Cost-effectiveness of eplerenone plus standard treatment compared with standard treatment in patients with myocardial infarction complicated by left ventricular systolic dysfunction and heart failure in the Netherlands

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Aims. Following the results of the EPHESUS study in patients with heart failure after myocardial infarction, a cost-effectiveness analysis was undertaken from a Dutch societal perspective to evaluate the lifetime benefits and costs of eplerenone as add-on to standard treatment.
Methods. Life-years gained in the eplerenone arm during the trial period were extrapolated to lifetime life-years gained using three sources of life expectancy data (Framingham Heart Study, Saskatchewan Health Database and Worcester Heart Attack Registry). Resource use measured included direct medical costs of hospitalisation, medications including eplerenone, outpatient diagnostic tests and procedures, and emergency room visits. Incremental cost-effectiveness ratios were calculated for life-years gained and quality-adjusted life-years gained.
Results. Eplerenone prolonged lifetime survival by five weeks at an additional cost of €803. The incremental cost-effectiveness ratio was about €8000 per life-year gained, well below the only published Dutch benchmark for cost-effectiveness of €18,000. Probabilistic sensitivity analyses showed the results to be robust when varying the discount rate applied to benefits and costs, the hospitalisation costs, and the source of life expectancy data used.
Conclusion. Treatment with adjunctive eplerenone is effective in preventing deaths and prolonging life. (*Neth Heart J* 2005;13:393-400.)

Keywords: heart failure, cost-effectiveness, aldosterone blockade, eplerenone

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Following acute myocardial infarction (AMI), approximately 22% of men and 46% of women develop heart failure (HF).[1] This debilitating condition in AMI patients increases the risk of dying by 55% and is associated with a 2.15 times greater risk of recurrent AMI or death at 30 days.[2] Spencer et al.[3] have shown a decrease in the incidence of HF post-AMI from 38% in 1975 to 33% in 1995, due to improvements in the understanding and management of the disease. Thus, with the incidence of AMI at around 29,500 for the Netherlands in 2003,[4] it can be estimated that HF post-AMI could develop in 7000 to 10,000 patients a year.

The economic burden of HF is high, representing 1 to 2% of total healthcare expenditure in developed countries. The majority of new patients with HF are elderly with a history of hypertension, cardiovascular disease or AMI.[5] Patients who develop HF post-MI incur longer hospital stays, higher readmission rates, and higher mortality rates during hospitalisation and for six months after discharge, compared with AMI patients without HF.[6,7] Economic evaluations have

shown that the major cost driver in the treatment of HF is hospitalisation, accounting for 60 to 70% of the total costs. In comparison, the cost of drug treatment is lower.[8,9]

Drug treatment for HF has been shown to reduce the rate of progression and mortality, as well as HF-related hospitalisations.[8] Dutch treatment guidelines (2002) recommend the use of diuretics to reduce HF symptoms, and/or ACE inhibitors and β-blockers to improve survival and morbidity.[10] Nondrug treatment options include cardiac resynchronisation therapy, implantable cardiac defibrillators and heart transplantation. In addition, nonselective aldosterone blockade has been shown to reduce mortality in patients with chronic severe HF when used in combination with ACE inhibitors, diuretics and sometimes digoxin.[11]

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that selective aldosterone blockade with eplerenone significantly reduced mortality and morbidity in patients with AMI complicated by left ventricular systolic dysfunction (LVSD) and HF who were already receiving optimal medical care.[12] This was the first study to show improved outcomes in patients with HF post-AMI taking an adjunctive therapeutic agent to standard treatment (with an ACE inhibitor or angiotensin receptor blocker (ARB) and a β-blocker).

To further evaluate the benefits of eplerenone, economic data collected during the EPHESUS trial were used to assess the cost-effectiveness of eplerenone plus standard treatment versus standard treatment alone. Results of the US cost-effectiveness analysis have recently been published.[13] This paper deals with the cost-effectiveness of eplerenone in the Dutch healthcare setting.

Methods

EPHESUS trial design

The EPHESUS trial, a randomised double-blind multicentre trial in patients with AMI complicated by HF and LVSD (n=6632) on standard treatment, compared adjunctive eplerenone with placebo.[12] Patients were recruited between December 1999 and December 2001 from 671 centres in 37 countries, including the Netherlands. Inclusion criteria included LVSD (documented ejection fraction ≤40%) and documented HF (by pulmonary rales, venous congestion on chest radiography, or presence of a third heart sound). Patients received standard treatment and were randomised to receive eplerenone (25 mg/day titrated to a maximum of 50 mg/day after four weeks; 3313 patients) or placebo (3319 patients), starting 3 to 14 days after an AMI. Standard treatment was defined as treatment with one or more of the following drugs: ACE inhibitors or ARBs, β-blockers, diuretics, statin therapy and coronary reperfusion. The two primary endpoints were death from any cause, and death from cardiovascular causes or first hospitalisation for a cardiovascular event (including HF, recurrent AMI, stroke or ventricular arrhythmia). The two main secondary endpoints were death from cardiovascular causes, and death from any cause or any hospitalisation. The average follow-up time of the trial was 16 months.

Economic analysis

The cost-effectiveness analysis compared results from both treatment arms (eplerenone and placebo arm), extrapolated over a patient's lifetime. The analysis included effects, resource utilisation and related costs and incremental cost-effectiveness ratios (ICER), from a Dutch societal perspective.

Effects

Lifetime life-years extrapolation

Lifetime life-years were estimated using event rates (any cause death) from the trial, and estimated life-years gained with eplerenone, based on life expectancy rates derived from three sources: the Framingham Heart Study,[14] the Saskatchewan Health Database[15,16] and the Worcester Heart Attack Registry.[17] The Framingham Heart Study provides estimates of expected survival for HF patients by age and gender. Data from the Saskatchewan database and Worcester Heart Attack Registry on patients with HF after an AMI were analysed, using piecewise regression to obtain death hazard functions over time. These were adjusted according to patient characteristics using separate Cox proportional hazards models. Life-years lost (LYL) were estimated for patients who died in the trial by subtracting the trial survival time from the age- and sex-matched life expectancy derived from one of the three sources. Patients who survived in the trial had zero LYL. The average LYL was then calculated for each treatment group, and the difference between these figures ($LYL_{placebo}$ – $LYL_{eplerenone}$) provided an estimate of life-years gained (LYG) with eplerenone. Life-years were discounted at 4% annually.

Utilities

Utility values were measured in a subset of 1792 patients at baseline, 1530 patients at six months, and 1123 patients at 12 months using a well-recognised generic quality-of-life instrument (the EQ-5D).[18] All patients in the subsets were from English-speaking countries.[12] Quality-adjusted life-years (QALYs) were then calculated by multiplying survival years for the total population by utility values. For patients with a missing utility score, the average utility value of all patients with a score in that treatment arm was used. The 12-month utility score was carried forward for utility values beyond 12 months.

Costs

The analysis included direct medical costs of hospitalisation, medication including eplerenone, outpatient diagnostic tests and procedures, emergency room visits

and the total value of these follow-up costs. Resource usage for each treatment group was measured in the trial. Data on indirect costs due to lost productivity were not collected in the trial, and due to the advanced age of patients were not considered necessary in this analysis. Costs beyond the trial period were estimated by calculating the costs for each year during the trial, and carrying forward the average cost of year two and three of the trial. All costs were expressed in 2003 Euros (€) and a 4% discount rate was applied to the costs as well as effects.

Data on differences in length of hospitalisation were not fully available at the time of the analysis, so hospitalisation costs were based on a diagnosis-related group (DRG) system. All hospitalisations were assigned a US DRG code, which assigns a fixed cost to a specific hospital diagnosis. European DRG systems also exist, but were not available in the Netherlands at the time of the analysis. Therefore Dutch equivalent costs had to be estimated using one of the following methods.

1) If European DRGs could be matched to the US DRG codes, then average daily costs were calculated from DRG costs for France, Germany, UK, Italy, Spain as well as Australia. These average daily costs were then used as proxies for the Dutch costs. The length of hospital stay (LOS) for the Netherlands was available from the Dutch hospital registration system (PRISMANT).
   'DRG' cost $_{NL}$ = LOS$_{NL}$ * mean cost per day$_{DRG\text{-}countries}$
2) If European DRGs could not be matched to US ones, a ratio of matched Dutch cost to US DRG cost was calculated. This ratio was then applied to the unmatched US DRG costs to obtain the missing Dutch costs. This method has previously been described by Schulman et al.[19] The average daily costs included costs of all resources used (e.g. staff, materials and overheads).

A similar conversion approach was used to calculate the unit costs of medical procedures (CPT). CTG tariffs[20] were used where available. However, if a procedure had no CTG tariffs, the US unit cost was multiplied by the ratio of Dutch to US costs for known procedure costs.

The drug costs used were pharmacy retail prices excluding VAT, and listed in the official price list (Z-index). Eplerenone cost €2.20 per tablet regardless of the daily dose used (25 mg or 50 mg per day).

Cost-effectiveness analysis and willingness to pay

The incremental cost-effectiveness ratio (ICER) is a ratio of the additional cost of using adjunctive eplerenone to the additional benefit versus standard treatment. Two ICERs were calculated:

- Cost per life-year gained (LYG) with adjunctive eplerenone compared with standard treatment (extrapolated to lifetime LYG using the Framingham data).
- Cost per QALY gained with adjunctive eplerenone compared with standard treatment (extrapolated to lifetime QALYs gained using the Framingham data).

The ICER for the use of adjunctive eplerenone versus standard treatment was calculated as:
$(C_{eplerenone} - C_{standard\ treatment}) / (LYG_{eplerenone} - LYG_{standard\ treatment})$, with $(C_{eplerenone} - C_{standard\ treatment})$ representing the difference in mean cost of the eplerenone arm and standard treatment arm, and $(LYG_{eplerenone} - LYG_{standard\ treatment})$ representing the mean life-years gained in the eplerenone arm compared with the standard treatment arm. Confidence intervals were obtained using non-parametric bootstrap methods, employing 5000 iterations. A willingness-to-pay approach was used to evaluate the health benefits of eplerenone. This approach used a cost-effectiveness acceptability curve (CEAC) to illustrate the probability that adjunctive eplerenone was cost-effective compared with standard treatment, at different willingness-to-pay (WTP) values. Results show the probability that treatment with eplerenone is cost-effective at WTP values of €20,000 and €50,000.

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the results. The parameters that were varied included the discount rate, unit costs of hospitalisations for both treatment groups and life-expectancy extrapolation data. The discount rate was changed to 0% for both costs and effects. The unit costs of hospitalisations were varied by assuming constant unit costs of €280/day or by assuming that the first day and a half were spent in intensive care at a cost of €1130/day with subsequent days incurring a cost of €280/day. These costs are the Dutch national costs of the average day in hospital with or without intensive care.[21] The extrapolation of life-years gained to lifetime life-years gained was based on Saskatchewan data[15] and Worcester data[17] as well as Framingham data.

A probabilistic sensitivity analysis using the bootstrap method was used to estimate the percentage of simulations that are cost-effective for each ICER, and can therefore support the main analysis result.

Results

Clinical results

During a mean follow-up of 16 months, there were fewer deaths from any cause in the eplerenone group compared with the placebo group (478 vs. 554, p=0.008) as well as fewer deaths from cardiovascular causes (407 vs. 483, p=0.005). The eplerenone group also had fewer 'deaths from cardiovascular causes and cardiovascular hospitalisations' than the placebo group (885 vs. 993, p=0.002), as well as fewer 'deaths from any cause or any hospitalisation' (1730 vs. 1829, p=0.02). The addition of eplerenone to optimal medical therapy reduced morbidity and mortality among patients with AMI complicated by LVDS and HF.[12]

Effectiveness results

Table 1 shows the lifetime LYL and QALYs lost with eplerenone and standard therapy, and the gain with

Table 1. Life-years and QALYs gained with eplerenone compared with standard treatment in patients with HF post-AMI (extrapolated from Framingham, discounted at 4%).

	Eplerenone (n=3319)	Standard treatment (n=3313)	Gain with eplerenone (95% CI*) (standard therapy, eplerenone)
Life-years	0.5274 (1.3843) LYL	0.6266 (1.5028) LYL	0.0992 (0.0325, 0.1751)
QALYs	0.3855 (1.0096) QALYs lost	0.4516 (1.0793) QALYs lost	0.0661 (0.0153, 0.1154)

*Using bootstrap method. LYL=life-years lost, QALY=quality-adjusted life-years.

eplerenone over standard therapy. Adjunctive eplerenone, compared with standard treatment, prolonged mean lifetime survival by five weeks (95% CI between 1.5 and 9 weeks) and provided an extra month in terms of QALYs. This represents an LYG of 0.0992 (95% CI 0.0325, 0.1751) with eplerenone.

Cost results

Total follow-up costs were on average almost €5235 for patients on standard treatment and about €6035 for patients on eplerenone. The difference in costs for standard treatment compared with eplerenone was €803 (95% CI €465 to €1160). Over the trial period, the costs of all rehospitalisations made up 73% of the total follow-up costs in the standard treatment arm and 61% in the eplerenone arm. Hospitalisations for cardiovascular events made up 37% of all-cause hospitalisations in the standard treatment arm versus only 28% in the eplerenone arm. Hospitalisation for HF was also lower with eplerenone compared with standard treatment. The costs for emergency room visits were less than 1% in both arms (tables 2 and 3).

Results of the cost-effectiveness analysis

Willingness to pay for life-years gained

The mean incremental cost for eplerenone treatment was €803. When extrapolating lifetime LYG, an average of five weeks of life were gained with additional eplerenone treatment at a cost of €803, corresponding to an ICER of about €8100 per LYG (95% CI €3600 to €25,500). At this ICER, and assuming a willingness to pay of €20,000, the eplerenone strategy was accepted in more than 92% of

Table 2. Mean costs (SE) for eplerenone compared with standard treatment in patients with heart failure post-MI (discounted at 4%).

Costs (€)	Eplerenone (n=3319)	Standard treatment (n=3313)	Difference (95% CI*) (eplerenone, standard treatment)
Rehospitalisation	3673.5 (6149.2)	3835.6±6547.2	-162.0 (-472.0, 135.7)
Medication	874.7 (802.9)	871.2±804.6	3.5 (-35.0, 41.6)
Outpatient diagnostic procedure	526.7 (2437.2)	482.9±2180.4	43.8 (-62.9, 154.1)
Emergency room visit	38.6 (101.2)	42.6±118.2	-3.9 (-8.8, 1.8)
Eplerenone	922.0 (481.8)	-	922.0 (-22.3, 1866.3)
Total follow-up costs	6035.6 (7190.0)	5232.2 (7418.9)	803.3 (465.3, 1161.2)

SE=standard error.

Table 3. Mean rehospitalisation costs (SE) for heart failure and cardiovascular hospitalisations (discounted at 4%).

	Eplerenone (n=3319)	Standard treatment (n=3313)	Difference (95% CI*) (eplerenone, standard treatment)
CV hospitalisations**	977.4 (2502.0)	1143.7 (3034.2)	-166.3 (-303.2, -31.9)
HF hospitalisations	597.0 (2025.8)	775.2 (2661.5)	-178.2 (-290.8, -64.4)

*Using bootstrap. **Including heart failure (HF), myocardial infarction, ventricular arrhythmia and stroke.

Table 4. Incremental cost-effectiveness ratios (LYL, QALYs) for eplerenone versus placebo by life-years gained and quality-adjusted life-years gained, using Framingham extrapolation data.

	ICER in LYG (95%CI)	ICER in QALYs (95%CI)
Using Framingham extrapolation	8098.5 (3626.1, 25,587.3)	12,147.8 (5094.2, 44,986.7)

LYL=life-years lost, QALY=quality-adjusted life-years, ICER=incremental cost-effectiveness ratios.

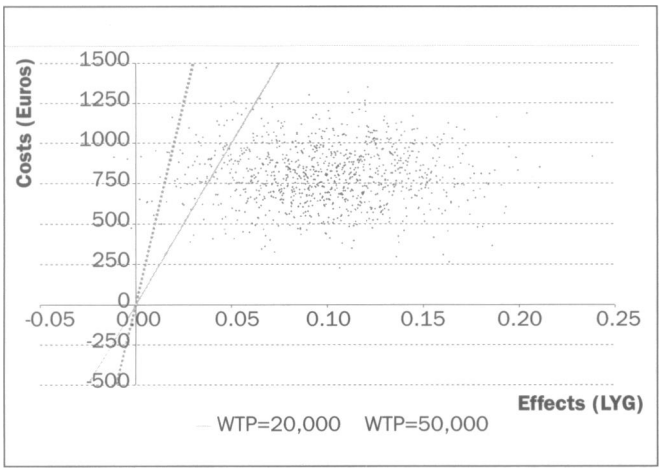

Figure 1. Cost-effectiveness plane for eplerenone compared with standard treatment (life-years gained extrapolated to lifetime life-years gained using Framingham data and discounted at 4%).

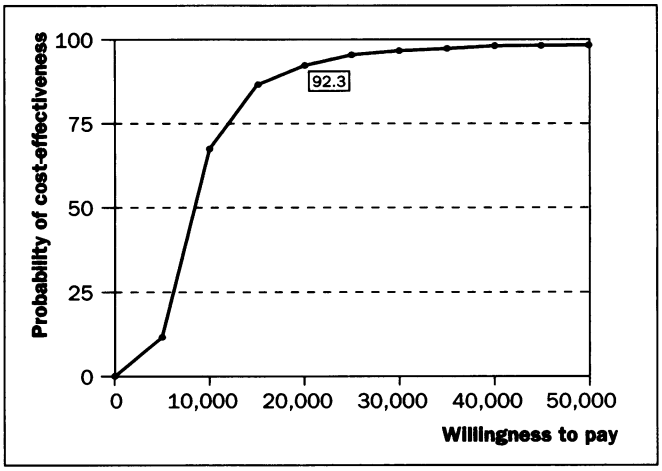

Figure 2. Acceptability curve for eplerenone compared with standard treatment (life-years gained extrapolated to lifetime life-years gained using Framingham data and discounted at 4%).

the bootstrap samples increasing to 98% when assuming a willingness to pay of €50,000 (table 4, figures 1 and 2).

Willingness to pay for QALYs gained

On average one month was gained in terms of QALYs for the extra cost of eplerenone treatment of €803, corresponding to an ICER of about €12,150 per QALY gained (95% CI €5000 to €45,000). When assuming a willingness to pay of €20,000 the eplerenone strategy was accepted in more than 84% of the samples, increasing to 98% for an assumed willingness to pay of €50,000 (figure 3).

Results of the sensitivity analyses

When the discount rate was set at 0% instead of 4% for both costs and effects, the ICER was about €7500 per LYG, using Framingham data (table 5). The eplerenone strategy was accepted in more than 97% of the samples assuming a willingness to pay of €20,000, and 99.5% of samples when assuming a willingness to pay of €50,000.

The effect of varying unit costs of a day in hospital had a minimal effect on total follow-up costs and ICERs. Using the Saskatchewan data to extrapolate lifetime LYG resulted in a smaller difference in the number of LYG than with the Framingham data. Conversely, when applying the Worcester data the number of LYG was higher. Thus, varying the extrapolation data

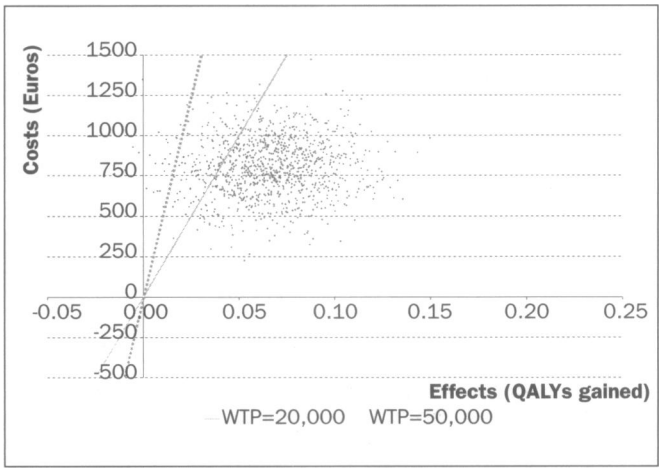

Figure 3. Cost-effectiveness plane for eplerenone compared with standard treatment (lifetime QALYs based Framingham data and discounted at 4%).

resulted in a higher ICER for the Saskatchewan data (about €12,800) and a lower ICER for the Worcester data (almost €5400) (table 6). Assuming a willingness to pay of €20,000, the acceptability of eplerenone treatment over standard treatment was 84% based on Saskatchewan data and 98% based on Worcester data. When assuming a willingness to pay of €50,000, the acceptability of eplerenone treatment over standard

Table 5. Sensitivity analysis: total follow-up costs, life-years, QALYs and ICER (extrapolated from Framingham, 0% discount rate).

	Eplerenone (n=3319)	Standard treatment (n=3313)	Difference (95% CI*) (eplerenone, standard treatment)
Total follow-up costs (€)	6085.9 (7251.2)	5271.0 (7471.1)	814.7 (474.9,1176.2)
Life-years	0.5759 (1.5296) LYL	0.6842 (1.6605) LYL	0.1083 (0.0269, 0.1786)
QALYs	0.4934 (1.0194) QALYs lost	0.4212 (1.1176) QALYs lost	0.072 (0.0176, 0.1316)
ICER (life-years)			7523.7 (3337.6, 23,717.30)
ICER (QALYs)			11,288 (4876.5, 40,790.7)

* Using bootstrap method. LYL=life-years lost, QALY=quality-adjusted life-years, ICER=incremental cost-effectiveness ratios.

Table 6. Sensitivity analysis: life-years lost extrapolated to lifetime life-years lost using Saskatchewan and Worcester data (discounted at 4%).

	Advantage with eplenenone
Life-years gained (Saskatchewan data)	0.0628 (0.0218, 0.1036)
ICER (Saskatchewan data)	12,794.7 (6026.0, 36,874.3)
Life-years gained (Worcester data)	0.1497 (0.0378, 0.2508,)
ICER (Worcester data)	5364.9 (2404.8, 18,025.5)

ICER=incremental cost-effectiveness ratios.

treatment was 99% based on Saskatchewan data and 99% based on Worcester data. These results were similar when costs and effects were discounted at 0%.

Discussion

This study has shown that eplerenone is cost-effective when compared with placebo in the treatment of heart failure after AMI for patients already treated optimally with β-blockers and either ACE inhibitors or ARBs. An incremental cost-effectiveness ratio of about €8000 per LYG was calculated. Therefore, assuming a willingness to pay of €20,000, the eplerenone strategy was accepted in more than 92% of the samples increasing to 98% when assuming a willingness to pay of €50,000. The sensitivity analyses have shown that these results are robust; the ICERs for LYG varied between €5000 and €13,000, and results for QALYs gained produced similar results. In the Netherlands, the cholesterol consensus implied that an intervention is more likely to be viewed favourably if it costs less than €18,000 per LYG. There is no strong evidence to support this figure; however, this is the only published figure for the Netherlands (originally DFL 40,000) and originates from a study of the ten-year risk for a cardiovascular event.[22] In the UK, the National Institute of Clinical Excellence (NICE) assumes a benchmark of £30,000 per QALY gained and in the US, this benchmark varies between US$ 50,000 and US$ 100,000.[23]

Results of a retrospective analysis on length of hospital stay data from the EPHESUS study have recently become available. Eplerenone treatment is shown to reduce the length of hospital stay per episode of HF hospitalisation by 1.6 days in the overall EPHESUS trial population, and to reduce the number of days of HF hospitalisation per patient by 3.6 days in the overall population. The length of stay estimations used for the cost-effectiveness analysis were more conservative, therefore the effects of eplerenone using this new data could be even more favourable.

The EPHESUS study is the first study to demonstrate the efficacy of aldosterone blockade for reducing mortality and morbidity in post-AMI patients with HF. Eplerenone is the only agent proven to add this incremental benefit in patients already on optimal therapy with β-blockers and ACE inhibitors that have demonstrated clinical and cost effectiveness in the treatment of HF.[12,24] No other economic evaluations were found in the literature for patients with HF following AMI. Results of a study investigating the cost-effectiveness of torasemide in chronic heart failure cannot be compared due to the different effectiveness parameter used (NYHA class).[25]

Patients from the Netherlands were included in the clinical trial, therefore standard treatment applied in

the trial also reflected Dutch current practice. The Framingham population was assumed to match the Dutch trial population regarding age, diabetes prevalence, and other variables. Using the Saskatchewan or Worcester data instead of the Framingham data showed that eplerenone treatment remains cost-effective for the Netherlands, assuming a willingness to pay of €20,000. This result was further supported by the results for the QALY-based incremental cost-effectiveness ratios.

Limitations of the study

The length of follow-up in the EPHESUS trial varied; therefore, cost-effectiveness was calculated for the average follow-up period of 16 months. Treatment with eplerenone was assumed to last for 16 months only, and survival curves were assumed to remain parallel beyond the trial period. This study cannot address the issue of how long eplerenone should be taken.

The survival benefit with eplerenone seen in the trial was estimated over a lifetime to provide a more meaningful picture. Therefore three survival estimates were calculated based on three sources of life expectancy data. The Framingham data were selected as they are from a well-known epidemiological database. The Saskatchewan and Worcester data were chosen because they included patients who were similar to those in the EPHESUS trial and included long-term data. The degree to which these sources yield accurate estimates of lifetime life-years saved for the trial population is not clear. Mortality rates in the EPHESUS trial were lower after one year than those seen with both the Saskatchewan and Worcester data. Therefore the survival projections made using these data may be too conservative, yielding higher ICERs.[26]

The economic evaluation was based on data collected alongside the clinical trial, providing high quality resource use data, and few gaps in data collection. A disadvantage of this method, however, is that some costs are 'protocol driven'. This means for instance that the number of tests performed during the trial may be higher than in normal clinical practice, or patients may have been more closely monitored and therefore more often rehospitalised. However, since the trial was double-blinded, such procedures may be equally prevalent in both arms, balancing differences in the cost-effectiveness ratios.

The wide confidence intervals suggest large variations in costs between patients. However, as the confidence intervals for patients getting eplerenone or standard treatment do not differ much, we can assume that the cost variations are equally large in both groups.

Missing Dutch unit costs were estimated from unit costs available from other countries. The method used was developed by Schulman et al.[19] to determine unit costs for use in multinational prospective economic studies. This method improves comparability of unit costs across countries. The validity of this approach depends upon the comparability of diagnosis descriptions across the different classification systems but, in general, DRG descriptions are comparable between countries. Now that a DRG-like system is being developed in the Netherlands, it would be interesting to compare the results using these latest costs with the results presented here.

Conclusion

Eplerenone treatment reduces morbidity and mortality in patients with AMI complicated by LVSD and HF. Furthermore selective aldosterone blockade with eplerenone in this setting is a cost-effective strategy, with an incremental cost-effectiveness ratio of about €8000 per life-year gained, well below a Dutch benchmark of €18,000. In conclusion, treatment with adjunctive eplerenone is effective in preventing deaths, prolonging life and reducing resource utilisation. ■

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