptomatic ventricular tachycardia or clinically unstable congestive heart failure; or contraindications to ACE inhibitors.

The ATLAS trial randomized 3164 patients from 19 countries to either high-dose lisinopril (32.5-35.0 mg/day; $n = 1568$) or low-dose lisinopril (2.5-5.0 mg/day; $n = 1596$) therapy. US patients comprised 38% of the trial population (592 in the high-dose

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Angiotensin-converting enzyme (ACE) inhibitors reduce the risk of death and hospitalization in patients with chronic heart failure.^{1,2} Treatment guidelines developed by professional societies and public health agencies recommend ACE inhibitor treatment in all heart failure

group, 606 in the low-dose group). Following randomization, target doses were achieved in 91.3% of the high-dose group and 92.7% of the low-dose group. Rates of medication discontinuation due to adverse events were similar in both groups (17.0% and 18.0% in the high- and low-dose groups, respectively).

The high-dose lisinopril group had an 8% lower risk of death (666 vs 717, $P = 0.128$), a 12% lower risk of death or hospitalization (1250 vs 1338, $P = 0.002$), a 10% lower risk of cardiovascular death (583 vs 641, $P = 0.073$), 13% fewer hospitalizations (3819 vs 4397, $P = .021$), a 24% lower risk of heart failure hospitalization (1199 vs 1576, $P = .002$), and a 16% lower risk of cardiovascular hospitalizations (2456 vs 2923, $P = .050$) compared with the low-dose group. NYHA class improved in both high- and low-dose groups subsequent to enrollment, with no significant differences between the two groups.

Evidence-based practice guidelines are increasingly important components of efforts to improve patient outcomes, reduce inappropriate practice variation, and control costs of medical care. Until recently, assessment of compliance with practice guidelines has focused primarily on whether or not a recommended intervention was initiated. Less attention has been paid to the details of physician adherence with practice guideline components. ACE inhibitors, like drugs for many chronic diseases, are initiated at relatively low-doses and require titration over time to achieve target doses and maximal clinical effects. While the ATLAS trial demonstrated that titration of lisinopril reduced the composite outcome of death or hospitalization, such titration also increases drug costs. Thus, the objective of this study was to assess the economic impact of high-versus low-dose lisinopril for heart failure patients enrolled in the ATLAS trial, using estimated US costs. We hypothesized that savings from reduced hospitalizations offset the additional drug costs attributable to high-dose lisinopril therapy. We further hypothesized that the economic benefits of high-dose lisinopril were primarily attributable to reductions in heart failure hospitalizations, with little effect on other cardiovascular or noncardiovascular hospitalizations.

METHODS

Cost Analysis

The economic analysis was performed using an intent-to-treat analysis from the US third party

payer perspective. Data on clinical outcomes and major cost events (hospitalizations and drug utilization) were collected prospectively in the ATLAS trial.¹¹ Hospitalizations, hospital days and drug utilization were obtained for all annual intervals in which a patient was enrolled, including intervals in which a patient died, discontinued study lisinopril, or was switched to open-label ACE inhibitors. Costs were stratified into yearly intervals and discounted at a 3% annual rate.¹² Duration of follow-up for patients who completed the trial ranged from 39 to 58 months (median 45.7 months). The Kaplan-Meier technique for survival analysis can be used with a separate estimate of the average cost per patient in each corresponding period to estimate the average treatment cost.¹³ In this economic analysis, no adjustment was made for the differential follow-up, as such censoring was unlikely biased in the double-blind, randomized ATLAS trial. However, because survival was higher (although not statistically significant, $P = .128$) in the high-dose group than in the low-dose group and because only surviving patients incur costs (which biases the results against the more effective treatment strategy), we also assessed mean cost per surviving patient by year. A surviving patient is defined as a patient alive and in the trial at the beginning of a specific year since randomization.

A professional medical record nurse blinded to study group assignment reviewed the reason(s) for each hospitalization from the case report forms and assigned the appropriate diagnosis-related-group (DRG) code. When there was more than one appropriate DRG code for a hospitalization, the DRG code with the higher or highest mean national reimbursement rate was assigned.¹⁴ For example, instead of DRG 127 (heart failure and shock), DRG 87 (pulmonary edema and respiratory failure) was assigned for hospitalizations with heart failure and pulmonary edema; DRG 316 (renal failure) was assigned for hospitalizations with heart failure and renal failure. Hospitalizations generally not reimbursable by Medicare or managed care plans in the US (3 for overnight apnea evaluation, 3 for cancer home care, 2 for social or family respite) were excluded. Same-day emergency department (ED) visits without admission to an inpatient setting also were excluded from this US-focused economic analysis. As there were 600 same-day ED visits in the high-dose group and 698 in the low-dose group, this exclusion slightly reduced the estimated cost savings for the high-dose treatment. Obviously, this exclusion needs to be re-examined if this economic

analysis is transferred to the other countries in the ATLAS trial.

United States hospital costs were estimated using an age-dependent assignment of Medicare and managed care DRG reimbursement rates, including both physician fees and hospital payments. For patients ≥ 65 years of age, hospital costs were estimated using national mean Medicare allowable DRG reimbursement rates. For patients <65 , managed care DRG reimbursement rates were estimated from representative allowable costs of a large national managed care plan at a major teaching hospital in Philadelphia. Out-of-hospital death was assigned a fixed cost of \$1000, or approximately one eighth of the cost of a heart failure hospitalization. Assigning such death zero or the full cost of a heart failure hospitalization led to similar results.

Total ACE inhibitor drug costs were calculated based on actual use of study lisinopril and open-label ACE inhibitors. Since the use of other major non-ACE-inhibitor cardiovascular drugs were similar between the high and low-dose groups (and often slightly higher in the latter group), the costs of non-ACE inhibitor drugs were not assessed. Drug costs for lisinopril were estimated using US average wholesale prices (AWPs) published in July 1999.¹⁵ When more than 1 price was available for a drug dosage, the lower, lowest or generic price was used. When there was no price corresponding to the actual dose, the next higher commercially available dose or the least expensive combination of 2 doses was used. For example, the 30 mg AWP was used for lisinopril doses between 20 mg and 30 mg; the sum of 20 mg and 30 mg AWP was used for lisinopril 50 mg.

As the ATLAS trial protocol required the same number of physician visits for both the high and low-dose lisinopril groups, there was no difference in dosage titration costs in our primary analysis. Assuming 3 additional visits for dosage titration in the high-dose group led to similar results.

Because there was a statistically insignificant reduction in mortality in the high-dose group, we could not estimate the usual incremental cost per year of life saved. For the same reason, we could not estimate the best/worst cost-effectiveness scenario using different assumptions on effectiveness (years of life saved). We might estimate the incremental drug cost per hospitalization avoided but determined that a pragmatic approach to estimate the mean difference in total (hospital and drug) treatment cost per patient is more meaningful from the third party perspective.

In addition to the primary analysis described above, sensitivity analyses were conducted using the Medicare DRG reimbursement rates for all ATLAS patients, the managed care DRG reimbursement rates for all ATLAS patients, and the age-dependent mix of Medicare and managed care DRG reimbursement rates for only US-based ATLAS patients. To test the hypothesis that high-dose lisinopril primarily led to a reduction of heart failure hospitalizations, we also estimated the mean difference in heart failure hospitalization (DRGs 87 [pulmonary edema], 127 [heart failure], and 316 [renal failure]) and drug cost per patient. Sensitivity analyses also were performed using a 5% annual discount rate.

Statistical Analysis

Chi-square analysis was used to test the difference between US and non-US ATLAS patients in reason(s) for hospitalizations, with DRGs aggregated into Major Diagnostic Categories (MDCs).¹⁴ Statistical significance for the number of hospitalizations, hospital days, hospital costs, and drug costs was assessed using the *t* test. As medical events and costs often are not normally distributed, statistical significance also was assessed using the nonparametric Wilcoxon rank sum test and the *t* test for log transformed geometric means with \$1 assigned to all nonhospitalized patients. In the ATLAS trial, more than 30% of patients in both high and low-dose lisinopril groups were not hospitalized. Hospitalization costs varied significantly, from approximately \$8000 for heart failure (1023 in high-dose group, 1254 in low-dose group) to over \$200 000 for heart transplantation (19 in high-dose group, 20 in low-dose group). As results were similar using the 3 methods, we only report results using the *t* test and Wilcoxon rank sum test.

For the primary analysis and sensitivity analyses of mean difference in total (hospital and drug) treatment cost per patient, the 95% confidence interval (CI) for the mean cost difference (2.5 and 97.5 percentiles) was estimated using the nonparametric bootstrap method (ie, resampling with replacement 1000 times).¹⁶⁻¹⁸

RESULTS

Table 1 presents baseline characteristics of the ATLAS patients. The 2 groups were similar with respect to all baseline characteristics. The 6637 hospitalizations lasting one day or more (3098 in high-dose group; 3539 in low-dose group) were dis-

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tributed among a total of 221 DRG codes. There was no difference between US (1198) and non-US (1996) ATLAS patients in the reason(s) for hospitalizations by MDC: 1544 US and 2266 non-US hospitalizations belonged to MDC 5 (Diseases and Disorders of the Circulatory System) and 1127 US and 1700 non-

US hospitalizations belonged to the other MDCs (Chi-square test $P = .588$).

Mean total hospitalization and mean heart failure hospitalization per patient were less frequent in the high-dose lisinopril group than in the low-dose lisinopril group (total hospitalization 1.98 vs 2.22, $P = .014$; heart failure hospitalization .64 vs .80, $P = .006$) (Table 2). Mean other cardiovascular hospitalization and mean noncardiovascular hospitalization per patient were similar between the high- and low-dose groups (other cardiovascular hospitalization 0.56 vs 0.59, $P = .417$; noncardiovascular hospitalization .77 vs .83, $P = .292$). The high-dose group had fewer mean hospital days per patient (18.28 days vs 22.22 days, $P = .002$) and mean heart failure hospital days per patient (6.02 days vs 7.45 days, $P = .028$) compared with the low-dose group. There were no significant differences between the 2 dose groups for other cardiovascular hospital days or noncardiovascular hospital days.

There was a trend toward lower mean total hospital cost per patient in the high-dose group (\$16 684 vs \$18 093, $P = .108$) than in the low-dose group (Table 3). This trend started in the second year of the

Table 1. Baseline Characteristics of the ATLAS Patients

Characteristics	High-Dose Group (n = 1568)	Low-Dose Group (n = 1596)
Age (mean [SD])	63.6 (10.5)	63.6 (10.3)
Male (number [%])	1251 (79.8)	1265 (79.3)
New York Heart Association Class*		
Class II (number [%])	262 (16.7)	231 (14.5)
Class III (number [%])	1194 (76.1)	1252 (78.4)
Class IV (number [%])	112 (7.1)	113 (7.0)
Coronary artery disease (number [%])	999 (63.7)	1036 (64.9)
Left ventricular ejection fraction (mean [SD])	22.6 (5.7)	22.6 (5.6)
Systolic blood pressure (mm HG) (mean [SD])	125.3 (19.3)	125.9 (19.6)
Heart rate (mean beats per min [SD])	79.6 (13.7)	80.0 (14.7)
Previous use of ACE inhibitor (number [%])	1,390 (88.6)	1,420 (89.0)

ACE indicates angiotensin-converting enzyme.

*Due to rounding, these figures may not sum to 100%.

Table 2. Mean Hospitalization and Hospital Day per Patient in High and Low-Dose Lisinopril Groups

	High-Dose Group (n = 1568)	Low-Dose Group (n = 1596)	t test P	Wilcoxon P
Hospitalization				
Heart failure	0.64 (1.51)	0.80 (1.72)	.006	.004
Other cardiovascular	0.56 (1.05)	0.59 (1.14)	.417	.824
Noncardiovascular	0.77 (1.38)	0.83 (1.34)	.292	.154
Total hospitalization	1.98 (2.62)	2.22 (2.88)	.014	.032
Hospital day				
Heart failure	6.02 (16.48)	7.45 (20.16)	.028	.006
Other cardiovascular	4.65 (12.86)	5.53 (19.55)	.137	.701
Noncardiovascular	7.61 (18.84)	9.24 (25.45)	.040	.140
Total hospital day	18.28 (30.07)	22.22 (40.00)	.002	.005

Data are displayed as mean (standard deviation).

Table 3. Mean Hospital and Drug Cost per Patient (US \$) in High and Low-dose Lisinopril Groups

	High-Dose Group (n = 1568)	Low-Dose Group (n = 1596)	t test P	Wilcoxon P
Hospital cost				
Heart failure	5114 (11 890)	6361 (13 623)	.006	.003
Other cardiovascular	5147 (13 891)	5219 (14 078)	.885	.908
Noncardiovascular	6423 (13 083)	6513 (10 875)	.834	.212
Total hospital cost	16 684 (24 546)	18 093 (24 791)	.108	.029
Drug cost				
Lisinopril (study drug)	1281 (688)	737 (428)	.0001	.0001
Open-label ACE inhibitor	87 (401)	118 (461)	.046	.014
Total drug cost	1368 (706)	855 (552)	.0001	.0001

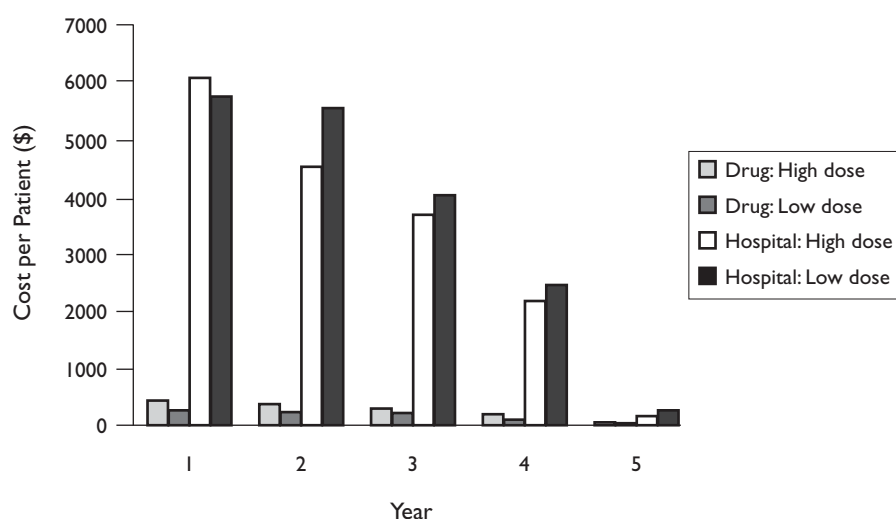
Data are displayed as mean (standard deviation).

*ACE indicates angiotensin-converting enzyme.

trial and persisted over time (Figure 1). In both groups, mean hospital costs de-creased with time due to selection bias, as patients incurring higher hospital costs were more likely to suffer from severe heart failure and die. Results were similar in the high- and low-dose group using either Medicare DRG reimbursement rates (\$16 889 vs \$18 354, $P = .113$) or managed care DRG reimbursement rates (\$16 602 vs \$18 267, $P = .057$). Differences in hospital expenditures were primarily attributable to lower heart failure hospitalization costs in the high-dose group (primary analysis: \$5114 vs \$6361, $P = .006$; Medicare DRG reimbursement rate: \$4977 vs \$6187, $P = .006$; managed care DRG reimbursement rate: \$5280 vs \$6560, $P = .007$).

Mean total ACE inhibitor drug cost per patient was higher in the high-dose lisinopril group (\$1368) than in the low-dose group (\$855; $P = .0001$) (Table 3). The differences were greatest in the first year but persisted over time (Figure 1). In the high-dose

Figure 1. Mean Drug and Hospital Costs per Patient* by Year Since Randomization (Discounted Costs in US \$) in High- and Low-Dose Lisinopril Groups in the ATLAS Trial

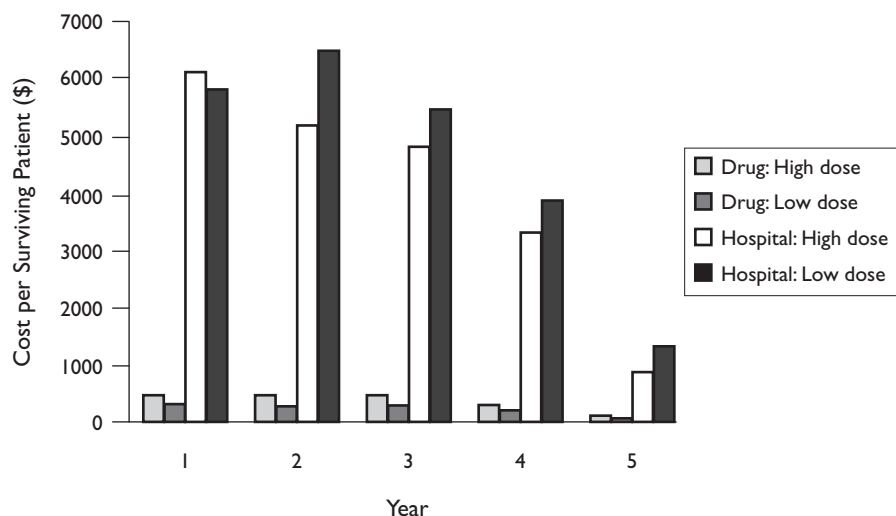


*Including patients who died during or finished the trial.

group, higher mean cost of study lisinopril per patient (\$1281 vs \$737 in low-dose group, $P = .0001$) was only partially offset by lower mean cost of open-label ACE inhibitors per patient (\$87 vs \$118 in low-dose group, $P = .046$).

There was no difference in mean total (hospital and drug) cost per patient between the high- and low-dose lisinopril groups (primary bootstrap

Figure 2. Mean Drug and Hospital Costs per Surviving Patient* by Year Since Randomization (Discounted Costs in US \$) in High- and Low-Dose Lisinopril Groups in the ATLAS Trial



*A surviving patient is defined as a patient alive and in the trial at the beginning of a specific year since randomization.

analysis: mean difference $-\$875$, 95% CI $-\$2613$ to $\$884$) (Table 4). Sensitivity analyses using the Medicare DRG reimbursement rates, the managed care DRG reimbursement rates, only US-based ATLAS patients, only heart failure hospitalization and drug costs, and a 5% annual discount rate confirmed the finding (Table 4).

The observed differences in mean hospital cost and mean total cost between high- and low-dose groups widened when the analysis was conducted on cost per surviving patient by year (Figure 2).

DISCUSSION

Heart failure is a major cause of mortality, morbidity, and medical care costs. Heart failure affects approximately 5 million Americans. About 400 000 new cases are diagnosed each year, with the annual incidence increasing as the population ages and as Americans increasingly survive more acute episodes of cardiac and non-cardiac events.¹⁹⁻²¹ Heart failure results in more than 875 000 hospitalizations, is a contributing factor in 1.8 million additional hospitalizations and accounts for 3 million office visits and more than 65 000 home health visits each year.²² Annual costs for medical management of heart failure are estimated to exceed $\$20$ billion.²²

ACE inhibitors improve hemodynamics, clinical signs and symptoms, and survival for heart failure patients.^{1,2,23,24} Cost-effectiveness analyses consistently have found ACE inhibitor therapy in patients with left ventricular systolic dysfunction cost effective and frequently cost saving.²⁵⁻³¹ In the ATLAS trial, ACE inhibition with high-dose lisinopril therapy reduced the combined risk of death or hospitalization compared with low-dose lisinopril therapy among patients with class II-IV heart failure and moderate-to-severe left ventricular systolic dysfunction. This economic analysis indicates that this reduction in

major clinical events was achieved without increased net costs. Savings from reductions in hospitalizations, especially heart failure hospitalizations, offset the increased drug costs incurred in the high-dose lisinopril group. This study extends prior research by demonstrating that the improved clinical outcomes attributable to high ACE inhibitor doses used in clinical trials and incorporated into practice guidelines can be achieved without increasing the overall costs of care.

All studies, even the best designed and most rigorously conducted clinical trials, present challenges regarding generalizability of results to other patients who inherently differ from those enrolled. Economic analyses present additional challenges, resulting from differences across countries in healthcare delivery systems, medical insurance, costs of care, and local practice patterns. The greater variation in medical costs relative to clinical end points makes economic analyses of clinical trials subject to greater type II (beta) errors. The main limitation of this economic analysis is the application of US-specific hospital and drug costs to the clinical and outcome data in the 19-nation ATLAS trial. Therefore, this economic analysis was subject to an extensive series of sensitivity analyses, examining the impact of alternative assumptions on study findings. These sensitivity analyses generally confirmed the findings

across country of enrollment (US, non-US, and all ATLAS enrollees), type of hospital cost (age-dependent primary analysis, Medicare, or managed care) and annual discount rate. The main findings that the reduction in the composite end point of death or hospitalization observed in the high-dose lisinopril group was achieved at no increased overall costs and that heart failure hospitalizations were reduced both in number and costs remained unchanged.

While the question examined in this analysis was specific to ACE inhibitor dose in patients with heart failure, it has potential implications for other medical interventions. The development and dissemination of expert-derived, evidence-based practice guidelines has increased substantially over the past 2 decades. Such practice guidelines are a core strategy to reduce inappropriate practice variation, improve quality, and control costs of medical care. Even though much attention has been devoted to increasing physician adoption of clinical practice guidelines, less attention has been paid to the details of guideline components. For example, professional guidelines often advocate clinical targets (eg, low-density lipoprotein cholesterol [LDL-C] in hyperlipidemia and coronary heart disease; hemoglobin A_{1C} [A_{1C}] in diabetes) or dose targets (eg, ACE inhibitor use in heart failure). Until recently, efforts to improve care have focused on the more general issue of use versus nonuse rather than on the titration to appropriate clinical or dose targets. Drugs such as ACE inhibitors require initiation at lower doses and titration to target doses over time. Many physicians who initiate treatment fail to titrate drugs upward as required. Stakeholders concerned with quality of care increasingly recognize this problem. For example, the National Committee on Quality Assurance (NCQA) Health Employer Data and Information Set (HEDIS) used to measure physician adherence with recommended practices solely on the basis of whether an action was initiated (eg, measurement of LDL-C in coronary heart disease or of A_{1C} in diabetes). New NCQA HEDIS criteria measure the percent of patients achieving target levels of A_{1C} and LDL-C.

The ATLAS trial suggests that efforts to adopt appropriate medical interventions should be accompanied by concomitant attention to the details of use. Use of lisinopril in a dose comparable to that of

Table 4. Mean Total Cost Difference per Patient and 95% Confidence Interval (CI) (US \$) From the Primary Analysis and Sensitivity Analyses Using the Bootstrap Method

	Mean Total Cost Difference (High-Dose Group Low-Dose Group) (95% CI)*
Primary analysis	-875 (-2613 to 884)
Sensitivity analyses	
Medicare hospital costs	-902 (-2665 to 921)
Managed care hospital costs	-1166 (-2746 to 517)
Only US-based ATLAS patients	-248 (-2842 to 2386)
Only heart failure hospitalizations	-738 (-1649 to 151)
5% annual discount rate	-927 (-2514 to 738)

*CI indicates confidence interval.

ACE inhibitors demonstrated effective in other clinical trials was associated with a reduction in the composite end point of death or hospitalization. The observed incremental benefit was modest but real. In such situations, economic analyses are helpful in assessing whether the incremental benefit accrued is worth the incremental cost incurred. This economic analysis demonstrates that for patients with moderate-to-severe left ventricular heart failure, the clinical benefits associated with the recommended lisinopril dose in the ATLAS trial were achieved without increasing net costs. Increased ACE inhibitor costs were offset by savings from reduced heart failure hospitalizations. Use of the recommended ACE inhibitor dose in these patients was both clinically effective and cost effective.

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