An economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events due to diabetes mellitus

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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 ramipril (Tritace), an angiotensin-converting enzyme inhibitor, for the prevention of cardiovascular disease (CVD) in patients with Type II diabetes mellitus. The dose of ramipril was 10 mg once daily.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with Type II diabetes who were at risk of CVD.

Setting
The setting was primary and secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were derived from a study published in 2000. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the main details of which had already been published, and from some authors' assumptions.

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

Study sample
Limited information on the method of sample selection was reported. A total group of 3,557 patients was included in the study. The mean age of the sample was 66 years.

Study design
This was a prospective, randomised, double-blind, placebo-controlled trial that was conducted in several centres. The length of follow-up was 5 years. Further information on the study design was not provided.
Analysis of effectiveness
The primary outcome measure used in the analysis was all-cause mortality. Other clinical end points were the rates of myocardial infarction, stroke, revascularisation, overt nephropathy, congestive heart failure, transient ischaemic attack, and worsening angina. The life expectancy for survivors at the end of the trial, which was calculated using the declining exponential approximation of life expectancy (DEALE) method, was also estimated.

Effectiveness results
The rates of all-cause mortality were 0.1084 with ramipril and 0.1402 with placebo. The difference was -0.0318 (95% confidence interval, CI: -0.0534 - -0.0102).

The rates of myocardial infarction were 0.1023 with ramipril and 0.1295 with placebo. The difference was -0.0271 (95% CI: -0.0481 - -0.0062).

The rates of stroke were 0.0420 with ramipril and 0.0611 with placebo. The difference was -0.0190 (95% CI: -0.0335 - -0.0045).

The rates of revascularisation were 0.1405 with ramipril and 0.1645 with placebo. The difference was -0.0240 (95% CI: -0.0476 - -0.0005).

The rates of overt nephropathy were 0.0647 with ramipril and 0.0842 with placebo. The difference was -0.0195 (95% CI: -0.0367 - -0.0023).

The rates of congestive heart failure were 0.1095 with ramipril and 0.1334 with placebo. The difference was -0.0239 (95% CI: -0.0453 - -0.0025).

The rates of transient ischaemic attack were 0.0442 with ramipril and 0.0588 with placebo. The difference was -0.0145 (95% CI: -0.0290 - -0.0001).

The rates of worsening angina were 0.2008 with ramipril and 0.2244 with placebo. The difference was -0.0236 (95% CI: -0.0505 - -0.0032).

The estimated life expectancy for survivors at the end of the trial was 5.56 years (range: 5.15 - 6).

Clinical conclusions
The effectiveness study showed that ramipril was more effective than placebo in significantly reducing the mortality rate. The probabilities of CVD events were used to calculate the costs.

Methods used to derive estimates of effectiveness
The authors made some assumptions due to the lack of patient-level data from the trial.

Estimates of effectiveness and key assumptions
The calculation of survival using the DEALE method assumed a constant risk of death per unit time. It was also assumed that patients surviving the trial period had the standard life expectancy for a patient with diabetes.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected life expectancy beyond the trial period. An annual discount rate of 6% was applied to the benefits. Both discounted and undiscounted results were presented.

Direct costs
An annual rate of 6% was applied in order to discount the costs, which were incurred during more than 2 years. Both
undiscounted and discounted results were presented. The unit costs were presented separately from the quantities of resources used, but a detailed breakdown of the cost items was not provided. The health services included in the economic evaluation were drugs and treatment of specific conditions (myocardial infarction, stroke, revascularisation, overt nephropathy, congestive heart failure, transient ischaemic attack, and worsening angina). The cost/resource boundary of the study was that of the NHS. The rates of events considered in the economic analysis and drug usage were derived from trial data. The costs were estimated from NHS sources. The price year was 2000.

Statistical analysis of costs
The costs were treated deterministically and were presented as mean values with interquartile ranges.

Indirect Costs
The indirect costs were not considered.

Currency
UK pounds sterling (£).

Sensitivity analysis
Sensitivity analyses were conducted to investigate variability in the data. Best- and worst-case scenarios were considered. Sensitivity analyses on the timing of the occurrence of clinical events within the year of the trial that they occurred, were also carried out.

Estimated benefits used in the economic analysis
The estimated undiscounted life expectancy was 9.65 years with ramipril and 9.39 years with placebo (difference 0.27 years).

The estimated discounted life expectancy was 7.46 years with ramipril and 7.27 years with placebo (difference 0.19 years).

Cost results
The estimated undiscounted cost per patient was 1,623 with ramipril and 980 with placebo (difference 642).

The estimated discounted cost per patient was 1,452 with ramipril and 875 with placebo (difference 576).

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER) was calculated to combine the costs and benefits of ramipril over placebo.

The incremental cost per additional life-year saved was 2,395 (undiscounted 2,971).

The estimated ICER was robust to the variations considered in the sensitivity analyses. It ranged from a minimum of 1,954 to a maximum of 2,964 (undiscounted values).

Authors' conclusions
The use of ramipril to prevent cardiovascular disease (CVD) in patients with Type II diabetes proved to be a cost-effective treatment. The cost-effectiveness ratio was well below the recommended threshold values for funding new health interventions in the UK.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected in order to assess the active value of ramipril. Further, placebo was the comparator of choice in the trial that provided the evidence. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The basis of the analysis of effectiveness was a prospective randomised trial, which was appropriate for the study question. However, only limited details of the design and method of the primary study, which was published in a separate paper, were reported. Consequently, it was difficult to assess the internal validity of the study. However, the design of the study appears to have been robust due to randomisation and blind assessment of the outcome.

Validity of estimate of measure of benefit
Survival was used as the summary benefit measure. It appears to have been appropriate, not only because it appropriately reflected the impact of the treatment on patient health, but also because it facilitates comparisons with the benefits of other health care interventions. Both discounted and undiscounted results were presented. The impact of the treatment on quality of life was not assessed.

Validity of estimate of costs
The authors stated explicitly the perspective that was adopted in the study. It appears that all the relevant categories of costs were included in the analysis. Few details on the method used to calculate the costs were provided, and a breakdown of all the categories of costs included in the analysis was not given. The source of the cost data reflected the perspective of the study and the price year was implicitly reported. The costs were treated deterministically, but all the cost estimates were varied within reasonable ranges to account for variability and uncertainty in the data. Discounting was relevant and was performed.

Other issues
The authors did not compare their findings with those from other studies. They implicitly addressed the issue of the generalisability of the study results to other settings by performing extensive sensitivity analyses. The results of the main analysis and of the sensitivity analyses were presented satisfactorily and this, to some extent, enhanced the external validity of the analysis. The study referred to patients with Type II diabetes and at risk of CVD, and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggested that ramipril could represent an efficient use of NHS resources.

Source of funding
None stated.

Bibliographic details

Other publications of related interest

Backhouse ME, Richter A, Gaffney L. Economic evaluation of ramipril in the treatment of patients at high risk of

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Cardiovascular Diseases /prevention & control; Cost-Benefit Analysis; Diabetes Mellitus /therapy; Diabetic Angiopathies /prevention & control; Ramipril /economics; Risk Factors

**AccessionNumber**
22002008068

**Date bibliographic record published**
30/11/2004

**Date abstract record published**
30/11/2004