Cost-effectiveness of the treatment of heart failure with ramipril: a Spanish analysis of the AIRE 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 use of ramipril, an angiotensin-converting enzyme (ACE) inhibitor, for the treatment of heart failure after acute myocardial infarction (AMI). The initial dosage was 2.5 mg twice daily. The treatment was initiated between day 3 and day 10 after AMI (day 1 = day of index infarction).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of patients after AMI at high risk of premature death, denoted by clinically observed signs of either transient or ongoing heart failure. Patients with severe heart failure (usually New York Health Association grade IV), heart failure of primary valvular or congenital aetiology, unstable angina, or any of the recognised contraindications to ACE inhibitor treatments, were excluded.

Setting
The setting was secondary care (outpatient ambulatory). The economic study was carried out in Spain.

Dates to which data relate
The effectiveness evidence was gathered between 1989 and 1993. No dates for the resource use were reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a single study (the Acute Infarction Ramipril Efficacy, AIRE). The main details of this study, in terms of the methodology and results, were published elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was performed retrospectively on a different patient sample from that used in the effectiveness study.

Study sample
Preliminary power calculations (power of 80% and significance level of 5%) suggested that the trial required about 2,000 patients to fulfil some assumptions, such as a predicted average follow-up of 15 months and a 25% reduction in
all-cause mortality. Eligible patients were those older than 17 years of age, who were admitted to coronary care, intensive care or general medical units with a definite AMI and clinical evidence of heart failure at any time after the index AMI. Of a total of 52,019 patients initially reviewed for inclusion, a final sample of 1,986 was included in the analysis. There were 1,004 patients in the ramipril group and 982 patients in the placebo group. The patients in the ramipril group were aged 64.9 (+/- 10.8) years and 73% were men. The patients in the placebo group were aged 65.1 (+/- 10.8) years and 74% were men. The main reasons for exclusion were no evidence of AMI (21,302 patients), no evidence of cardiac failure (16,989 patients), death (2,784 patients) and unstable angina (2,314 patients).

**Study design**

This was a randomised, multi-centre (144 centres), multi-national (14 countries), double-blind placebo-controlled trial. Randomisation was performed in blocks of 10 patients and stratified by centre. The patients were seen at 4 and 12 weeks after randomisation and then every 12 weeks. The average length of follow-up was 15 months with a minimum of 6 months. Only one patient was lost to follow-up. The blinding method was not reported.

**Analysis of effectiveness**

The basis for the analysis of the clinical study was intention to treat. The primary health outcome was all-cause mortality and survival curves were obtained using the Kaplan-Meier approach. Thus, the incremental life-years gained (LYG) with ramipril, in comparison with placebo, were calculated for four follow-up periods (1, 2, 3 and 3.8 years). The study groups were well balanced at baseline in terms of their demographics, clinical characteristics and use of concomitant medications.

**Effectiveness results**

There were 170 deaths (17%) in the ramipril group and 222 (23%) in the placebo group, with a 27% reduction in the risk of death (95% confidence interval: 11 - 40; p=0.002).

The annual incremental LYG were 0.027 after 1 year, 0.063 after 2 years, 0.080 after 3 years, and 0.119 after 3.8 years.

**Clinical conclusions**

The effectiveness study showed that ramipril significantly reduced all-cause death and improved survival in comparison with placebo.

**Modelling**

The authors stated that they used a modelling approach that combined clinical evidence from the AIRE study and cost data derived from the Spanish context. The details of the model were not specified, but the methods used permitted sensitivity analyses to be performed on key parameters.

**Measure of benefits used in the economic analysis**

The benefit measure used in the analysis was the LYG. This was derived directly from the effectiveness study using the Kaplan-Meier approach. The benefits were discounted using a 6% rate.

**Direct costs**

A 6% discount rate, which was currently recommended in Spain, was applied since the costs were incurred over more than 2 years. The unit costs were reported separately from the quantities of resources used. The health services included in the analysis were hospital stay, ramipril and additional outpatient visits. It was assumed that the consumption of other resources was not statistically different between the study groups, thus diagnostic procedures, surgical interventions and use of further medication were not included in the analysis. It was also assumed that two extra outpatient visits were required to manage a hospital episode. The cost/resource boundary adopted in the analysis was that of the Spanish NHS. The costs were estimated using the Spanish Catalogue of Pharmaceutical Specialties for ramipril and average prices for
the inpatient stay in cardiology and outpatient visits in an ambulatory setting. Resource use was estimated using actual
data derived from a Spanish database involving more than 65 hospitals. No dates for resource use were reported. All the
costs were updated to 2000 prices using the general consumer price index in Spain.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

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

**Currency**
Euros.

**Sensitivity analysis**
One-way sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios to
variations in discount rate, length of hospital stay, cost per inpatient day and additional non-hospital costs. A two-way
sensitivity analysis was conducted, simultaneously varying the cost and the duration of inpatient stay.

**Estimated benefits used in the economic analysis**
The annual discounted incremental LYG were 0.027 after 1 year, 0.059 after 2 years, 0.071 after 3 years, and 0.100
after 3.8 years.

**Cost results**
The total additional cost per ramipril patient over conventional therapy was Euro 129.2 in year 1, Euro 197.6 in year 2,
Euro 435.5 in year 3, and Euro 399.2 in year 3.8.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the two strategies under
study. Compared with conventional therapy, the incremental cost per LYG with ramipril was Euro 4,784 in year 1, Euro
2,286 in year 2, Euro 2,763 in year 3, and Euro 1,550 in year 3.8. The sensitivity analyses showed that the estimated
cost per LYG was robust to wide variations in the baseline values used in the analysis.

**Authors’ conclusions**
The addition of ramipril to conventional treatment was cost-effective, compared with conventional treatment alone, for
the management of patients with heart failure after acute myocardial infarction (AMI), from the perspective of the
Spanish NHS. This was because the cost per life-year gained (LYG) was far below Euro 5,000, even under conservative
assumptions.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. The conventional strategy was selected, as the aim of the study
was to evaluate the active value of ramipril for the treatment of patients with heart failure after MI. You should decide
whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used a randomised controlled trial, which was appropriate for the study question. The
internal validity of the analysis was high on account of several factors. For example, the randomisation (carried out by stratification and blocks), the performance of preliminary power calculations, the double-blinded design, the length of follow-up, and the intention to treat principle on which the analysis of the clinical study was based. Further, the study was multi-centred and the method of sample selection was reported. These issues enhanced the internal validity of the analysis.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was the LYG, which allowed the benefit of the present study technology to be compared with those from other interventions implemented in the health care system. Appropriate discounting was performed and the Kaplan-Meier approach was used to calculate survival.

Validity of estimate of costs
The perspective adopted in the study was explicitly reported. It appears that all the relevant categories of costs have been included in the analysis. The authors stated that some specific cost items were not statistically significantly different between the two strategies. Hence, they were not considered in the computation of the total costs. The price year, unit costs and quantities of resources used were reported, thus facilitating the reproducibility of the cost analysis. The costs were treated deterministically, but sensitivity analyses were conducted on the key cost and resource estimates. The cost of the drug under study was not varied because the value used in the base-case analysis represented the current established price in Spain. Resource consumption was partially based on assumptions made by the authors, which were not supported by any published evidence.

Other issues
The authors compared their findings with those of other ACE inhibitor-based treatments for heart failure. However, they stated that care should be exercised when comparing the different ACI inhibitors because of differences in terms of study population.

Implications of the study
The main implication of the study is that ramipril should be added to conventional therapy for the treatment of patients with heart failure after AMI.

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Other publications of related interest

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