Cost effectiveness in the treatment of heart failure with ramipril: a Swedish substudy 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
Adding the angiotensin converting enzyme (ACE) inhibitor ramipril to conventional treatment in patients with heart failure after acute myocardial infarction (AMI).

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with clinical evidence of heart failure at any time after an AMI. The excluded patients were as follows: those with severe heart failure, heart failure of primary valvular or congenital aetiology, unstable angina, or any of the recognised contraindications to ACE inhibitor treatment. In the first year of the study, the inclusion criteria were extended to include patients with non-Q as well as Q-wave infarction and the protocol was clarified to emphasise that patients with transient cardiac failure after myocardial infarction were eligible to be randomised.

Setting
Hospital. The economic analysis was carried out in Sweden.

Dates to which data relate
Effectiveness and resource use data corresponded to patients recruited between 1989 and 27 August 1992, and were followed up to 28 Feb 1993. The price year was 1993.

Source of effectiveness data
The evidence for the final outcomes was based on a single study (the Acute Infarction Ramipril Efficacy study (the AIRE study)).

Link between effectiveness and cost data
Costing on hospitalisation was retrospectively conducted on a sub-sample of the patient sample used in the AIRE study (4 out of 10 participating Swedish hospitals). The costing on ramipril was based on the resource use data from the AIRE study, which was prospectively performed.

Study sample
Power calculations were used to determine the sample size (the study was estimated to require about 2,000 patients
based on predicted average patient follow-up of 15 months, predicted placebo mortality of 20% versus 15% in the treatment group at 15 months, statistical power of at least 80%, and significance level of 5% with a two-tailed test). A total of 52,019 patients had been reviewed. The AIRE study included 2,006 patients (1,014 in the treatment group and 992 patients in the placebo group), of whom 1,986 were evaluable (one centre with 20 patients was removed from the analysis because of inconsistent data; this was done prior to the study end). A total of 1,004 patients with a mean (SD) age of 64.9 (10.8) were randomised to ramipril and 982 with a mean (SD) age of 65.1 (10.8) to placebo; randomisation to drug or placebo was well balanced within the 14 countries. The Swedish sub-sample used in the economic analysis consisted of 162 patients (62% of the Swedish sample who had participated in the AIRE study), 83 in the treatment group and 79 in the placebo group.

**Study design**

This was a multi-centre, multinational, double-blind, randomised, placebo-controlled study, carried out in 144 centres in 14 countries. All patients, including those withdrawn from randomised treatment, were seen at 4 and 12 weeks after randomisation and thereafter every 12 weeks until study close. The average follow-up period was 15 months (minimum 6 months, maximum 3.8 years). In total, there were 352 premature withdrawals from the ramipril group and 318 from the placebo group. Randomisation between Ramipril and matching placebo was arranged in blocks of 10 patients, and was stratified by centre. Apart from study medication, the patients were treated according to local clinical practice, including conventional treatment with diuretics and digitalis for heart failure. All statistical endpoints were reviewed and validated by a subcommittee of the international steering committee. Patients with severe heart failure were no longer randomised for treatment but instead received optimal therapy that, in most cases, was open-label treatment with ACE inhibitors. A planned interim analysis was performed after 175 deaths, half way through the projected total of 350 deaths. A very stringent stopping rule was specified in the protocol (p<0.001 was the guideline for early termination) so that no adjustment was required to the final analysis to compensate for this interim analysis.

**Analysis of effectiveness**

The principle used in the analysis of effectiveness was intention-to-treat. The pre-specified primary outcome measure was all-case, all-cause mortality. Survival curves were obtained by use of the Kaplan-Meier estimate. A Cox proportional hazards regression model was used to obtain the relative hazard and corresponding confidence intervals. Subgroup effects were examined by including interaction terms in the Cox model. The secondary endpoint was the time to the first validated secondary event, namely, death, progression to severe resistant heart failure, infarction or stroke. Serious adverse events included the above-mentioned outcomes as well as adverse effects of treatment. The study groups were well matched in all aspects at baseline.

**Effectiveness results**

The effectiveness results were as follows:

On intention-to-treat analysis, mortality from all causes was significantly lower for patients randomised to receive ramipril (170 deaths; 17%) than for those randomised to receive placebo (222 deaths; 23%).

The observed risk reduction was 27% (95% CI: 11% - 40%; p=0.002).

Analysis of pre-specified secondary outcomes revealed a risk reduction of 19% for the first validated outcome (i.e., first event in an individual patient), namely, death, severe/resistant heart failure, myocardial infarction, or stroke (95% CI: 5% - 31%, p=0.008).

There were fewer patients with reported serious adverse events on ramipril, 581 (58%), than placebo, 625 (64%).

**Clinical conclusions**

Oral administration of ramipril to patients with clinical evidence of either transient or ongoing heart failure, initiated between the second and ninth day after myocardial infarction, resulted in a substantial reduction in premature death from all causes. This benefit was apparent as early as 30 days and was consistent across a range of subgroups.
Measure of benefits used in the economic analysis
The benefit measure was the number of life years saved, which was estimated for 3 groups of patients; those who were followed for 1, 2, and 3.8 years, respectively. Original data from all 1,986 patients in the AIRE sample were used to estimate the number of life-years saved, as the area between the 2 Weibull survival curves.

Direct costs
The costs were discounted. Resource use quantities were reported separately from the costs. Cost items were reported separately. Cost analysis covered the costs of various investigations and interventions, hospitalisations (including type of ward), and ramipril. The perspective adopted in the cost analysis was that of third-party payers (county councils). The resource use related to the length of stay and type of ward, and various investigations and interventions were based on a retrospective questionnaire sent to the 4 largest recruiters (62% of the Swedish sample) of the 10 participating Swedish clinics in the AIRE study. The resource use data related to the study drug (the daily dosage and the treatment period) plus the probabilities regarding hospital readmission which were based on the data from the AIRE study. The costs of ramipril and hospital days were obtained from Swedish institutions. The price year was 1993. The treatment costs in the main analyses included the cost of ramipril and hospitalisation, and excluded the costs associated with other resource consumption (such as concomitant medication, diagnostic tests, etc.) since they were not significantly different in the 2 AIRE study groups; costs related to adverse effects of ramipril were negligible, as the frequency of discontinued treatment was marginally higher in the ramipril group. Other costs not included in the analyses were costs for recurrent myocardial infarction, additional interventions and investigations.

Statistical analysis of costs
A statistical analysis appears to have been performed on resource use data only, and not on cost data. No further information was provided.

Indirect Costs
Not included.

Currency
Swedish kronor (Sek). The conversion rates were US$1 = Sek 7.70, 1 = SEK12.40.

Sensitivity analysis
One-way and two-way sensitivity analyses were conducted on hospitalisation costs, various investigations and interventions, discount rate, and the life-years saved using the Kaplan-Meier method instead of Weibull.

Estimated benefits used in the economic analysis
The number of life years saved was 0.03 over a treatment period of 1 year, 0.09 over a treatment period of 2 years, and 0.22 over a treatment period of 3.8 years. The discount rate for the health benefits was 5%.

Cost results
The discount rate was 5%. The total cost per patient was Sek 991 over the 1 year treatment period, Sek 1,579 over the 2 year treatment period, and Sek 2,826 over the 3.8 year treatment period.

Synthesis of costs and benefits
The incremental cost-effectiveness ratios of the treatment were estimated over 3 treatment periods: 1, 2, and 3.8 years. The cost per life-years saved was Sek 33,033 for the 1 year treatment period, Sek 17,544 for the 2 year treatment period, and Sek 9,745 for the 3.8 year treatment period, when only costs were discounted. When both benefits and costs...
were discounted the corresponding values were Sek 33,033 for the 1 year treatment period, Sek 18,153 for the 2 year treatment period, and Sek 14,148 for the 3.8 year treatment period. The sensitivity analyses indicated that the study results were robust to changes in most of the parameters.

**Authors' conclusions**

Adding ramipril to conventional treatment for heart failure after acute myocardial infarction is cost-effective, and compares favourably with the cost-effectiveness of other common medical therapies in the cardiovascular field.

**CRD COMMENTARY - Selection of comparators**

The use of placebo was regarded as the comparator. This allowed the active value of the intervention to be evaluated.

**Validity of estimate of measure of effectiveness**

The internal validity of the effectiveness results is likely to be high due to the double-blind randomised nature of the AIRE study design, the power calculations performed to justify the sample size, and the intention-to-treat analysis conducted. The study groups were comparable in terms of the baseline characteristics. The study sample appears to have been representative of the study population.

**Validity of estimate of measure of benefit**

Estimation of benefits was obtained directly from the effectiveness analysis. The choice of the estimates was justified. It was noted that the study may not have captured the full set of benefits associated with the treatment; the long term survival in the ramipril group can be expected to be higher because fewer patients in the ramipril group developed severe heart failure and the ramipril group had a higher survival after 3.8 years of observation. Furthermore, ramipril also prevents the development of chronic heart failure, which implies an improvement in quality of life.

**Validity of estimate of costs**

The authors provided detailed information on the methodology of the cost analysis: resource use quantities were reported separately from the costs; and the price year, conversion rates, and perspective adopted in the cost analysis, were reported. Furthermore, statistical analyses were performed on resource use data; a series of sensitivity analyses was performed to account for the uncertainties in the data. However, it is not entirely clear whether true costs were used or charge data; costing for some elements of the cost analysis was performed retrospectively on a Swedish sub-sample rather than on the original sample and prospectively; the effects of alternative procedures on indirect costs were not addressed; and statistical analyses were not performed on cost data.

**Other issues**

The authors’ conclusions appear to be justified given the sensitivity analyses performed to address uncertainties in the data. Regarding the issue of generalisability to other settings or countries, it was acknowledged that, besides the fact that the data on hospitalisation were collected retrospectively and for only 62% of the Swedish sample, it is likely that the probability of hospitalisation varied among the 14 countries in the AIRE study. Appropriate comparisons were made with other studies. The issue of whether the study sample was representative of the study population was discussed by noting that the inclusion criteria in the AIRE study were significantly broader than those in the Survival and Ventricular Enlargement (SAVE) study. It was however acknowledged that one should be cautious in making direct comparisons between the different major ACE inhibitor studies, as they did not use the same patient populations.

**Implications of the study**

Increasing use of ACE inhibitors in patients with heart failure may be recommended in addition to the standard heart failure therapy of digitalis and diuretics.
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