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


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Patients with heart failure, classified by the New York Heart Association (NYHA) as falling into Classes II - IV and who had a left ventricular ejection fraction (LVEF) of less than or equal to 30%, were given high-dose (32.5 - 35.0 mg/day) lisinopril therapy. These patients were compared with similar patients receiving low-dose (2.5 - 5.0 mg/day) lisinopril therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised heart failure patients with an LVEF of less than or equal to 30%. Patients were excluded if they had myocardial infarction, unstable angina, coronary revascularisation within the last 2 months, current symptomatic ventricular tachycardia, clinically unstable congestive heart failure, or contraindications to angiotensin-converting enzyme (ACE) inhibitors.

Setting
The setting was secondary care, but it was unclear whether the drugs were administered in a primary or secondary care setting. The economic study was carried out in the USA.

Dates to which data relate
The dates to which the effectiveness and resource evidence related were not given, but the original effectiveness paper was published in 1999. Year 1999 was used for the drug prices.

Source of effectiveness data
The effectiveness data were derived from a single study. The effectiveness results were published in full elsewhere (Packer et al. 1999, see ‘Other Publications of Related Interest’ below for bibliographic details).

Link between effectiveness and cost data
The costing was carried out prospectively on the same patients who provided the effectiveness data.

Study sample
Power calculations were not reported in this paper, nor were details of the sample selection. The ATLAS trial randomised 3,164 patients from 19 countries to either high-dose lisinopril (n=1,568) or low-dose lisinopril (n=1,596) therapy.

**Study design**
This was a multi-centred, randomised controlled trial in which the patients were randomised to either a high or low dose of lisinopril. Seventy per cent of the high-dose groups and 18.0% of the low-dose groups discontinued participation in the trial because of adverse events. Following randomisation, target doses were achieved in 91.3% of the high-dose group and 92.7% of the low-dose group. The duration of follow-up for patients who continued the trial ranged from 39 to 58 months (median 45.7 months). A professional medical record nurse examined the reasons for each hospitalisation and was blinded to the patient's dosage group.

**Analysis of effectiveness**
The basis of the analysis was intention to treat. The patients were shown to be similar at baseline in terms of demographic and heart disease characteristics. The following outcomes were used to evaluate patient health:

- hospitalisation (measured as the number of hospitalisations and the number of hospital days) due to heart failure, other cardiovascular problems and noncardiovascular problems; and
- the probabilities of death and cardiovascular death.

**Effectiveness results**
The mean total hospitalisations were 1.98 (standard deviation, SD=2.62) in the high-dose group and 2.22 (SD=2.88) in the low-dose group, (p=0.014). When broken down into the three categories, the results for the high- and low-dose groups, respectively, were:

- 0.64 (SD=1.51) and 0.80 (SD 1.72) hospitalisations due to heart failure, (p=0.006),
- 0.56 (SD=1.05) and 0.59 (SD=1.14) hospitalisations due to other cardiovascular problems, (p= 0.417), and
- 0.77 (SD=1.38) and 0.83 (SD=1.34) hospitalisations for noncardiovascular problems, (p=0.292).

The mean hospital days per patient were 18.28 (SD=30.07) in the high-dose group and 22.22 (SD=40.00) in the low-dose group, (p=0.002). When broken down into the three categories, the results for the high- and low-dose groups, respectively, were:

- 6.02 (SD=16.48) and 7.45 (SD=20.16) hospital days for heart failure, (p=0.28),
- 4.65 (SD=12.86) and 5.53 (SD=19.55) hospital days for other cardiovascular problems, (p=0.137), and
- 7.61 (SD=18.84) and 9.24 (SD=25.45) hospital days for noncardiovascular problems, (p=0.040).

The number of deaths was lower in the high-dose group than in the low-dose group, (666 versus 717; p=0.128). Similarly, the number of cardiovascular deaths was also lower (583 versus 641; p=0.073).

**Clinical conclusions**
The authors concluded that patients in the high-dose group had better clinical outcomes than the low-dose group, as measured by the degree of hospitalisation and the number of deaths.

**Measure of benefits used in the economic analysis**
No summary measure of benefits was produced. Te authors, in effect, carried out a cost-consequences analysis.
Direct costs
A discount rate of 3% was used. The quantities and the costs were not broken down separately. The costs were broken down into hospital costs, lisinopril costs and open-label ACE inhibitor costs. The hospital costs were broken down into those resulting from heart failure, other cardiovascular problems and noncardiovascular problems. The costs were estimated from actual data. Hospital costs were derived from Medicare (for patient aged 65 years or over) and representative managed care diagnosis-related-group (DRG) reimbursement rates (for patients under 65 years) for a managed care plan at a teaching hospital in Philadelphia USA, which included both physician fees and hospital payments. If patients fell into more than one DRG code, the more expensive one was used. Certain hospitalisations were not included in the cost calculations. For example, those that would not have been reimbursed by Medicare or a managed care plan in the USA, and emergency department visits which did not result in admission as an inpatient.

In the main analysis there was no difference in dosage titration costs between the two groups, as the same number of physician visits was required for both groups. Out-of-hospital death was assigned a cost of $1,000. The cost of ACE inhibitor drugs was based on actual consumption and the US average wholesale price. The costs of non-ACE inhibitor cardiovascular drugs were not included as consumption was similar between the two groups. The price year for the drugs costs was 1999.

Statistical analysis of costs
The 95% confidence interval (CI) for the mean cost-difference was estimated using a nonparametric bootstrap method.

Indirect Costs
No indirect costs were calculated.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were carried out in which:

it was assumed that three additional physician visits occurred in the high-dose groups

a 5% discount rate was used for the costs;

Medicare DRG rates were used for all patients;

managed care DRG rates were used for all patients;

the age-dependent mix of rates was used for US patients only; and

the cost of an out-of-hospital death was varied (assigned a zero value and also the full cost of a heart failure).

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean hospital cost was $16,684 (SD=24,546) in the high-dose group and $18,093 (SD=24,791) in the low-dose group, (p=0.108).

Differences in hospital expenditures were primarily attributable to lower heart failure hospitalisation costs in the high-
dose group:

primary analysis, $5,114 versus $6,361, (p=0.006);

Medicare DRG reimbursement rate, $4,977 versus $6,187, (p=0.006);

managed care DRG reimbursement rate, $5,280 versus $6,560, (p=0.007).

The mean total ACE inhibitor drug cost per patient was $1,368 (SD=706) in the high-dose group and $855 (SD=552) in the low-dose group, (p=0.0001).

The primary bootstrap analysis showed no difference in the mean total cost per patient between the two groups, mean difference -$875 (95% CI: -2,613 - 884).

The discount rate was 3%. The costs were calculated for 5 years after the patients were enrolled in the trial. The costs of adverse effects were included if they satisfied the criteria described earlier.

**Synthesis of costs and benefits**
The costs and benefits were not combined as the study was a cost-consequences analysis.

The conclusion was not changed by sensitivity analyses in which:

- it was assumed that three additional physician visits occurred in the high-dose group;
- a discount rate of 5% was used;
- the reimbursement rates were varied;
- only the data for US patients were used;
- only heart failure hospitalisations were examined; and
- the cost of an out-of-hospital death was varied.

The difference in costs between the two patient groups was not statistically significant.

**Authors’ conclusions**
High-dose lisinopril for patients with Class II - IV New York Heart Association (NYHA) heart failure and a left ventricular ejection fraction (LVEF) of less than or equal to 30% produces better clinical results than low-dose lisinopril, and does not result in higher costs.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator (low-dose lisinopril) was justified by it being in common use. You should decide if it is a widely used practice in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were obtained from a single study, but not all of the effectiveness data were presented in the current paper which focused on the economic aspects of the study. The study design, a randomised controlled trial, was appropriate for the question. As far as can be determined from the information given in the current paper, the study sample was representative of the study population. The patient groups appear to have been comparable at analysis, although statistical tests were not reported. In some ways the analysis of effectiveness was handled credibly, but the authors’ chosen outcome measures appear limited in that measurement was only concerned with hospital and
death. For example, there was no measurement of patients changing their NYHA category and no measurement of quality of life.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefits. The analysis was one of cost-consequences and, therefore, the health benefits are those associated with the effectiveness outcomes.

**Validity of estimate of costs**
> From the cost perspective adopted (i.e. US health care provider), all the relevant categories of costs were included. However, it would have been of interest to have analysed the total hospital costs and not just those qualifying for payment, and to know the non-hospital medical costs. It is difficult to know whether these omissions would have biased the cost results between the two dosages of lisinopril. There was no analysis of informal care, which limits the usefulness of the cost results to decision-makers in other settings.

The costs were not separated from the quantities, which limits the generalisability of the results to other settings. The resource use quantities were obtained from a single study, while the prices were taken from the reimbursement rates of Medicare and from a teaching hospital in Philadelphia. No statistical analyses of either the quantities or prices were carried out. However, some sensitivity analyses were conducted. There was no price year for the hospital costs, which will prevent any future reflation exercises. Discounting was carried out, appropriately, as all the costs were incurred during more than 2 years.

**Other issues**
The authors compared their work with other effectiveness studies but not other economic studies. The issue of generalisability was discussed, but it was not clear that the authors appreciated the limits of applying US prices to resources used and only including resources which were eligible for payment under Medicare and a US medical payment plan. The authors did not present all their results comprehensively. There was an inconsistency between the results given in the 'Introduction' and those given later in the text. There was a lack of detail in the cost results when the authors presented results over time but did not provide any statistical results. The effectiveness results did not adequately describe changes in health outcomes and the cost results were not comprehensive enough.

**Implications of the study**
The authors argued that their study shows an improvement in health outcomes for patients and no increase in costs resulting from patients taking high-dose compared with low-dose lisinopril. However, the data presented in the paper did not support such a strong conclusion.

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**Other publications of related interest**
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