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ORIGINAL ARTICLE

Cost-effectiveness of eplerenone in patients with systolic heart failure and mild symptoms

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ABSTRACT

Aim In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), aldosterone blockade with eplerenone decreased mortality and hospitalisation in patients with mild symptoms (New York Heart Association class II) and chronic systolic heart failure (HF). The present study evaluated the cost-effectiveness of eplerenone in the treatment of these patients in the UK and Spain.

Methods and results Results from the EMPHASIS-HF trial were used to develop a discrete-event simulation model estimating lifetime direct costs and effects (life years and quality-adjusted life years (QALYs) gained) of the addition of eplerenone to standard care among patients with chronic systolic HF and mild symptoms. Eplerenone plus standard care compared with standard care alone increased lifetime direct costs per patient by £4284 for the UK and €7358 for Spain, with additional quality-adjusted life expectancy of 1.22 QALYs for the UK and 1.33 QALYs for Spain. Mean lifetime costs were £3520 per QALY in the UK and €5532 per QALY in Spain. Probabilistic sensitivity analysis suggested a 100% likelihood of eplerenone being regarded as cost-effective at a willingness-to-pay threshold of £20 000 per QALY (UK) or €30 000 per QALY (Spain).

Conclusions By currently accepted standards of value for money, the addition of eplerenone to optimal medical therapy for patients with chronic systolic HF and mild symptoms is likely to be cost-effective.

Until recently, mineralocorticoid receptor antagonists (MRAs) were recommended (class I, evidence level B) only in patients with moderate-to-severe symptoms (NYHA class III or IV) on the basis of the Randomized Aldactone Evaluation Study (RALES).⁶ This recommendation has now been strengthened (class I, evidence level A) and broadened (to include all patients with symptomatic HF-REF) following the Eplerenone in Mild patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), which showed a reduction in mortality and all-cause hospitalisation when an MRA was added to optimal evidence-based therapy in patients with mild symptoms (NYHA class II HF), LVEF $\leq 30\%$ (or, if $>30\%$ – 35% , a QRS duration of >130 ms on electrocardiography) and recent hospitalisation for a cardiovascular (CV) reason, elevated plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP.⁷ These findings are supported by a further trial, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), in patients with myocardial infarction complicated by left ventricular systolic dysfunction and HF.⁸

We have evaluated the cost-effectiveness of eplerenone in patients with HF-REF and mild symptoms (NYHA class II) because, beside efficacy and safety, the adoption of new treatments is also influenced by whether the added value is worth the added cost. We have done this from the perspective of two European countries, the UK and Spain.

INTRODUCTION

Around 1%–2% of adults in Europe have heart failure (HF) which causes an immense symptom burden due to breathlessness, fatigue and oedema, greatly reduces quality of life and is a leading cause of hospital admission and, therefore, healthcare expenditure.^{1–2} Mortality within 12 months of a HF hospital admission is 30%–40%, rising to a 5-year mortality rate of 50%–75%.^{3–4}

The primary goals of the treatment of HF are, therefore, to relieve symptoms, reduce the rate of hospitalisation and improve survival.⁵ ACE inhibitors and β -blockers have been shown to achieve these goals in patients with HF and reduced EF (HF-REF), irrespective of symptom severity (New York Heart Association (NYHA) class II–IV), and are thus strongly recommended (class I, evidence level A) in clinical guidelines on the basis of multiple clinical trials.⁵

METHODS

Model description

A discrete-event simulation model was developed to project the rates and times of important clinical events and assign to these lifetime costs and quality-of-life consequences (figure 1). Two treatment pathways were simulated, in line with the trial protocol: standard therapy with the addition of eplerenone (starting dose of 25 mg once daily; at 4 weeks, increased to 50 mg once daily) and standard therapy with no additional active treatment (standard care). Model outputs are presented in terms of mean life expectancy, quality-adjusted life expectancy, direct costs and incremental cost-effectiveness ratios (ICERs).

The simulated patient population in the model was derived from that enrolled in EMPHASIS-HF.⁷ All patients were in NYHA class II, with a mean



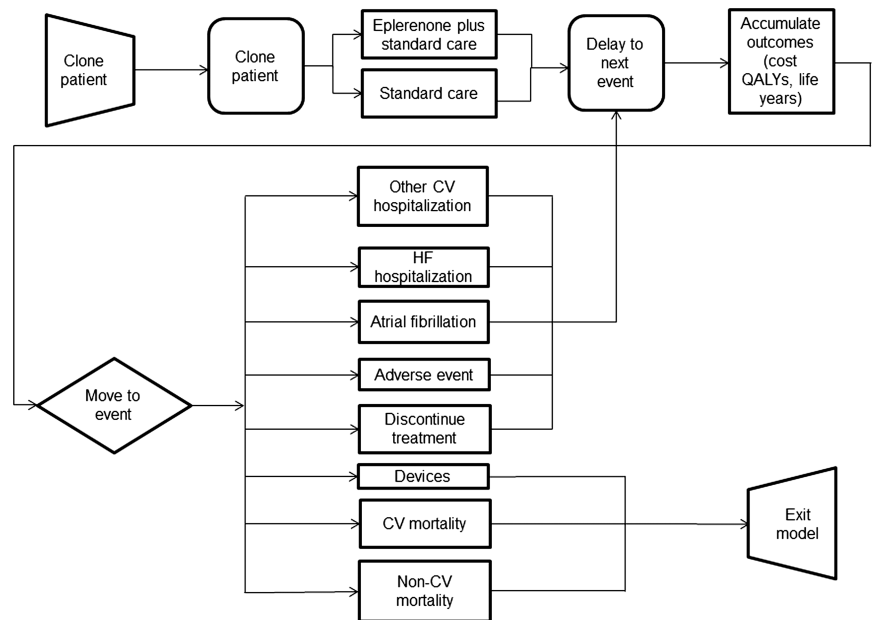
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Figure 1 Model structure. CV, cardiovascular; HF, heart failure; QALY, quality-adjusted life year.



age of 69, had a mean LVEF of 26% and 78% of patients were men. Only concomitant medication usage at enrolment was reported in the trial and so it was assumed subjects remained on the same medication for their lifetimes.

A discrete-event simulation models time to clinically and economically meaningful events on the basis of individually-simulated patients. This method was chosen in preference to a Markov model as it is possible to model an unlimited number of events for each patient and make the probability of events contingent on time, the number and type of events the patient has already experienced, and the patient's characteristics (such as age).⁹

Patient-level data from EMPHASIS-HF were used to determine risk equations for each event by fitting a distribution to the time to each event. Treatment effectiveness was captured in the model by tracking progress to the following health states reported in the trial: HF hospitalisation, other CV hospitalisation, new-onset atrial fibrillation, implantation of cardiac resynchronisation therapy (CRT) or implantable cardioverter-defibrillator (ICD) devices, adverse events, discontinuation of eplerenone, CV mortality, and non-CV mortality.

The adverse events included within the model are the key events reported in EMPHASIS-HF: hyperkalaemia, hypokalaemia, renal failure, hypotension and gynaecomastia.⁷ New-onset diabetes, heart transplants, dialysis and kidney transplants were not included in the model because the rates were low and either similar or the same for both trial arms, meaning that inclusion would not change the model results.¹⁰ In addition, consideration was given to modelling the change in NYHA class as time progressed, but as there was no significant change in NYHA class between the two arms ($p=0.14$), the majority of patients remained in class II ($\geq 75\%$ of patients at all time points up to month 42 were in NYHA class on both arms) and available evidence to extrapolate beyond the trial is limited, this was not included. This implies that the reported benefits of eplerenone are instead based upon the reduction in mortality, hospitalisations and new-onset atrial fibrillation.

Figure 1 provides an overview of the model flow. In brief, simulated patients were created and individual times to events were randomly assigned to them based upon the risk equations for each model event (see online supplementary appendix),

derived from EMPHASIS-HF data for each arm separately, except non-CV mortality which was assumed to be the same for eplerenone and standard care. Each patient was then copied and the two identical patients were assigned to treatment with either standard care or eplerenone plus standard care.

The model simulated 25 000 patients for each treatment in order to minimise stochastic error and provide an appropriate level of certainty in the ICER (SD in the ICER over repeated simulations $<£100$ (€120)).

At the start of the model, patient's times to event were simulated and the patient progressed to the first event to occur. Following the event there were two possible options:

1. The patient exited the model if:
 - A. death occurred
 - B. an ICD or CRT device was implanted: remaining life years, costs and quality-adjusted life years (QALYs) were assigned to patients at this point based upon an assessment conducted for the National Institute of Health and Care Excellence on the effectiveness of these devices;¹¹ the EMPHASIS trial information was not sufficient to estimate device effect due to lack of sufficient follow-up post device implantation.
2. The patient remained in the model and the time to the next event was calculated.

If the event was deemed to influence the time of other events, the times to these events were recalculated. Events that were deemed to interact in this way were: HF (and other CV) hospitalisations, which increase the likelihood of both CV mortality and repeat hospitalisations, and adverse events, which increase the likelihood of future adverse events.

Parametric survival models (Weibull, exponential and log-normal) were tested and the best fitting models used to describe time-to-event. Similar parametric models were fitted where necessary to outcomes with multiple events following the method recommended by Harrell.¹²

Patients were followed over the course of the simulation with their characteristics updated over time. It was assumed that patients who discontinued treatment (after a hospitalisation or adverse event) with eplerenone returned to standard care. Patient discontinuation rates were based on the EMPHASIS-HF data.

It should be noted that the clinical data used in the model included recurrent events and not just the first events reported in the main results paper from EMPHASIS-HF.^{7 13}

A scenario is included where patients only exit the model on death, and devices are not included within the model, to test the sensitivity of the results.

In the base-case analysis, a lifetime horizon was chosen to fully capture the costs and quality-of-life benefits resulting from treatment with eplerenone given the increased survival. There were no modelled differences between the two countries in the standard-treatment practices or the comparators. The model implementation used Simul8 15.0 and Microsoft Excel 2010.

All cost, quality-of-life and length-of-life outcomes were discounted at 3.5% annually within the UK model and 3.0% annually within the Spanish model, in line with their national reimbursement reference cases.

Costs and perspective

Cost inputs for the model are given in table 1. Only initial acute event costs were accounted for when hospitalisations occurred. No data were available to estimate the direct costs of death, and these were not included in the model. This is a conservative assumption.

The costs for other CV hospitalisations, adverse events and devices were based on the proportion of patients from the EMPHASIS-HF trial experiencing each subcategory of event. The cost of each adverse event is higher on the standard care arm compared with the eplerenone arm; the types of events experienced are different and a higher proportion of patients experiencing adverse events required hospitalisation (23% of

adverse events experienced by patients on the standard care arm required hospitalisation compared with 15% on the eplerenone arm). When a patient was fitted with a device, costs were applied for fitting of the device and each pulse generator replacement that would be required for the patient's remaining life span.

Data on prescribed medication were taken from the trial publication and a weighted average of concomitant medications (excluding eplerenone) calculated to account for medication resource usage. Eplerenone was assumed to be prescribed for a patient's lifetime or until discontinuation.

The cost of two hospital visits and sets of blood chemistry tests is included on initiation of treatment with eplerenone. Thereafter, annual disease management and monitoring costs are assumed to be the same for standard care and treatment with eplerenone.

Quality of life

Quality of life was calculated using the utility formula from Göhler *et al*¹⁴ using the baseline characteristics of the patients in the EMPHASIS-HF trial. Utility decrements were assigned to patients as they experienced events. The utility values used within the model are summarised in table 1.

Sensitivity analysis

A range of deterministic sensitivity analyses were carried out to test the robustness of the model projections by varying key inputs and assumptions. One-way parameter sensitivity analyses were performed by varying each parameter within its likely range

Table 1 Utilities and medication and event costs used within the model

Parameter	Input value—UK model	Input value—Spanish model	Reference
Per annum treatment costs			
Eplerenone drug costs	£557	€1086	23 24
Standard care drug costs	£0	€0	Assumed
Concomitant medications	£229	€290	23 24
Eplerenone treatment initiation (one-off)*	£463	€119	25–27
Disease management and monitoring	£443	€60	25–27
Event-based costs			
HF hospitalisation	£3463	€3321	25 27
Other CV hospitalisation	£3001	€4980	25 27
Adverse event—eplerenone†	£237	€786	25 27
Adverse event—standard care†	£280	€1133	25 27
Cost of CRT and ICD devices	£5842	€9005	25 27
Average CRT and ICD device life	5.8 years	5.8 years	11
Quality-of-life utilities			
Baseline utility	0.84	0.84	14
Utility decrement for patients who experience one hospitalisation	−0.024	−0.024	14
Utility decrement for patients who experience two hospitalisations	−0.031	−0.031	14
Utility decrement for patients who experience three hospitalisations	−0.055	−0.055	14
Utility decrement for new-onset atrial fibrillation	−0.084	−0.084	28
Lifetime utility decrement for adverse events—eplerenone	−0.0003	−0.0003	19
Lifetime utility decrement for adverse events—standard care	−0.0001	−0.0001	19
Short-term utility decrement for adverse events—eplerenone‡	−0.0012	−0.0012	19 29
Short-term utility decrement for adverse events—standard care‡	−0.0008	−0.0008	19

*Two hospital appointments with a consultant and two sets of blood chemistry tests.

†The unit costs of the adverse events for each of the five events modelled for the two arms were assumed to be the same. The proportion of patients experiencing each type of event (hospitalised and non-hospitalised) was calculated using the trial results. Costs are higher on the placebo arm as more patients were hospitalised (23% of adverse events vs 15%) and more patients experienced renal failure which is the most costly of the five key adverse events included.

‡Applied for 21 days based upon clinician advice.

CRT, cardiac resynchronisation therapy; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter-defibrillator.

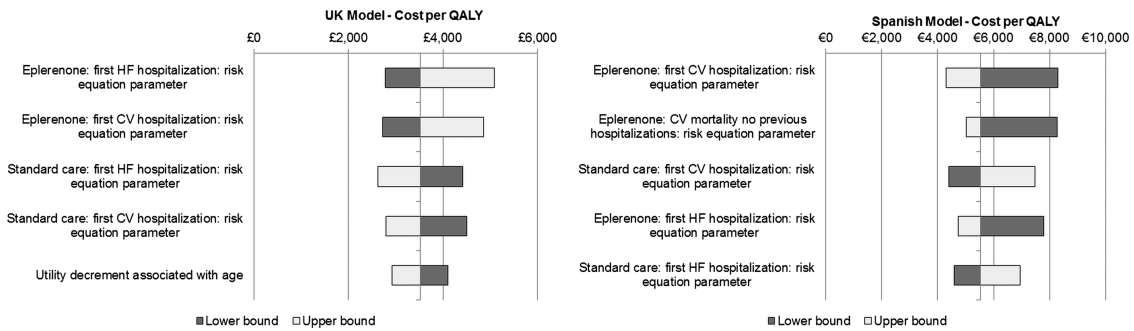


Figure 2 Deterministic sensitivity analysis tornado plots. CV, cardiovascular; HF, heart failure; QALY, quality-adjusted life year.

using the 95% CIs of the parameter distributions (figure 2). In addition, a range of scenario analyses were conducted.

A probabilistic sensitivity analysis (PSA) was also performed, producing 100 pairs of incremental effectiveness and cost results. These were plotted on a cost-effectiveness plane to illustrate the probability of being cost-effective for both countries' willingness-to-pay (WTP) thresholds (figure 3).

RESULTS

The results of the base-case analysis projected lifetime improvements in clinical outcomes with increased costs for subjects receiving eplerenone in addition to standard care compared with standard care alone and are shown in table 2.

Over a patient's lifetime, there were higher costs associated with eplerenone than standard care. The increases in costs produced by the model were £4284 for the UK and €7358 for Spain. The main differences in costs between the two countries were due to the cost of eplerenone (which is higher in Spain than the UK) and the costs of disease management and monitoring (which are higher in the UK).

Over a patient's lifetime, the mean quality-adjusted life expectancy for eplerenone using a discount rate of 3.5% (UK simulation) was 6.19 versus 4.98 QALYs for standard care (a difference of 1.22 QALYs). There was a larger improvement in absolute discounted life expectancy: 7.74 versus 6.23 years for eplerenone and standard care, respectively.

Using a discount rate of 3% (Spanish simulation), the mean quality-adjusted life expectancy was 6.53 versus 5.20 QALYs for eplerenone and standard care, respectively (a difference of 1.33 QALYs). There was a larger improvement in absolute discounted life expectancy: 8.18 versus 6.52 years for eplerenone and standard care, respectively. These outcomes produced ICERs of £3520 per QALY for the UK and €5532 for Spain.

The results of the deterministic sensitivity analyses are presented in figure 2. In all cases, the ICER remains below £5500

per QALY in the UK model and below €8500 per QALY in the Spanish model, indicating that the model is very stable in its predictions and not sensitive to any one parameter. These ICERs are well below the accepted WTP thresholds in both of these countries (£20–30 000 per QALY in the UK and €30 000 per QALY in Spain).

Results from scenario analyses are presented in table 3 and show that the ICER remains approximately equal to the accepted WTP thresholds in both countries even when the EMPHASIS-HF data are used with no extrapolation at all. The model results are not sensitive to either the utility decrements applied for events or the rates of device implantation. The ICER improves as the modelled time horizon increases because longer time horizons allow for more time for the modelled benefits of eplerenone to be realised.

The mean results of the PSA are very similar to the deterministic base case described above. When incorporating the uncertainty around all model inputs, the 100 simulations gave an overall mean ICER of £6939 (95% Bayesian credibility interval (£6656; £7222)) for the UK model and €7217 (95% Bayesian credibility interval (€6905; €7528)) for the Spanish model.

Scatter plots of the 100 pairs of incremental quality-adjusted life expectancies and lifetime costs are presented in figure 3. In all cases, eplerenone provides a QALY benefit over standard care and the values simulated fall below the £20 000 WTP threshold within the UK model and below the €30 000 threshold within the Spanish model, showing that eplerenone is consistently cost-effective.

DISCUSSION

Based upon the EMPHASIS-HF trial, this modelling analysis shows that the use of eplerenone in patients with HF-REF and mild symptoms reduced hospitalisations (particularly HF hospitalisations) and the costs associated with these. These savings partially offset the additional cost of eplerenone treatment (and

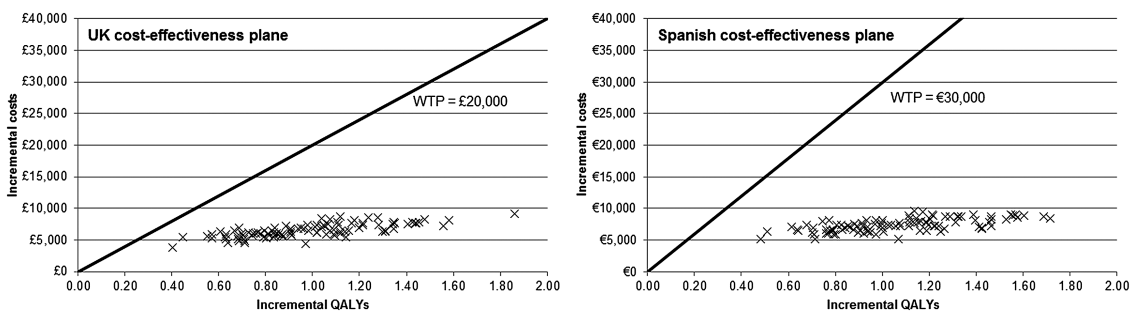


Figure 3 Incremental quality-adjusted life expectancy and lifetime costs. QALY, quality-adjusted life year; WTP, willingness-to-pay threshold.

Table 2 Base-case scenario results from the discrete-event simulation model

	UK			Spain		
	Eplerenone	Standard care	Difference	Eplerenone	Standard care	Difference
Other CV hospitalisations	1.27	1.23	0.04	As UK		
HF hospitalisations	1.32	1.60	-0.28			
Diagnosis of atrial fibrillation	0.09	0.12	-0.03			
CV mortality	0.71	0.77	-0.05			
Non-CV mortality	0.08	0.06	0.02			
Adverse events	0.67	0.43	0.24			
ICD or CRT	0.59	0.46	0.13			
Discontinuation of eplerenone	0.42	-	0.42			
Cost of CV hospitalisations	£3236	£3240	-£4	€5493	€5478	€15
Cost of HF hospitalisations	£3888	£4862	-£973	€3815	€4748	-€932
Cost of active treatment	£3873	£0	£3873	€7080	€0	€7080
Cost of concomitant treatment	£1773*	£1426	£347	€2371	€1889	€481
Cost of devices	£3597*	£3046	£551	€3641	€3048	€592
Cost of disease management and monitoring	£3433*	£2761	£672	€488	€389	€99
Cost of adverse events	£137	£108	£30	€465	€443	€22
Total cost	£18 559	£14 275	£4284	€23 353	€15 995	€7358
Total QALYs	6.19	4.98	1.22	6.53	5.20	1.33
Total life years	7.74	6.23	1.52	8.18	6.52	1.66
ICER	£3520			€5532		
Cost per life year gained	£2825			€4431		

*While the rate of use of devices, management and monitoring, and concomitant treatment requirements is either the same for the two arms or lower on the eplerenone arm, as patients are expected to live longer, the total cost over a patient's lifetime is higher.

CRT, cardiac resynchronisation therapy; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter-defibrillator; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

extension of life) resulting in very modest ICERs of £3520 and €5532 per QALY gained for eplerenone versus standard care in the UK and Spain, respectively. These ICERs are much lower than the £20 000 WTP threshold in the UK and the €30 000 threshold in Spain, indicating that eplerenone, as an add-on therapy in the treatment of HF-REF with mild symptoms (NYHA class II), represents a cost-effective option, generating additional clinical benefit at an acceptable incremental cost in both countries. The results were robust to deterministic and probabilistic sensitivity analyses.

Table 3 Scenario analysis results from the discrete-event simulation model

Scenario	Country	Incremental costs	Incremental QALYs	ICER
Using EMPHASIS-HF data with no extrapolation	UK	£940	0.05	£20 730
	Spain	€1427	0.05	€31 138
Time horizon 2 years	UK	£717	0.04	£20 101
	Spain	€1157	0.04	€32 208
Time horizon 5 years	UK	£1160	0.19	£6016
	Spain	€2340	0.20	€11 932
No utility decrement for adverse events, atrial fibrillation or hospitalisations	UK	£4284	1.20	£3558
	Spain	€7358	1.32	€5584
Increased use of devices	UK	£4495	1.22	£3693
	Spain	€7396	1.33	€5560
No use of devices	UK	£3440	1.23	£2802
	Spain	€5223	1.34	€3893

EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Our findings are in keeping with the favourable cost-effectiveness of other disease-modifying therapies in HF-REF, including ACE inhibitors, angiotensin receptor blockers and β -blockers.¹⁵⁻¹⁸ The common theme, from an economic perspective, is the ability of all of these agents to reduce the rate of hospitalisation for worsening HF, which is the major driver of the cost of this condition to health services and payers. Indeed, the reduction is so substantial that the cost savings either largely balance or even eliminate the additional costs of treatment (drug and monitoring) and increased longevity (ie, surviving patients require treatment, including procedures, and remain at risk of hospitalisation). Although we did not analyse the cost-effectiveness of eplerenone in other European countries, previous studies with other effective treatments in HF have shown consistent findings in a variety of countries including Germany and France and there is no reason to believe that eplerenone would be different.¹⁷

When considering the results from a computer simulation model, it is ideal to be able to validate the clinical outcomes against empirical data. Unsurprisingly, the model accurately projects the within-trial outcomes (see online supplementary appendix). For the time beyond the trial follow-up period, the model also provides a reasonable approximation of current survival estimates for chronic systolic HF patients, with a mean survival of approximately 8 years in the standard care arm.³ Within-trial analysis, for which we have complete certainty in outcomes, estimated ICERs below the WTP thresholds for both the UK and Spain.

The much less expensive MRA spironolactone is approved for the treatment of patients with chronic systolic HF and moderate to severe symptoms (NYHA class III and IV), based upon the results of the RALES trial.⁶ It is not known whether the spironolactone would have had the same clinical effects

(and therefore economic consequences) as eplerenone in EMPHASIS-HF. Eplerenone is a selective MRA whereas spironolactone is non-selective and the two agents have different tolerability profiles.¹⁹ Poorer tolerability and persistence of spironolactone could result in additional costs that may affect the difference in drug costs.¹⁹

LIMITATIONS

Although the model has been shown to produce clinically realistic projections, there are a number of limitations with this work that should be noted. First, this is a modelling study and does not represent empirically collected resource and quality-of-life outcomes associated with clinical findings. However, in the absence of more detailed data from the trial, a computer simulation such as this represents the next best solution. Second, as the EMPHASIS-HF trial was stopped early, due to early benefit in the eplerenone-treated group compared with the standard care arm, there is some uncertainty regarding the long-term outcomes of eplerenone in the available clinical data. Truncation issues are particularly likely to impact the absolute cost estimates for symptomatic decline (eg, device use) as outcomes are modelled based on projections from limited data. Truncated trials often associated with greater effect sizes, with moderate overestimation in trials such as EMPHASIS-HF where more than 500 events were observed.²⁰ Uncertainty around the data has, however, been included within the modelling approach used and examined within both probabilistic and deterministic sensitivity analyses. The extent to which EMPHASIS-HF can be generalised is also limited by design features and other characteristics of the patients enrolled, including the tendency for trial patients to be younger and have less comorbidity than 'real-world' patients. The model did not take account of indirect costs, such as loss of earnings and pension payments to survivors, or other costs such as those related to admission to nursing homes.^{21 22}

Key messages

What is known on this subject?

Addition of a mineralocorticoid receptor antagonist to treatment with an ACE inhibitor (or angiotensin receptor blocker) and β -blocker in patients with chronic systolic heart failure (HF) and mild symptoms reduced the risk of death and hospital admission in the Eplerenone in Mild patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), but the cost-effectiveness of this extra treatment is not known.

What might this study add?

Using a computer simulation model based on the outcomes of EMPHASIS-HF to replicate the trial outcomes, extrapolate these over a patient's lifetime and capture resource and health-related quality-of-life (utility) consequences produced incremental cost-effectiveness ratios (ICERs) of £3520 per quality-adjusted life year (QALY) for the UK and €5532 for Spain. These ICERs were well within the willingness-to-pay thresholds of £20 000 per QALY (UK) or €30 000 per QALY (Spain).

How might this impact on clinical practice?

The ICERs for eplerenone based upon EMPHASIS-HF indicate that eplerenone is cost-effective as well as clinically effective.

CONCLUSIONS

The addition of eplerenone to standard therapy (with an ACE inhibitor and β -blocker) reduces the risk of all-cause mortality and all-cause hospitalisation in patients with chronic systolic HF and mild symptoms (NYHA class II). These clinical benefits offset a substantial portion of the additional drug cost associated with eplerenone, yielding favourable cost-effectiveness ratios well below standard WTP thresholds in the two European countries studied. Overall, this economic evaluation supports the use of eplerenone as a cost-effective treatment in eligible patients with chronic systolic HF and mild symptoms.

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