Clinical and economic benefits of ramipril: an Australian analysis of the HOPE study

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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 addition of ramipril (10 mg/day) to standard therapy, for the prevention of cardiovascular events in an at-risk population, was examined. Standard therapy included aspirin, cholesterol-lowering agents, beta-blockers, diuretics, calcium-channel blockers and oral hypoglycaemic agents.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a cohort of people aged 55 years and older with a history of coronary artery disease, stroke or peripheral artery disease, or diabetes, with at least one other cardiovascular risk factor. Cardiovascular risk factors included hypertension, elevated total cholesterol or low high-density lipoprotein cholesterol levels, cigarette smoking, or documented micro-albuminuria. People with heart failure or known compromised ejection fraction (< 40%) were excluded from the trial.

Setting
The setting is likely to have been secondary care. The economic study was conducted in Australia.

Dates to which data relate
The effectiveness evidence and some resource use data were derived from a study published in 2000. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

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

Study sample
Limited information on the primary study was reported, as most of the details had been published elsewhere. There were 4,645 patients in the ramipril group and 4,652 patients in the control group.
Study design
This was a prospective, randomised, double-blinded clinical trial that was conducted in multiple centres. The length of follow-up was 5 years. Other details of the design of the trial were not reported.

Analysis of effectiveness
The outcome measure used in the analysis was a composite end point of cardiovascular death, myocardial infarction (MI) and stroke. These outcomes were also analysed separately. The rate of revascularisation procedures was also reported as a secondary outcome.

Effectiveness results
The rate of cardiovascular death, MI and stroke was 14% in the ramipril group and 17.8% in the control group. The relative risk (RR) was 0.78 (95% confidence interval, CI: 0.70 - 0.86) and the number-needed-to-treat (NNT) was 26 (95% CI: 19 - 43), (p<0.001).

The rates of MI were 9.9% (ramipril) and 12.3% (control), respectively, with an RR of 0.80 (95% CI: 0.70 - 0.90) and an NNT of 42 (95% CI: 27 - 91), (p<0.001).

The rates of stroke were 3.4% (ramipril) and 4.9% (control), respectively, with an RR of 0.68 (95% CI: 0.56 - 0.84) and an NNT of 67 (95% CI: 43 - 143), (p<0.001).

The rates of cardiovascular-related deaths were 6.1% (ramipril) and 8.1% (control), respectively, with an RR of 0.74 (95% CI: 0.64 - 0.87) and an NNT of 49 (95% CI: 33 - 100), (p<0.001).

The rates of revascularisation procedures were 16% (ramipril) and 18.3% (control), respectively, with an RR of 0.85 (95% CI: 0.77 - 0.94) and an NNT of 43 (95% CI: 26 - 125), (p=0.002).

Clinical conclusions
The effectiveness analysis showed that ramipril added to standard therapy for the prevention of cardiovascular events was more effective than standard therapy alone.

Measure of benefits used in the economic analysis
The summary benefit measure was the number of life-years saved (LYS) with ramipril over standard therapy. This was obtained from the reduction in clinical outcomes estimated in the effectiveness analysis. The authors described the formula used to assess it. An annual discount rate of 3% was used. The LYS were calculated in the population of eligible Australian patients (i.e. 615,623 individuals). The number of events avoided in the Australian cohort if all HOPE patients were treated with ramipril was also calculated.

Direct costs
Discounting was relevant, as the costs were incurred during a 5-year period, and an annual rate of 5% was applied. The unit costs were not presented separately from the quantities of resources used and a detailed breakdown of cost categories was not provided. The health services included in the economic evaluation were ramipril therapy (prescription and pathology testing), management of MI and stroke (including acute and rehabilitation services), and revascularisation procedures. Reductions in the use of other drugs were also considered. The cost/resource boundary of the third-party payer appears to have been adopted. Resource use was estimated using the rates derived from the HOPE study and from authors’ assumptions. The costs were estimated from national sources such as the Schedule of Pharmaceutical Benefits, Medicare Benefits Schedule Book, and National Hospital Cost Data Collection. The costs were inflated to current prices using the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Australian dollars (Aus$).

**Sensitivity analysis**
Sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios to variations in the baseline parameters. A Monte Carlo simulation was performed to estimate the CIs around the point estimate of the cost-effectiveness ratio. The most appropriate probabilistic distributions and CIs were attributed to each parameter. Univariate analyses were also conducted. The variation of the parameters with the greatest impact was displayed in a tornado diagram.

**Estimated benefits used in the economic analysis**
The actual number of LYS was not reported. The number of events avoided in the Australian cohort if all HOPE patients were treated with ramipril over a 5-year period was:

- 9,188 (95% CI: 4,305 - 14,317) for stroke,
- 14,658 (95% CI: 6,765 - 22,801) for MI,
- 14,317 (95% CI: 4,925 - 23,678) for revascularisation procedures, and
- 12,534 (95% CI: 6,156 - 18,655) for cardiovascular-related deaths.

**Cost results**
The estimated total costs were not reported.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was conducted to combine the costs and benefits.

The incremental cost per additional LYS with ramipril relative to standard therapy over a 5-year period was Aus$17,214 (95% CI: 8,338 - 39,536).

The sensitivity analysis showed that the incremental cost-effectiveness ratio was affected primarily by variations in the risk of cardiovascular death and the cost of revascularisation.

Overall, small changes in the cost-effectiveness ratios were observed, suggesting that the base-case estimate was quite robust.

**Authors' conclusions**
Ramipril therapy, for the prevention of cardiovascular events in an at-risk population in Australia, was an effective strategy that compared favourably with the cost-effectiveness of other health care interventions.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Standard therapy reflected the traditional pattern of care for
patients at risk of cardiovascular events. The comparator represented the standard approach in the HOPE study. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a published clinical trial, which was randomised, multi-centred and double-blind. The sample size was large and the length of follow-up was fairly long. These issues enhance the robustness of the evidence. However, more details on the primary study would have been interesting.

Validity of estimate of measure of benefit
The summary benefit measure was appropriate and it detected the impact of the intervention on the patients' health. An assessment of quality of life would have been interesting, although survival represents a commonly used end point in the secondary prevention of cardiovascular events. Discounting was applied, as recommended in Australia. Life-years are comparable with the benefits of other health care interventions. The total benefits were not reported. The authors noted that the benefits associated with ramipril could have been underestimated.

Validity of estimate of costs
The cost analysis was carried out from the perspective of the Australian third-party payer. It appears that all the relevant categories of costs have been included in the analysis, although a detailed breakdown of the cost items was not reported and the costs were presented in macro-categories. The source of the data was provided for all items, while some resource use data were derived from authors' assumptions pertaining to treatment patterns. The price year was not reported, which makes reflation exercises in other settings difficult. The costs were treated deterministically in the base-case, but the cost estimates were varied in the sensitivity analysis. The costs estimated in each treatment group were not reported.

Other issues
The authors made few comparisons of their findings with those from other studies that used different methodologies to assess the long-term impact of ramipril (beyond trial follow-up). The issue of the generalisability of the results of the analysis to other settings was not explicitly addressed, but several sensitivity analyses were conducted. These partially improved the external validity of the analysis. The study referred to patients at risk of cardiovascular events and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that the use of ramipril (10 mg/day) in Australians at high cardiovascular risk represented a clinically and economically important addition to current management practices.

Source of funding
None stated.

Bibliographic details

PubMedID
14511193

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Angiotensin-Converting Enzyme Inhibitors /economics /therapeutic use; Australia; Cardiovascular Diseases /drug therapy /mortality; Cost-Benefit Analysis; Diabetic Angiopathies /drug therapy /mortality; Humans; Ramipril /economics /therapeutic use; Risk Factors

AccessionNumber
22003001323

Date bibliographic record published
28/02/2005

Date abstract record published
28/02/2005