Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure


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
Patients who had had an acute myocardial infarction (AMI) and were then suffering from heart failure were given eplerenone, starting 3 to 14 days after the AMI. The dosage was 25 mg/day for 4 weeks, after which it was increased to 50 mg/day. This was in addition to what was considered standard therapy, which could include an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), a diuretic, a beta-blocker, or coronary reperfusion therapy. Full details were given in another study (Pitt et al. 2003, see 'Other Publications of Related Interest' below for bibliographic details). If at any time the serum potassium concentration was higher than 5.5 mmol/L, the dose of eplerenone was reduced or treatment was temporarily discontinued. A comparator group of patients was given what was considered standard therapy with a placebo.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
Patients who had had an AMI were included if they suffered from left ventricular systolic dysfunction (LVSD; documented ejection fraction <=40%) and heart failure (shown by pulmonary rales, venous congestion on chest X-ray, or the presence of a third heart sound). Patients with diabetes could be included without the evidence of heart failure. Patients were excluded if they used potassium-sparing diuretics, had a serum creatinine concentration of more than 2.5 mg/dL (220 micromol/L), or had a serum potassium concentration of more than 5.0 mmol/L before randomisation (see Pitt et al. 2003 for details).

Setting
The setting was secondary care. The study was conducted in 37 countries.

Dates to which data relate
In terms of effectiveness evidence, patients were recruited from December 1999 to December 2001. The resource evidence also referred to December 1999 to December 2001. Prices used were for 2001, except for eplerenone which used the first marketed price (i.e. 2004).

Source of effectiveness data
The effectiveness data were mainly derived from a single study. Life expectancy after the trial dates was estimated from three other sources (the Framingham Heart Study, the Saskatchewan Health Database and the Worcester Heart Attack Registry).
Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients that provided the effectiveness data.

Study sample
Power calculations were reported in Pitt et al. (2003). It was stated that the trial was designed to enrol 6,200 patients and to continue until 1,012 deaths occurred. Testing at the 0.04 level of significance (two-sided), the study had 88.3% power to detect an 18.5% difference between the two groups in their death rates from any cause. A total of 6,642 patients were randomised to the two groups. Ten patients were excluded from the randomisation for administrative reasons. There were 3,319 patients in the intervention group and 3,313 patients in the placebo group.

Study design
This was a randomised controlled trial (RCT) in which the patients were followed up for an average of 16 months (range: 0 to 33). The follow-up period continued until 1,012 deaths occurred in the study. There appear to have been no loss to follow-up, although this was not stated explicitly. This was a multi-centre trial, with 671 centres in 37 countries. A researcher blinded to the treatment group assigned patients to a diagnosis-related group.

Analysis of effectiveness
The analysis was conducted on an intention to treat basis. The primary health outcomes were time to death from any cause, and time to death or first hospitalisation resulting from a cardiovascular event. The secondary end points were death resulting from cardiovascular causes and death resulting from any cause or any hospitalisation. The groups were shown to be comparable at baseline.

Effectiveness results
The death rate from any cause was 14.4% in the eplerenone group and 16.7% in the placebo group, (p=0.008).

The percentage suffering from death or cardiovascular events was 26.7% in the eplerenone group and 30.3% in the placebo group, (p=0.002).

The percentage suffering death or hospitalisation from any cause was 52.1% in the eplerenone group and 55.2% in the placebo group, (p=0.02).

The percentage dying from cardiac disease was 12.3% in the eplerenone group and 14.6% in the placebo group, (p=0.005).

Clinical conclusions
The authors concluded that the addition of eplerenone to the standard treatment for patients with LVSD who were suffering from heart failure after an AMI, improved their health and increased their life expectancy.

Modelling
Death hazard functions over time were obtained from the three other sources, and were adjusted for patient characteristics using separate Cox proportional-hazard models.

Measure of benefits used in the economic analysis
The measures of benefit used were the life-years gained (LYG) and the quality-adjusted life-years (QALYs) gained. The LYG was calculated using three series of data that provided information on mortality from heart disease (the Framingham Heart Study, the Saskatchewan Health Database and the Worcester Heart Attack Registry). The gain in QALYS in a person's life used utility estimates from the EQ-5D, based on a sub-sample of 1,792 patients, as well as the three data series already mentioned. Utility after 12 months was addressed using the 12-month value.
Direct costs
Discounting was carried out at a rate of 3%. The quantities and the total costs (not unit costs) of resources used were given. The costs measured were length of initial hospital stay, length of re-hospitalisation stay, eplerenone, other medication, outpatient procedures and emergency room visits. The costs were derived from actual data, while resources were obtained from patient records. The unit costs were from the average Medicare reimbursement rates obtained from the Medicare Part A data file, and professional costs were calculated using the method of Mitchell et al. 1995 (see 'Other Publications of Related Interest' below for bibliographic details). Medication costs were based on the Redbook average wholesale price. The price year was 2001, except for the cost of eplerenone which was the first market price (i.e. 2004).

Statistical analysis of costs
No statistical analysis of the costs was carried out.

Indirect Costs
Although the authors reported that a societal perspective was adopted, no indirect costs were calculated. Therefore, the perspective of the analysis was likely to have been that of the health care system.

Currency
US dollars ($).

Sensitivity analysis
The authors reported that the cost per QALY gained was evaluated in the sensitivity analysis section, owing to the lack of utility data for the overall study sample. The additional health care costs associated with LYG by the treatment were also taken into consideration in the sensitivity analysis. Cost-effectiveness analyses were also performed for different sub-groups (defined by age, gender, diabetes, and prior AMI). Bootstrap analyses were used to estimate the probability of different incremental cost-effectiveness ratios (ICERs).

Estimated benefits used in the economic analysis
The LYG per patient observed in the trial were 1.33 in the eplerenone group and 1.30 in the placebo group. The difference was 0.0304 LYG (95% confidence interval, CI: 0.0026 to 0.0567).

The LYG with eplerenone compared with placebo were 0.1014 when using the Framingham Heart Study, 0.0636 when using the Saskatchewan Health Database and 0.1337 when using the Worcester Heart Attack Registry. The gains in QALYS were 0.0676 (Framingham), 0.0429 (Saskatchewan) and 0.0907 (Worcester), respectively.

Side effects of the treatment were included in the QALY analysis.

Cost results
The initial hospitalisation cost was $6,140 in the eplerenone group and $6,164 in the placebo group.

The total follow-up cost (excluding initial hospitalisation) was $13,494 in the eplerenone group and $12,104 in the placebo group.

The increase in costs in the eplerenone group was $1,391 (95% CI656 to 2,165).

The authors reported that the only significant difference was the cost of eplerenone.

Any costs of adverse events that fell into the cost categories described above would have been included.
Synthesis of costs and benefits
When using the Framingham Heart Study, the ICER was $13,718 per LYG, with 96.7% of the estimates below $50,000 per LYG. When using the Saskatchewan Health Database, the ICER was $21,876 per LYG, with 93.8% of estimates under $50,000 per LYG. When using the Worcester Heart Attack Registry, the ICER was $10,402 per LYG, with 98.8% of estimates below $50,000 per LYG.

The ICER per QALY gained was $20,579 when using the Framingham Heart Study, $32,405 when using the Saskatchewan Health Database, and $15,330 when using the Worcester Heart Attack Registry.

At a ceiling ratio of $20,000 per life-year saved, eplerenone was cost-effective in more than 85% of estimates.

When different sub-groups were compared, patients with diabetes had a much higher ICER per LYG ($42,160 using the Framingham survival estimates).

Authors’ conclusions
Eplerenone should be used for patients with heart failure after an acute myocardial infarction (AMI). The authors argued that it is effective in reducing mortality, is cost-effective in increasing life-years saved, and compares favourably with the incremental cost-effectiveness ratios (ICERs) of other standard treatments in heart failure patients.

CRD COMMENTARY - Selection of comparators
The selection of the comparator, placebo, taken with standard treatment for heart failure was justified by it representing current practice in the authors’ setting. Standard treatment included ACE inhibitors or ARBs, diuretics, beta-blockers, statin therapy and coronary perfusion. You should decide if this is standard treatment in your own setting.

Validity of estimate of measure of effectiveness
The source of the effectiveness data was a single study. The study design, an RCT, was appropriate for the hypothesis, although its methodological design was only briefly reported. The main strengths of the study were the reporting of power calculations and study inclusion criteria, and appropriate statistical analyses to test for statistically significant differences between the two study groups. In addition, the study sample appears to have been representative of the study population, and the patient groups were shown to be comparable at analysis. However, some potential weaknesses should be pointed out. For example, blinding of the outcome assessment was not reported, and it was unclear whether all of the patients included in the study were accounted for in the analysis. These factors may introduce potential bias.

Validity of estimate of measure of benefit
Two measures of benefit were used, LYG and QALYs gained. The LYG were obtained directly from the effectiveness analysis, using data on life expectancy from three series of data. The QALYs gained were obtained by using the EQ-5D questionnaire on a sub-sample of patients.

Validity of estimate of costs
The authors stated that the costs were estimated from a societal perspective, but the indirect costs were not included. If the indirect costs had been included, the authors acknowledged that this might well have reduced the relative cost of eplerenone. Only hospital costs were estimated, no primary care costs were included. When the authors calculated the difference in costs between the two patient groups they seemed to ignore the costs of the initial hospitalisation. However, this would not affect the authors’ conclusions, as initial hospitalisation costs were similar between the two groups. The quantities of resources were reported, but not the unit costs. The resource use quantities were taken from a single study. No other sources were used for quantities. Costing after the trial period was based on projection of the costs within the trial period. Prices were taken from Medicare and, therefore, did not account for price differences between different countries. The authors also drew attention to the fact that Medicare costs might not be an accurate reflection of costs in the USA. No statistical, sensitivity, or any other kind of analysis of the quantities or prices was carried out. The price year was reported and discounting was conducted appropriately.
Other issues
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to the wider population of patients with post AMI heart failure was discussed. The authors did not present their results selectively. The authors reported further limitations of the study. First, the use of resource use data from many different countries. Second, US prices do not really give a good idea of costs in any one country. Third, the estimation of life expectancy was based on the assumption that the survival curves remained parallel after the trial period. Fourth, the accuracy of estimates of life expectancy derived from different sources is uncertain. Finally, the size of the diabetic sub-group was too small to permit firm conclusions to be drawn.

Implications of the study
The authors advocated the use of eplerenone for heart failure patients who have suffered an AMI. As the costs will vary widely between countries, it would be helpful to have country-specific ICERs when making decisions.

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