Cost effectiveness of ramipril treatment for cardiovascular risk reduction

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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 angiotensin-converting enzyme inhibitor ramipril was compared with placebo for the treatment of patients with different risk of cardiovascular death.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The cost-effectiveness of ramipril was evaluated in three hypothetical cohorts of 66-year-old males from the UK. These were:

a low-risk group (annual mortality rate 1%) similar to that of primary prevention studies;

a moderate-risk group similar to the HOPE study (whose placebo group had an annual mortality rate of 2.44%); and

a high-risk group (annual mortality 4.5%).

A very high-risk population (7% annual mortality) was also modelled.

Setting
The setting is likely to have been primary care. The economic study was carried out in the UK.

Dates to which data relate
Data on the effectiveness of ramipril were taken from the HOPE trial (2000). The definition of different risk groups and disease prevalence was taken from other studies (1994 to 1999). Actuarial data for modelling the UK population were from 1998. Resource use data were derived from the results of the HOPE trial and UK practices (1995). The price year was 2000 for the drugs and 1999 for cardiovascular events.

Source of effectiveness data
Although the effectiveness of ramipril was estimated from the HOPE trial, data from other published sources were used to construct the model in the different risk groups.

Modelling
The model attempted to represent the UK population of 66-year-old males (mean age of HOPE study participants). Using actuarial data from the UK population, the net gain (in life-years) was calculated for each risk cohort with
ramipril, using the life table method. The primary analysis was to evaluate the net cost-effectiveness with 5-, 10-, 15- and 20-year (lifetime) ramipril treatment assuming continued benefit.

**Outcomes assessed in the review**

The outcomes assessed in the review were:

- the annual probability of death for men in the UK and in the different risk groups;
- the relative reduction in mortality by ramipril; and
- the reduction in myocardial infarction, revascularisation and stroke.

**Study designs and other criteria for inclusion in the review**

The effectiveness of ramipril was based on the HOPE trial, a multi-centre randomised placebo-controlled trial. To select pretreatment cardiovascular risks required to evaluate the cost-effectiveness in other groups, trials of primary prevention (WOSCOPS) and in high-risk patients (ISIS-2) were used.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

Not reported.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

The effectiveness data were obtained from a single study (the HOPE trial). Other published sources were used to build the model (7 studies).

**Methods of combining primary studies**

A narrative method was used to combine the studies.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The base-case group (medium risk, based on the HOPE trial) had an annual mortality rate 1.31 times greater than that of men aged 56 to 69 years in the UK. The low-risk group had a mortality rate of 0.54 and the high-risk group a mortality rate of 2.4.

With ramipril, the relative risk of all-cause mortality was 0.84. It was assumed to be the same in all cohorts.

The rate of myocardial infarction was reduced from 12 to 9.8%, (p=0.0005), after taking ramipril. The rate of revascularisation decreased from 18.4 to 16.0%, (p=0.0013). The rate of stroke changed from 4.8 to 3.3%, (p=0.0002).
Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The authors assumed that the benefit of ramipril was accrued during the whole time horizon taken and was constant for life, and that ramipril was equally effective in all patients. The ratio of the mortality risk that was applied to the UK population, to calculate each cohort life expectancy, was assumed to remain constant for life.

Measure of benefits used in the economic analysis
The measure of benefit was the life-years gained (LYG). These were derived from the decision model. It was unclear whether future life-years were discounted.

Direct costs
The authors reported both undiscounted results and those using a 6% discount rate. The unit costs and the quantities of resources used were not presented separately. The perspective adopted was that of the UK health care provider. The costs estimated were for drug treatment, myocardial infarctions, revascularisation procedures (angioplasty and bypass surgery), and other coronary disease-related admissions for unstable angina and heart failure. The costs and quantities were estimated through modelling. The quantity and cost data was obtained from local data published from 1999 to 2000. The price year was 1999 to 2000. Although additional physician consultation, pharmacy handling costs and the need for extra serum electrolyte measurement may raise the total drug costs, the authors appear to have excluded these since their effect is small relative to the drug price.

Statistical analysis of costs
The costs were treated deterministically and were derived by modelling.

Indirect Costs
The indirect costs were not included.

Currency
UK pounds sterling (£).

Sensitivity analysis
Different one-way sensitivity analyses were carried out. These varied the drug treatment prices and cost-savings (arising from reductions in events) between 50 and 200% of the baseline values, based on authors' assumptions.

Estimated benefits used in the economic analysis
In the base-case analysis of the medium-risk group and a total eligible population of at least 3,000,000 patients, the model predicted 12,000 lives gained per year. For the ischaemic heart disease population, estimated at 1,400,000 eligible patients, 5,600 lives were gained per year. The corresponding figures were 600,000 (eligible population) and 2,400 (lives saved) for stroke, 1,700,000 (eligible population) and 6,800 (lives saved) for diabetes, and 1,000,000 (eligible population) and 4,000 (lives saved) for peripheral vascular disease. Side effects were not considered.

Cost results
In the base-case analysis of the medium-risk group and a total eligible population of at least 3,000,000 patients, the model predicted an increase in NHS drug costs of 500 million. However, the total net costs would increase by an additional 360 million/year due to reductions in health care use.
For the ischaemic heart disease population (1,400,000 eligible patients), the net cost would be 166 million/year (drug costs 240 million). The corresponding figures were 100 million/year (drug costs 102 million) for stroke (600,000 eligible patients), 144 million/year (drug costs 288 million) for diabetes (1,700,000 patients eligible) and 180 million/year (drug costs 180 million) for peripheral vascular disease (1,000,000 patients eligible).

The costs of side effects were not considered.

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of ramipril relative to placebo. In the medium-risk group, the 5-year undiscounted cost-effectiveness was 13,600 per LYG. With lifetime therapy (20-year horizon), the cost per LYG decreased to 1,900.

Applying a 6% discount rate, the corresponding figures were 14,700 (5 years) and 2,800 (lifetime treatment), respectively.

The cost-effectiveness figures were 36,000 (5 years) and 5,300 (lifetime therapy) per LYG in the low-risk group, and 4,000 (5 years) and 100 (lifetime therapy) per LYG in the high-risk group.

In the highest risk sub-group (7% annual mortality), the cost-effectiveness was 1,300 per LYG at 5 years, and -900 per LYG over 20 years (cost-saving).

Besides pretreatment risk, the drug cost was the other major cost-effectiveness determinant. For example, varying the drug costs between 50 and 200% of the initial values altered the lifetime cost-effectiveness from 400 to 4,900 per LYG in the medium-risk group (HOPE study population). For changing the cost-savings in the same range, the lifetime cost-effectiveness varied from 900 to 2,500 per LYG.

When the authors changed the assumption of sustained ramipril benefit and limited it to 5 years in the medium-risk group, the cost-effectiveness over 5 to 20 years remained stable at 12,000 and 13,000 per LYG.

**Authors’ conclusions**

Ramipril is a cost-effective treatment for cardiovascular risk reduction in patients at high, medium and low pretreatment risk, with a cost-effectiveness ratio comparable to statins.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparator was not explicitly justified, but it was implicitly justified. In the HOPE trial, the comparator was a placebo, which was selected so that the value of active treatment could be evaluated versus no treatment. You should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature was carried out. The data on ramipril effectiveness were obtained from a single, well-conducted multi-centre randomised trial. However, details on the main study were not reported and the methods used to identify other relevant primary studies were not discussed. It is therefore difficult to assess the internal validity of the effectiveness analysis.

**Validity of estimate of measure of benefit**

The estimation of ramipril benefit against no treatment measured in LYG was extrapolated using a life table model applied to the UK population. Details of the model were not provided. It was unclear whether the future benefits were discounted.

**Validity of estimate of costs**
Some cost categories relevant to the perspective adopted were excluded, more specifically, the costs of additional physician consultation, pharmacy handling and extra serum electrolytes. The authors stated that these costs had a small effect compared with the drug price. The savings excluded, which may underestimate the cost-effectiveness of ramipril, were the reduction of diabetes and overt nephropathy incidence. The costs and the quantities were not reported separately.

It was unclear from the paper whether the authors used a fixed incidence of events requiring resource use (e.g. myocardial infarction in the different risk groups), as the incidence of events was expected to be different among subgroups. Resource use data were taken from HOPE trial and from literature on current UK practice. A sensitivity analysis on the quantities does not seem to have been performed. However, a sensitivity analysis was conducted on the total costs. No statistical analysis of the costs or quantities was performed. The prices were taken from published sources and the cost date was unclear.

Other issues
The authors did not report the estimation of LYs for each strategy. The costs estimated for each of the strategies compared were not reported. Only the incremental costs of the ramipril strategy compared with placebo were reported. The authors seem to have evaluated only the point estimate of the relative risk reduction in mortality with ramipril. Therefore, the uncertainty related to this parameter is not reflected. This parameter uncertainty would increase the uncertainty around the cost-effectiveness ratio. The authors compared their results with studies of other health technologies to evaluate their relative cost-effectiveness.

Generalisability to other groups was addressed by including populations of different pretreatment risk in the analyses. However, the authors stated that generalisability to non-UK settings might be limited. The authors discussed and tested whether extrapolating the HOPE study results, assuming persistent versus medium-term benefit, altered the results. Other limitations of the study were highlighted. For example, mortality was a secondary end point in the HOPE trial and the relative risk reduction with ramipril was assumed to be equal in all sub-groups. Also, the cost-effectiveness could have been underestimated, as 30% of the patients in the HOPE trial were non-compliant or withdrew from treatment.

Implications of the study
According to the authors, this study presented a conservative estimate of the cost-effectiveness of ramipril and showed that ramipril is cost-effective in patients with proven vascular disease or diabetes mellitus plus an additional risk factor. Even in patients in the lower risk category, this study suggested that lifelong treatment with ramipril costs well below 25,000 per LYG, a standard below which treatment is generally considered acceptable. Implementing ramipril treatment in a medium-risk population would result in a major reduction in cardiovascular deaths, but would increase annual NHS spending by 360 million.

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