The cost and cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction

Cook J R, Glick H A, Gerth W, Kinosian B, Kostis J B

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
The use of enalapril for the treatment of hypertensive patients with left ventricular dysfunction.

Type of intervention

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients who had either elevated systolic blood pressure (SBP of at least 140 mmHg) or elevated diastolic blood pressure (DBP of at least 90 mmHg).

Setting
The setting of the study was not explicitly stated, but it may have been primary care. The economic study was carried out in the USA.

Dates to which data relate
The dates during which the effectiveness and resource use data were collected were not reported. The price year was 1996.

Source of effectiveness data
The effectiveness evidence came from data extrapolated from a published trial (the Studies of the Left Ventricular Dysfunction, SOLVD), whose design, methods and results were reported in several publications. The SOLVD comprised two trials, the Treatment Trial (TT) and the Prevention Trial (PT). The TT studied patients with overt heart failure requiring treatment with diuretics or digitalis, while the PT studied patients without overt heart failure.

Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations and the method of sample selection were not reported. The study sample comprised a sub-group of 1,917 patients (37.1% with and 62.9% without overt heart failure) involved in the SOLVD. Of these, 957 were in the placebo group (336 in the TT and 621 in the PT) and 960 in the enalapril group (376 in the TT and 584 in the PT). The method used to select the sample in the primary trial was also not reported (see Other Publications of Related Interest).
Study design
This was a double-blind, randomised placebo-controlled trial, which was carried out in several centres in Belgium, Canada and the USA. The methods of randomisation, blinding, and follow-up used in the primary trial were not reported (see Other Publications of Related Interest below). Results of the PT and TT were combined on the basis of a weighted average of the percentages of patients in the two groups.

Analysis of effectiveness
The basis of the analysis of the clinical study used in the primary study was not stated. The health outcomes evaluated in the present study were the relative risk reduction in death, the crude mortality rate, the number-needed-to-treat to prevent one death, and survival. The two groups were comparable at baseline in terms of their demographic and clinical characteristics, including the SBP and DBP.

Effectiveness results
In the combined analysis, the relative risk reduction in death was 18% (95% confidence interval, CI: 2 - 32; p=0.03).

The crude mortality rate was 26.1% for placebo and 21.5% for enalapril.

The number-needed-to-treat to prevent one death was 21.8.

The estimated survival was 2.87 years for enalapril and 2.76 years for placebo. The difference was 0.11 years (95% CI: 0.00 - 0.20).

Clinical conclusions
The effectiveness analysis showed that, compared with placebo, enalapril was effective in improving survival among patients in the treatment and prevention trials.

Modelling
A state-transition model was constructed to project lifetime survival in each of the four New York Heart Association (NYHA) classes. The authors stated that several assumptions were made to project the lifetime outcomes, but these assumptions were not reported.

Measure of benefits used in the economic analysis
The summary benefit measures used in the economic analysis were survival and the quality-adjusted life-years (QALYs). Both were calculated in the trial observation period analysis and lifetime projection analysis. Survival data were derived from the effectiveness study, then entered into the decision model to derive the lifetime results. Utility weights were derived from the Ladder of Life Scale in SOLVD. These were 0.71, 0.62, 0.52 and 0.47, respectively, for NYHA classes 1 to 4. The QALYs and survival were discounted at an annual rate of 5% due to the long time horizon of the analysis (nearly 3 years in the trial observation period analysis and lifetime in the projection analysis). The CIs for survival and QALYs were obtained using the jack-knife method.

Direct costs
A 5% discount rate was used since the lifetime costs were evaluated. The unit costs were not analysed separately from the quantities of resources used. The health services included in the economic evaluation were enalapril, hospitalisation (due to heart failure, angina, myocardial infarction and other cardiovascular diseases), death outside of the hospital, and ambulatory care. The cost/resource boundary adopted was not explicitly stated.

Resource use was estimated using data derived from the clinical trial that provided the effectiveness evidence. The hospital costs were estimated by multiplying the diagnosis-related group weight for each hospitalisation type by the
average federal reimbursement rate, which excluded adjustments made by the Health Care Financing Administration (HCFA) for capital expenditures, free care and medical education. The physician fees were derived from Medicare rates. The cost of a death outside of the hospital was based on an earlier study. The cost of ambulatory services was derived using data from the HCFA. The cost of enalapril was derived from the federal supply schedule price list, and an extra dispensing fee was added. The price year was 1996.

**Statistical analysis of costs**
The jack-knife method was used to construct CIs for the costs of the intervention.

**Indirect Costs**
The indirect costs were not included in the economic analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were conducted to evaluate the impact of variance on the estimated costs and benefits in the lifetime projection analysis. The variables investigated were the discount rate (2% and 7%), drug prices (retail prices) and hospitalisation costs (Medicare reimbursement rate that included adjustments made by the HCFA for capital expenditures, free care and medical education).

**Estimated benefits used in the economic analysis**
In the trial observation period analysis, the estimated survival was 2.87 years for enalapril and 2.76 years for placebo, as observed in the effectiveness study. The estimated QALYs were 1.87 with enalapril and 1.78 with placebo. The difference was 0.09 QALYs (95% CI: 0.02 - 0.16).

In the lifetime projection analysis, the estimated survival was 7.06 years for enalapril and 5.98 years for placebo. The difference was 1.08 years (95% CI: 0.04 - 2.12). The estimated QALYs were 4.60 with enalapril and 3.87 with placebo. The difference was 0.74 QALYs (95% CI: 0.02 - 1.44).

**Cost results**
The estimated total costs in the trial observation period analysis were $9,555 with enalapril and $11,211 with placebo. The difference was -$1,656 (95% CI: -3,502 - 191). The corresponding costs in the lifetime projection analysis were $24,090 (enalapril) and $25,546 (placebo), respectively. The difference was -$1,456 (95% CI: -12,527 - 9,243).

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was conducted to combine the costs and benefits. However, a cost-effectiveness ratio was not actually calculated because enalapril was dominant (more effective and less costly) in the base-case in both analyses (trial observation period and lifetime projection).

The cost-effectiveness acceptability curve showed that there was a less than 10% probability that enalapril treatment would increase the costs in comparison with placebo. In addition, there was a less than 3% probability that the cost per life-year gained would exceed $3,000 in the trial observation period analysis. In the lifetime projection analysis, the probability that enalapril dominated placebo was 0.94.

Enalapril remained dominant in most of the variations investigated in the sensitivity analyses.
Authors' conclusions
Treatment with enalapril was highly cost-effective because it improved (quality-adjusted) survival and was very likely to reduce the costs, even under lifetime scenarios.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected because the standard approach was usual therapy, while enalapril represented an adjunctive treatment. However, the authors did not explicitly define 'usual therapy'. You should decide whether it represents an appropriate comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a selection of specific data from a randomised, double-blind, placebo-controlled trial, which ensures a high internal validity of the source of evidence. However, the trial was published elsewhere and most of the methods were not reported in the present article. The study sample appears to have been representative of the study population, but the authors acknowledged that patients with uncontrolled hypertension were under-represented in the analysis. The authors noted that the original trial was not designed to study the impact of enalapril on hypertension on the sub-set of patients selected in the present study.

Validity of estimate of measure of benefit
Survival and QALYs were used as the summary benefit measures in the economic analysis. The authors reported the utility weights that had been estimated in a prior, published study. Appropriate discounting was performed. The use of QALYs and survival allows the benefits of the present study to be compared with those of other interventions.

Validity of estimate of costs
The perspective adopted in the study was not correctly classified. The authors stated that the costs relevant to society were evaluated, but indirect costs were not included in the analysis. Productivity losses did not represent a substantial cost component in the study population, nevertheless, it appears that the perspective has been misclassified. Most of the cost categories were relevant to the third-party payer. The unit costs and the quantities of resources used were not analysed separately, but data on the rates of hospitalisation were provided. The price year was reported, thus making reflation exercises in other settings easy. However, the cost estimates were specific to the study setting although sensitivity analyses were carried out on hospitalisation and drug costs. The CIs for the total costs were reported. A breakdown of the costs was provided.

Other issues
The authors stated that their findings were consistent with the results of an earlier study that analysed the cost-effectiveness of angiotensin-converting enzyme inhibitors. However, the authors did not address the issue of the generalisability of the study results to other settings. Few sensitivity analyses were conducted, but the aim of these was not to deal with different estimates reported in other settings. The authors noted some limitations of their analysis. For example, the fact that the economic evaluation was carried out retrospectively on data that were not explicitly designed to evaluate economic outcomes.

Implications of the study
The study results suggested that enalapril should be recommended for treatment and prevention in hypertensive patients with an indication for heart failure.

Source of funding
Partially supported by an Oak Ridge Institute for Science and Education fellowship.
Bibliographic details

PubMedID
9880125

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Cost-Benefit Analysis; Double-Blind Method; Enalapril /therapeutic use; Female; Health Care Costs; Hospitalization; Humans; Hypertension /drug therapy /physiopathology; Male; Ventricular Dysfunction, Left /drug therapy

AccessionNumber
21999000139

Date bibliographic record published
31/01/2004

Date abstract record published
31/01/2004