Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events

Backhouse M E, Richter A, Gaffney L

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
Oral ramipril (10 mg once per day) was compared with placebo (“conventional practice”) in patients at high cardiovascular risk.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients at high cardiovascular risk, but without left ventricular dysfunction or heart failure.

Setting
The setting was secondary care. The economic evaluation was carried out in the UK.

Dates to which data relate
The effectiveness evidence was derived from the HOPE trial, published in 2000 (see Other Publications of Related Interest). The costs of cardiovascular events were derived from NHS Reference Costs published in 1999. The price year was 1998/1999.

Source of effectiveness data
The effectiveness data were derived from a single published study.

Modelling
A simple clinical decision analysis model was constructed to estimate the long-term benefits and costs of ramipril. The life expectancy was extrapolated beyond the 5 years’ trial results, using the declining exponential approximation of life expectancy (DEALE) method.

Outcomes assessed in the review
The outcomes assessed were the probabilities of the following cardiovascular disease (CVD) events at 5 years:

all-cause mortality,
myocardial infarction,

stroke,

unstable angina,

congestive heart failure,

cardiac arrest,

revascularisation (percutaneous transluminal coronary angiography, PTCA),

other diabetic complications, and

post-trial average life expectancy.

**Study designs and other criteria for inclusion in the review**
The only source of effectiveness evidence was the HOPE trial, a randomised controlled trial.

**Sources searched to identify primary studies**
Not applicable.

**Criteria used to ensure the validity of primary studies**
Not applicable.

**Methods used to judge relevance and validity, and for extracting data**
Not applicable.

**Number of primary studies included**
One study, the HOPE trial, was included.

**Methods of combining primary studies**
Not applicable.

**Investigation of differences between primary studies**
Not applicable.

**Results of the review**
The absolute differences between placebo and ramipril, which were used in the model, were:

- for all-cause mortality, 0.0185 (95% confidence interval, CI: 0.0057 - 0.0314); at 5 years, mortality was 12.23% in the placebo group and 10.38% in the ramipril group;

- for myocardial infarction, 0.0237 (95% CI: 0.0110 - 0.0365);

- for stroke, 0.0150 (95% CI: 0.0069 - 0.0231);

- for unstable angina, 0.0022 (95% CI: -0.0110 - 0.0154);
for congestive heart failure, 0.0040 (95% CI: -0.0032 - 0.0112);
for cardiac arrest, 0.0047 (95% CI: 0.0006 - 0.0088);
for revascularisation (PTCA), 0.0234 (95% CI: 0.0081 - 0.0387);
for other diabetic complications, 0.0177 (95% CI: 0.0013 - 0.0221); and
for post-trial average life expectancy, 5.89 years (95% CI: 5.64 - 6.14 using the DEALE method, mean baseline age 66).

Methods used to derive estimates of effectiveness
The authors made assumptions to derive estimates of effectiveness.

Estimates of effectiveness and key assumptions
To express the results in life-years (LYs) saved for all life expectancy, estimates of effectiveness were based on two components. First, the LYs saved during the trial were estimated from 5-year trial data, assuming that the deaths observed in each treatment group were distributed according to a constant mortality rate. Second, for the long-term prognosis, it was assumed that the beyond-trial prognosis of ramipril and placebo patients was identical. The LYs saved were estimated using the DEALE method.

Measure of benefits used in the economic analysis
The measure of benefit used was the LYs gained. These were derived from 5-year trial data by applying the DEALE method. The LYs were discounted at a rate of 6%, as recommended by the UK treasury.

Direct costs
The direct costs of the health service were evaluated. These included major CVD events that would require hospitalisation (episode of care) and drug costs. An episode of care accounted for the full period of treatment for that event, as well as all items of resource use within a hospital. The drug costs covered ramipril tablets, monitoring, and patient death. Resource use took the CVD event rates from the HOPE trial published in 2000 (see Other Publications of Related Interest) and the average cost of each event from NHS Reference Costs (1999) into consideration. The authors excluded post-event ongoing costs, as well as the treatment costs of future events beyond the trial period. It was assumed that the event costs were the same regardless of the treatment group, as were the number of CVD events after the end of the trial (the additional events of more survivors with ramipril were assumed to be offset by the slightly lower post-trial event rate of survivors in the ramipril group).

The quantities and the costs were reported separately. The price year was 1998/1999. Discounting was carried out at a rate of 6%, as recommended by the UK treasury, which was relevant because of the long-term time horizon of the study. To apply discounting, the authors assumed that the CVD events were uniformly distributed over the 5-year period and occurred in the middle of the year.

Statistical analysis of costs
The resources used and unit costs were treated deterministically. Average values were used for the base-case analysis. The ranges used for the sensitivity analysis were 95% CIs for CVD event rates and interquartile ranges (IQR) for NHS trusts.

Indirect Costs
The authors specifically excluded this cost category. This was appropriate for the perspective adopted in the study.
Currency
UK pounds sterling ( £ ).

Sensitivity analysis
Sensitivity analyses were carried out to explore uncertainty in the effectiveness and costs, as well as in model assumptions.

Best- and worst-case scenarios were evaluated using the most favourable or unfavourable possibilities on mortality differences, event rates and unit costs. The limits of the 95% CIs or IQRs were used. Uncertainties surrounding estimates derived by the DEALE method were evaluated by deriving the cost-effectiveness results for different age groups (using the age range based on the 95% CI of patients included in the HOPE trial). Different scenarios, where the events and costs occurred at different times during each year (beginning or end), were evaluated.

Estimated benefits used in the economic analysis
The base-case analysis showed that ramipril conferred 0.1565 incremental undiscounted LYs (10.0173 ramipril and 9.8608 placebo) and 0.1115 incremental discounted LYs (7.6806 ramipril and 7.5691 placebo).

Cost results
The expected undiscounted cost per patient was 1,595 with ramipril and 905 with placebo. When discounting was applied, these costs were 1,426 (ramipril) and 808 (placebo), respectively.

The incremental costs of ramipril were 690 (undiscounted) and 618 (discounted).

Synthesis of costs and benefits
The base-case analysis showed a discounted incremental cost-effectiveness ratio (ICER) of 5,544 per LY. The corresponding undiscounted ICER was 4,406 per LY.

The ICERs did not vary substantially with the timing of the events (assuming the events occurred at the beginning or at the end of each year). The reductions or increases in the discounted ICERs were modest (8 to 9%).

The best-case scenario (lower CI 95% limits for mortality and CVD events, upper event cost estimates) yielded a discounted ICER of 5,131 per LY (3,967 per LY undiscounted. The worst-case scenario (upper CI 95% limits for mortality and CVD events, lower event costs) yielded a discounted ICER of 6,215 per LY (5,087 per LY undiscounted).

The results were somewhat sensitive to the assumptions made about post-trial life expectancy. The ICER declined by about 10% as post-trial survival was increased one year, and vice versa. The results were also particularly sensitive to the patient age group. The undiscounted ICER was 2,814 for 52-year-olds and 10,291 for 80-year-olds.

Authors' conclusions
The study's base-case estimate of cost-effectiveness suggested that treating patients at high cardiovascular risk with ramipril is likely to be a good investment for the National Health Service.

CRD COMMENTARY - Selection of comparators
The authors used a placebo as a comparator to the active drug. They referred to it as conventional treatment. Other angiotensin-converting enzyme inhibitors, which may have a class effect, were not included. You should judge if this is relevant in your own setting.

Validity of estimate of measure of effectiveness
A statistical model was used to derive the life expectancy following treatment with ramipril and placebo, using data from a single trial. As a secondary source, the methods of the trial were not reported. The authors made two major assumptions upon which the DEALE method was applied (see Estimates of Effectiveness and Key Assumptions). You should judge if these assumptions are appropriate.

**Validity of estimate of measure of benefit**
The LYs gained were derived from trial data and the patients’ baseline age, using the DEALE method and alternative assumptions about post-trial survival. The influence of these on the results was tested, making the study more robust.

**Validity of estimate of costs**
The authors reported that the study had been conducted from the perspective of the NHS. While some cost events were not included (e.g. the cost of treating patients beyond the episode of care, community care), the authors did include the "big ticket" figure of hospital event costs. These exclusions, as the authors stated, are probably conservative and will bias the results against ramipril. Although revascularisations were included, the authors only considered angioplasty. The reason for excluding bypass surgery was not stated. The authors stated that it was not possible to validate their assumption, that the number of CVD events after the end of the trial was the same regardless of treatment group, without longer-term data.

The quantities and the costs were reported separately and the price year was reported. This aids the transferability of the results. Event rates and practice patterns, such as PTCA use, were taken from the HOPE trial. Some of these may vary widely in different settings, giving variable effects on the results according to local clinical practice patterns. Nevertheless, a sensitivity analysis was undertaken on the quantities using appropriate ranges. This strengthened the study results and conclusions.

**Other issues**
The authors did not compare their results with similar studies on the subject, although they did compare their results with the cost-effectiveness of other technologies recommended in the UK. The authors addressed the issue of the generalisability of the results to other settings by evaluating effectiveness, baseline age, and cost ranges in the sensitivity analyses. The authors reported and addressed a number of limitations to their study. For example, being unable to access trial primary data, not taking quality of life issues into consideration, and the long-term extrapolation uncertainty. They also addressed issues relating to the method chosen for the estimation of life expectancy.

**Implications of the study**
Although the interpretation of the costs per LY saved estimated from this study will ultimately depend on the cost that the NHS is willing to pay for health benefits, the results of this study suggested that ramipril is potentially a cost-effective use of NHS resources. Future studies could help to refine the assessment of the longer-term effects, costs and quality of life effects of ramipril in this high-risk population.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**
Indexing Status
Subject indexing assigned by CRD

MeSH
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