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.

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]

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 ≤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.

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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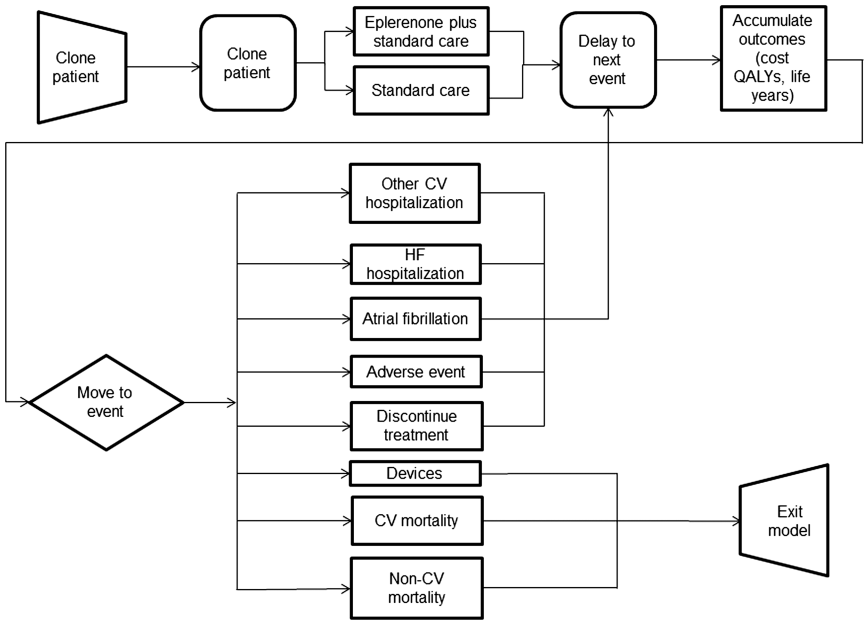

Figure 1 Model structure. CV, cardiovascular; HF, heart failure; QALY, quality-adjusted life year.

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 (≥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.

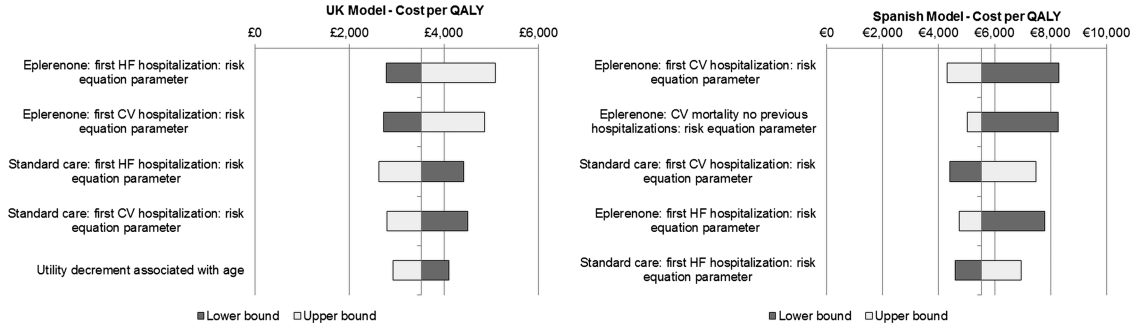

Figure 2 Deterministic sensitivity analysis tornado plots. CV, cardiovascular; HF, heart failure; QALY, quality-adjusted life year.

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 000per 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

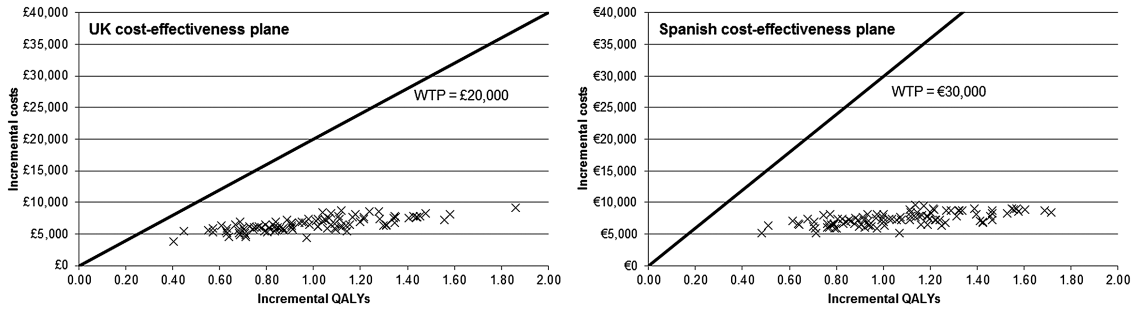

Figure 3 Incremental quality-adjusted life expectancy and lifetime costs. QALY, quality-adjusted life year; WTP, willingness-to-pay threshold.

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 b-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 EMPHAISIS-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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Model Input Parameters

Table S1: risk equations used for clinical efficacy inputs

Outcome	Drug	Previous events	Dist	Mean	95% CI
CV mortality	Epl	0 prev hosp	W	α = 0.82 β = 21612	α (0.71, 0.95) β = (11890, 39174)
		1 prev hosp	W	α = 0.89 β = 3265	α (0.75, 1.06) β = (2174,4921)
		2 prev hosp	W	α = 1.18 β = 2477	α (0.90,1.54) β = (1512,4058)
		3+ prev hosp	W	α = 1.91 β = 1244	α (1.36,2.70) β = (906,1710)
	Pl	0 prev hosp	W	α = 0.82 β = 12200	α (0.71, 0.95) β = (7413,20023)
		1 prev hosp	W	α = 0.89 β = 3447	α (0.75, 1.06) β = (2318,5132)
		2 prev hosp	W	α = 1.18 β = 1630	α (0.90,1.54) β = (1121,2370)
		3+ prev hosp	W	α = 1.91 β = 1613	α (1.36,2.70) β = (1132,2301)
HF hospitalization	Epl	0 prev hosp	W	α = 0.77 β = 9006	α (0.71, 0.84) β = (6721, 12063)
		1 prev hosp	W	α = 0.93 β = 190	α (0.82, 1.05) β = (142, 255)
		2 prev hosp	W	α = 1.01 β = 296	α (0.79,1.30) β = (183,478)
		3 prev hosp	W	α = 0.84 β = 136	α (0.65,1.09) β = (73,261)
		4 prev hosp	W	α = 1.06 β = 91	α (0.71,1.59) β = (42,197)
		5 prev hosp	W	α = 1.48 β = 93	α (0.85,2.53) β = (51,171)
		6 prev hosp	W	α = 1.01 β = 296	α (0.79,1.30) β = (183,478)
		7 prev hosp	W	α = 0.93 β = 190	α (0.82, 1.05) β = (142, 255)
		8+ prev hosp	W	α = 0.77 β = 9006	α (0.71, 0.84) β = (6721, 12063)
	Pl	0 prev hosp	W	α = 0.77 β = 4761	α (0.71, 0.84) β = (3781,5972)
		1 prev hosp	W	α = 0.93 β = 174	α (0.82, 1.05) β = (139,216)
		2 prev hosp	W	α = 1.01 β = 336	α (0.79,1.30) β = (228,490)
		3 prev hosp	W	α = 0.84 β = 175	α (0.65,1.09) β = (103,299)
		4 prev hosp	W	α = 1.06 β =180	α (0.71,1.59) β = (95,341)
		5 prev hosp	W	α = 1.48 β = 98	α (0.85,2.53) β = (44,218)
		6 prev hosp	W	α = 1.01 β = 336	α (0.79,1.30) β = (228,490)
		7 prev hosp	W	α = 0.93 β = 174	α (0.82, 1.05) β = (139,216)
		8+ prev hosp	W	α = 0.77 β = 4761	α (0.71, 0.84) β = (3781,5972)
CV hospitalization	Epl	0 prev hosp	W	α = 0.72 β = 8895	α (0.66, 0.79) β = (6451,12323)

Outcome	Drug	Previous events	Dist	Mean	95% CI
		1 prev hosp	W	α = 1.00 β = 308	α (0.85, 1.18) β = (226,418)
		2 prev hosp	W	α = 1.01 β = 296	α (0.79,1.30) β = (183,478)
		3 prev hosp	W	α = 0.80 β = 151	α (0.55,1.15) β = (56,405)
		4 prev hosp	W	α = 1.12 β = 287	α (0.55,2.24) β = (98,828)
		5 prev hosp	W	α = 1.52 β = 110	α (0.55,4.18) β = (41,290)
		6 prev hosp	W	α = 1.00 β = 110	α (1.00,1.00) β = (41,290)
		7 prev hosp	W	α = 1.00 β = 308	α (0.85, 1.18) β = (226,418)
		8+ prev hosp	W	α = 0.72 β = 8895	α (0.66, 0.79) β = (6451,12323)
	Pl	0 prev hosp	W	α = 0.72 β = 6838	α (0.66, 0.79) β = (5085,9235)
		1 prev hosp	W	α = 1.00 β = 343	α (0.85, 1.18) β = (255,462)
		2 prev hosp	W	α = 1.01 β = 336	α (0.79,1.30) β = (228,490)
		3 prev hosp	W	α = 0.80 β = 307	α (0.55,1.15) β = (150,627)
		4 prev hosp	W	α = 1.12 β = 71	α (0.55,2.24) β = (20,251)
		5 prev hosp	W	α = 1.52 β = 41	α (0.55,4.18) β = (11,149)
		6 prev hosp	W	α = 1.00 β = 41	α (1.00,1.00) β = (11,149)
		7 prev hosp	W	α = 1.00 β = 343	α (0.85, 1.18) β = (255,462)
		8+ prev hosp	W	α = 0.72 β = 6838	α (0.66, 0.79) β = (5085,9235)
Adverse events	Epl	0 prev adverse event	W	α = 0.62 β = 11920	α (0.56, 0.68) β = (8313,17000)
		1+ prev adverse event	W	α = 0.93 β = 213	α (0.77,1.13) β = (154,294)
	P	0 prev adverse event	W	α = 0.62 β = 17680	α (0.56, 0.68) β = (11693,26499)
		1+ prev adverse event	W	α = 0.93 β = 255	α (0.77,1.13) β = (148,339)
Atrial Fibrillation	Epl	n/a	E	α = 1 β = 25177	β = (17823,35627)
	Pl	n/a	E	α = 1 β = 14984	β = (11588,19526)
Other cause mortality	Epl & Pl	n/a	E	α = 1 β = 33597	β = (26120,43262)
Use of devices	Epl	n/a	E	α = 1 β = 12326	β = (9852,15458)
	Pl	n/a	E	α = 1 β = 10933	β = (8733,13707)
Other cause discontinuation	Epl	n/a	E	α = 1 β = 12315	β = (9761,15516)

Legend: CI, confidence interval; CV cardiovascular; Dist = distribution; E = exponential; Epl = eplerenone; hosp = hospitalization; Pl = placebo; prev = previous; W = weibull.

Covariance Information – CV Mortality, No Previous Hospitalizations

Parameter	*Coef.*	*Constant*	*Eplerenone*	*ln(p)*
Constant	9.409221	0.0641674	-0.00926018	0.016412
Eplerenone	0.571797	-0.00926018	0.04659389	0.003241
ln(p)	0.32673	0.01641151	0.00324082	0.005874

Covariance Information – CV Mortality, One Previous Hospitalization

Parameter	*Coef.*	*Constant*	*Eplerenone*	*ln(p)*
Constant	8.145338	0.041361	-0.02449	0.011904
Eplerenone	-0.0543	-0.02449	0.050459	-0.00053
ln(p)	0.113993	0.011904	-0.00053	0.008023

Covariance Information – CV Mortality, Two Previous Hospitalizations

Parameter	*Coef.*	*Constant*	*Eplerenone*	*ln(p)*
Constant	7.396492	0.036133	-0.02411	0.012426
Eplerenone	0.418356	-0.02411	0.074785	0.005601
ln(p)	-0.16144	0.012426	0.005601	0.018637

Covariance Information – CV Mortality, Three Previous Hospitalizations

Parameter	*Coef.*	*Constant*	*Eplerenone*	*ln(p)*
Constant	7.385974	0.033061	-0.02947	0.016034
Eplerenone	-0.25983	-0.02947	0.052244	-0.00905
ln(p)	0.224237	0.016034	-0.00905	0.03114

Covariance Information – HF Hospitalization, No Previous Hospitalizations / Eight or More Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	8.468271	0.01372665	-0.00446585	0.003679
Eplerenone	0.637353	-0.00446585	0.01770232	0.001147
ln(p)	0.261421	0.00367887	0.00114722	0.001917

Covariance Information – HF Hospitalization, One Previous Hospitalization / Seven or More Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.157638	0.012546	-0.01166	-0.00184
Eplerenone	0.090029	-0.01166	0.033098	-4.1E-05
ln(p)	0.072688	-0.00184	-4.1E-05	0.003914

Covariance Information – HF Hospitalization, Two Previous Hospitalizations / Six or More Previous Hospitalisations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.815855	0.038084	-0.036	-0.00566
Eplerenone	-0.12714	-0.036	0.093316	-0.00014
ln(p)	-0.01346	-0.00566	-0.00014	0.015779

Covariance Information – HF Hospitalization, Three Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.163061	0.074336	-0.06994	-0.01058
Eplerenone	-0.23199	-0.06994	0.170324	0.003395
ln(p)	0.177128	-0.01058	0.003395	0.017285

Covariance Information – HF Hospitalization, Four Previous Hospitalzsations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.194253	0.105528	-0.09855	-0.01721
Eplerenone	-0.67973	-0.09855	0.246259	0.000115
ln(p)	-0.06022	-0.01721	0.000115	0.042173

Covariance Information – HF Hospitalization, Five Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	4.58036	0.164662	-0.15729	-0.02975
Eplerenone	-0.04839	-0.15728	0.246447	0.010812
ln(p)	-0.38912	-0.02975	0.010812	0.076351

Covariance Information – CV Hospitalization, No Previous Hospitalizations / Eight or More Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	8.83024	0.02330086	-0.009374392	0.005461
Eplerenone	0.262967	-0.00937439	0.022752593	0.000564
ln(p)	0.32673	0.00546095	0.000564346	0.002363

Covariance Information – CV Hospitalization, One Previous Hospitalization / Seven or More Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	6.282757	0.009851	-0.00933	-0.00205
Eplerenone	-0.04146	-0.00933	0.019187	0.000234
ln(p)	-0.42635	-0.00205	0.000234	0.007221

Covariance Information – CV Hospitalization, Two Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	6.542929	0.007714	-0.00723	-0.0024
Eplerenone	-0.16027	-0.00723	0.019006	-0.00063
ln(p)	-0.80976	-0.0024	-0.00063	0.015143

Covariance Information – CV Hospitalization, Three Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	6.522251	0.023872	-0.02236	-0.00762
Eplerenone	-0.05888	-0.02236	0.06035	0.00058
ln(p)	-0.66069	-0.00762	0.00058	0.035374

Covariance Information – CV Hospitalization, Four Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	6.576833	0.136196	-0.13092	-0.02474
Eplerenone	-0.00437	-0.13092	0.220004	-0.00546
ln(p)	-0.66637	-0.02474	-0.00546	0.14173

Covariance Information – CV Hospitalization, Five Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.92959	0.039843	-0.03984	2.09E-18
Eplerenone	0.43647	-0.03984	0.062774	-0.02829
ln(p)	-1.61141	2.09E-18	-0.02829	0.265916

Covariance Information – CV Hospitalization, Six Previous Hospitalizations

Parameter	*Coef*	*Constant*	*Eplerenone*
Constant	5.92959	0.039843	-0.03984
Eplerenone	0.43647	-0.03984	0.062774
ln(p)	0		

Covariance Information – Adverse Events, No Previous Adverse Events

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	9.780193	0.0434739	-0.02068822	0.007896
Eplerenone	-0.394198	-0.0206882	0.03117204	-0.00103
ln(p)	0.482442	0.0078958	-0.00103094	0.002379

Covariance Information – Adverse Events, One Previous Adverse Event

Parameter	*Coef*	*Constant*	*Eplerenone*	*ln(p)*
Constant	5.415336	0.044537	-0.04282	-0.00436
Eplerenone	-0.05508	-0.04282	0.068071	0.000646
ln(p)	0.068987	-0.00436	0.000646	0.009419

Covariance Information – Other Cause Mortality

Parameter	*Coef*	*Constant*
Constant	10.4222	0.0192308
Eplerenone	0	
ln(p)	0	

Covariance Information – Atrial Fibrillation

Parameter	*Coef*	*Constant*	*Eplerenone*
Constant	9.6147	0.0192308	-0.0192308
Eplerenone	0.51899	-0.0192308	0.0504808
ln(p)	0		

Covariance Information – Use of Devices

Parameter	*Coef*	*Constant*	*Eplerenone*
Constant	9.29952	0.012987	-0.012987
Eplerenone	0.11997	-0.012987	0.0270715
ln(p)	0		

Covariance Information – Other Discontinuations

Parameter	*Coef*	*Constant*	*Eplerenone*
Constant	9.516843	0.015873	-0.015873
Eplerenone	-0.0981954	-0.015873	0.0299575
ln(p)	0		

Legend: CV = cardiovascular; HF = heart failure.

Table S2: Uncertainty for other model parameters

Parameter	Base Case	Distribution	SE	Reference
Resource Use				
% Receiving diuretic	85%	Beta	0.0068	Patient level data from the EMPHASIS trial[1]
% Receiving ACE inhibitor	78%		0.0080	
% Receiving ARB	19%		0.0075	
% Receiving beta-blocker	87%		0.0065	
% Receiving digitalis glycosides	27%		0.0085	
% Receiving antiarrhythmic drug	14%		0.0067	
% Receiving antithrombotic drug (antiplatelet or oral anticoagulant)	88%		0.0061	
% Receiving lipid-lowering agent	63%		0.0093	
% Receiving ICD	81%		0.0075	Patient level data from the EMPHASIS trial[1]
% Receiving CRT	50%		0.0096	
Device life ICD	5	Uniform: 2- 9		Fox et al.[2]
Device life CRT	6.5	Uniform: 5-8		
% having arrhythmia	28%	Beta	0.0199	Patient level data from the EMPHASIS trial[1]
% having myocardial infarction, unstable angina or chest pain	32%		0.0208	
% having stroke or TIA	12%		0.0147	
% having syncope/near syncope or hypotension	8%		0.0117	
% having cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event	14%		0.0155	
% having pulmonary embolism	1%		0.0034	
% having other peripheral arterial problem	5%		0.0096	
% having ruptured aneurysm	0%		0.0020	
Utilities				
Intercept	0.759	Beta	0.040	Gohler et al.[3]
Age	0.002		0.001	
Male	0.054		0.009	
History of diabetes	-0.041		0.009	
History of >2 AMIs	-0.061		0.009	
History of stroke/TIA	-0.074		0.014	
History of PVD	-0.046		0.012	
History of COPD	-0.035		0.013	
European origin	-0.060		0.009	
Recurrent hospitalization 1	-0.024		0.007	
Recurrent hospitalization 2	-0.031		0.009	
Recurrent hospitalization >=3	-0.055		0.001	
Gynecomastia	-0.003		0.007	
Atrial fibrillation	-0.084	+ or - 30%		Berg et al.[4]
UK Costs				
Diuretic*	£24.78	Uniform: £10.31 - £135.14		Scottish Tariff 2010-11[5]
ACE inhibitor*	£26.60	Uniform: £14.94 - £40.83		
ARB*	£198.90	Uniform: £31.05 - £480.30		
Beta-blocker*	£57.68	Uniform £14.87 - £730.50		
Digitalis glycosides*	£14.61	N/a – only 1 brand		
Antiarrhythmic drug*	£28.96	Uniform: £28.96 to £424.86		
Antithrombotic drug (antiplatelet or oral anticoagulant) *	£22.60	Uniform: £10.83 to		

Parameter	Base Case	Distribution	SE	Reference
		£62.38		
Lipid-lowering agent*	£113.34	Uniform: £13.18 to £343.20		
ICD	£3,666		£2,488	
CRT	£5,738		£1,558	
Heart failure hospitalization	£3,463		£1,449	
Arrhythmia	£1,618		£1,100	
Myocardial infarction, unstable Angina or chest pain	£2,545		£1,175	
Stroke or TIA	£3,963		£1,529	
Syncope/near syncope or hypotension	£1,255		£1,079	
Cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event	£4,663		£6,215	
Pulmonary embolism	£2,682		£1,259	
Other peripheral arterial problem	£9,201	Gamma	£9,981	
Ruptured aneurysm	£4,343		£1,739	
Hyperkalemia - non hospitalized	£154.08		£0.64	
Hyperkalemia - hospitalized	£652.00		£185.30	
Hypokalemia - non hospitalized	£154.08		£0.64	
Hypokalemia - hospitalized	£652.00		£185.30	
Renal failure - non hospitalized	£145.39		£5.23	
Renal failure - hospitalized	£1,011.00		£265.84	
Hypotension - non hospitalized	£125.06		£57.08	
Hypotension - hospitalized	£376.06		£69.63	
Cardiology	£113.05		£30.50	
GP visit	£53.00		£0.00	
Biochemistry	£1.29		£0.41	
Spanish Costs				
Diuretic*	€15.71	Uniform: €1.10 to €15.71		
ACE inhibitor*	€39.03	Uniform: €21.18 to €82.55		
ARB*	€450.29	Uniform: €437.57 to €456.56		
Beta-blocker*	€47.38	Uniform: €30.68 to €78.16		Consejo general de colegios oficiales de farmaceuticos[6]
Digitalis glycosides*	€16.44	N/a – only 1 brand		
Antiarrhythmic drug*	€70.86			
Antithrombotic drug (antiplatelet or oral anticoagulant) *	€49.31	Uniform: €24.47 to €179.63		
Lipid-lowering agent*	€96.56	Uniform: €40.54 to €135.51		
ICD	€8,480.76		€169.48	Oblikue Consulting[7]. Callejo et al.[8]
CRT	€4,257.00		€428.59	
Heart failure hospitalization	€3,320.61		€332.06	
Arrhythmia	€1,694.76		€169.48	
Myocardial infarction, unstable angina or chest pain	€4,285.86		€428.59	
Stroke or TIA	€6,196.64	Gamma	€619.66	
Syncope/near syncope or hypotension	€4,482.72		€448.27	Oblikue Consulting[7]
Cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event	€12,976.22		€1,297.62	
Pulmonary embolism	€4,260.80		€426.08	

Parameter	Base Case	Distribution	SE	Reference
Other Peripheral Arterial Problem	€2,780.38		€278.04	
Ruptured Aneurysm	€5,113.63		€511.36	
Hyperkalemia - non hospitalized	€103.44		€10.34	
Hyperkalemia - hospitalized	€103.44		€10.34	
Hypokalemia - non hospitalized	€75.44		€7.54	
Hypokalemia - hospitalized	€75.44		€7.54	
Renal failure - non hospitalized	€4,505.22		€450.52	
Renal failure - hospitalized	€4,505.22		€450.52	
Hypotension - non hospitalized	€0.00		€0.00	
Hypotension - hospitalized	€98.22		€9.82	
Cardiology	€56.69		€5.97	

Legend: ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator; PVD = peripheral vascular disease; SE = standard error; TIA = transient ischemic attack.
*upper and lower bounds calculated based upon the least and most expensive drug brands available

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was also carried out where input parameters for times to events, costs and utility values were assigned a probability distribution and were varied concurrently. The model was run 100 times using a Monte Carlo simulation method, randomly drawing sets of inputs from their respective distributions, producing 100 pairs of incremental effectiveness and cost results.

Model Validation
Three types of validation have been carried out:

- Comparison of modelled estimates of event rates within the first 21 months to EMPHASIS trial results
- Comparison of event rates from EMPHASIS with the modelled results based upon Kaplan–Meier data
- Comparison of the modelled results to available published information

Comparison of Modelled Data to EMPHASIS Trial Results

Table S3 shows the rates of the different events modelled over 2 years approximated to 21 months (using a ratio of 21/24) compared to the EMPHASIS trial results, which were reported for a median of 21 months. The rates of the different types of events are similar within the model and the EMPHASIS trial data for the majority of events. The modelled results, however, are consistently higher in events where recurrent incidences are modelled. This is due to the fact that censored patients do not appear to behave in the same way as uncensored patients within the trial data (i.e. patients are more likely to be censored if they have recurrent hospitalizations).

Table S3: Comparison of modelled results with EMPHASIS results

	Eplerenone		Standard care		Difference (standard care – eplerenone)		Difference (ratio eplerenone : standard care)	
	EMPHASIS*	Model*	EMPHASIS*	Model*	EMPHASIS	Model	EMPHASIS	Model
Cardiovascular hospitalization	0.173 (0.142,0.205)	0.305 (0.294,0.317)	0.197 (0.165,0.229)	0.338 (0.325,0.351)	0.02	0.03	0.88	0.90
Heart failure hospitalization	0.200 (0.157,0.244)	0.310 (0.297,0.323)	0.312 (0.264,0.361)	0.461 (0.446,0.476)	0.11	0.15	0.64	0.67
Cardiovascular death	0.108 (0.089,0.127)	0.084 (0.081,0.088)	0.135 (0.114,0.156)	0.119 (0.115,0.123)	0.03	0.03	0.80	0.71
All cause death	0.017 (0.009,0.025)	0.018 (0.016,0.020)	0.020 (0.012,0.028)	0.018 (0.017,0.020)	0.00	0.00	0.85	1.00**
Adverse events	0.187 (0.161,0.213)	0.265 (0.257,0.274)	0.142 (0.119,0.165)	0.195 (0.187,0.202)	-0.05	-0.07	1.32	1.36

ICD or CRT	0.052 (0.039,0.066)	0.048 (0.045,0.050)	0.056 (0.042,0.070)	0.054 (0.051,0.057)	0.004	0.006	0.93	0.89
Discontinuation	0.121 (0.102,0.141)	0.132 (0.128,0.136)						

Legend: CI = confidence interval; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator.
*95% CI shown in brackets; ** all cause death assumed the same for both arms in the model as no visible or significant difference in trial results

It can be seen from the above, that the model estimates a higher number of hospitalizations and adverse events relative to those reported in the EMPHASIS trial. The same applies to cardiovascular (CV) mortality. The conditional probabilities for a second or subsequent event are taken from the EMPHASIS trial so at first glance this is puzzling. We believe the explanation lies in the fact that people who have had an event, and even more so two events, are more likely to have been censored in the trial than those who have had no events. Thus the model simulates events that may well have occurred in these patients but were not recorded within EMPHASIS because the patient has been censored. Earlier parts of the simulation, before many people would have had a first event, fit the trial data well and the proportion of patients experiencing events that do not recur matches well to the trial data, therefore this is believed to be the most plausible explanation.

For all events where no interaction is assumed within the model the model predicts the EMPHASIS trial results at approximately 21 months follow-up well, with the confidence intervals for the probability of events for eplerenone and standard care overlapping and the actual events rates predicted by the model being a close estimate of the EMPHASIS trial information. Additionally when the ratios between the two treatment arms from the trial compared to the model are analyses results are consistent for the majority of endpoints with no consistent directional bias in the differences between model and trial results.

Comparison of Modelled Data Event Rates with EMPHASIS

Figure S1 to Figure S8 show a comparison between the modelled data for the proportion of patients experiencing an event and the data from the EMPHASIS trial. The time to first event curves fit well for the data from the beginning of the EMPHASIS trial, diverging slightly as the trial progresses. This is due to the very high level of censoring within the EMPHASIS trial at later time points (therefore data early on in the trial is given much greater weight).

Table S4: Illustration of censoring – CV hospitalization, eplerenone

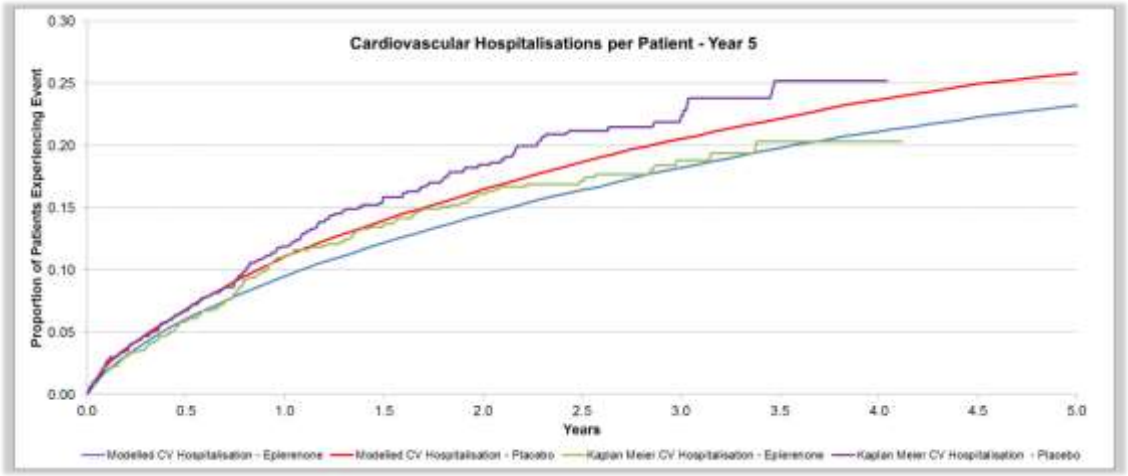
Days	Years	Events	N in data	N no longer in data	Mean events
50	0.14	44	1364	0	0.0323
150	0.41	72	1222	142	0.0589
250	0.68	100	1096	268	0.0912
350	0.96	108	1007	357	0.1072
450	1.23	111	922	442	0.1204
550	1.51	92	806	558	0.1141
650	1.78	91	721	643	0.1262
750	2.05	94	633	731	0.1485
850	2.33	71	520	844	0.1365
950	2.60	69	434	930	0.1590
1050	2.87	54	331	1033	0.1631
1150	3.15	47	246	1118	0.1911

Legend: CV = cardiovascular.

Table S4 provides an illustration of the rate of censoring within the trial. It can be seen that after 1 year the number of patients censored increases rapidly with more than half of the trial patients censored at 2 years. This illustrates why the modelled curves generally fit the beginning of the trial data well and not the end of trial information.

A high proportion of patients that have adverse events or are hospitalized due to CV or heart failure (HF) events had their treatment stopped in the clinical trial. This would not normally be a problem. However, in this study, data were collected for subsequent events within a few days of treatment being stopped but after that the data were censored. Therefore further events or death have not been recorded. Since we know from the data that a patient that has had one event is far more likely to have a subsequent event, then we are missing data on potentially a large number of events. This is the same for both arms of the trial. Therefore, the frequency of events is under reported. The clinical trial publications all concentrated on time to first event, which is unaffected by the censoring, but all events need to be considered for cost estimates. The model predictions for hospitalizations etc. should therefore be higher than those reported by the EMPHASIS trial, which they are. If data had continued to be collected for patients where treatment was stopped, it would have been easy to use these data to validate the model. Since the data were censored, there is no way of checking the model predictions precisely against actual values.

Figure S1: Comparison of modelled and EMPHASIS trial data, CV hospitalization



Legend: CV = cardiovascular

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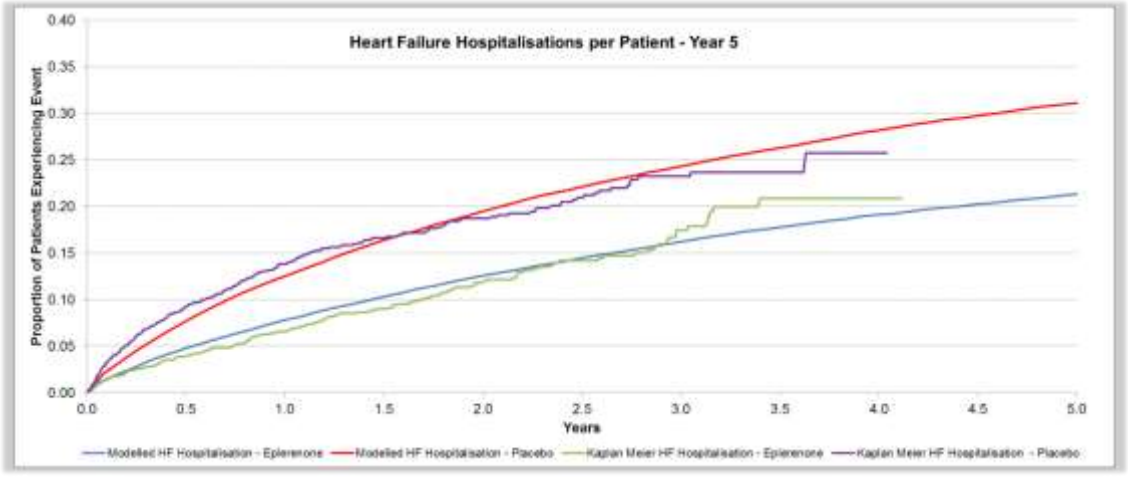
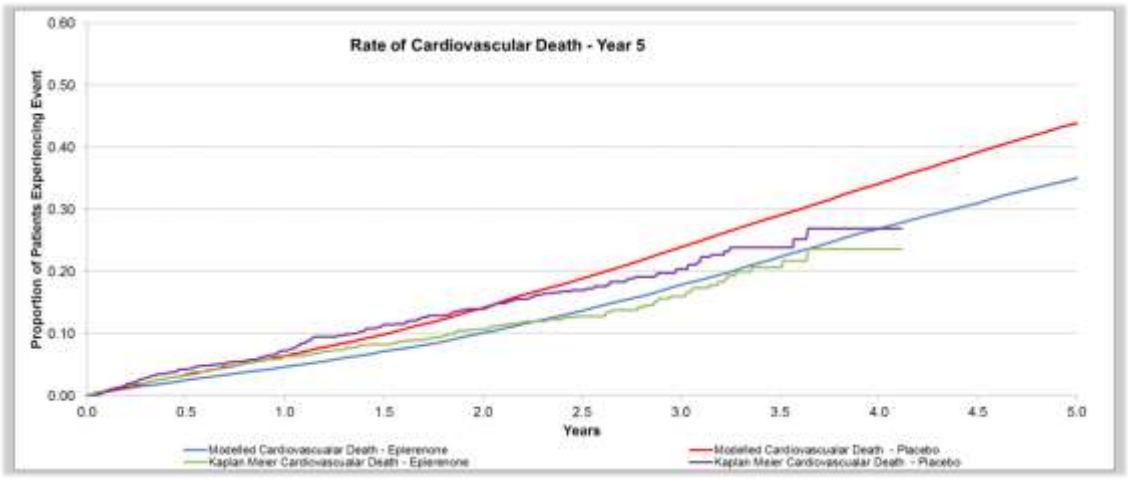
Figure S2: Comparison of modelled and EMPHASIS trial data, HF hospitalization



Legend: HF, heart failure.

Figure S3: Comparison of modelled and EMPHASIS trial data, CV mortality



Legend: CV = cardiovascular.

Figure S4: Comparison of modelled and EMPHASIS trial data, all cause mortality

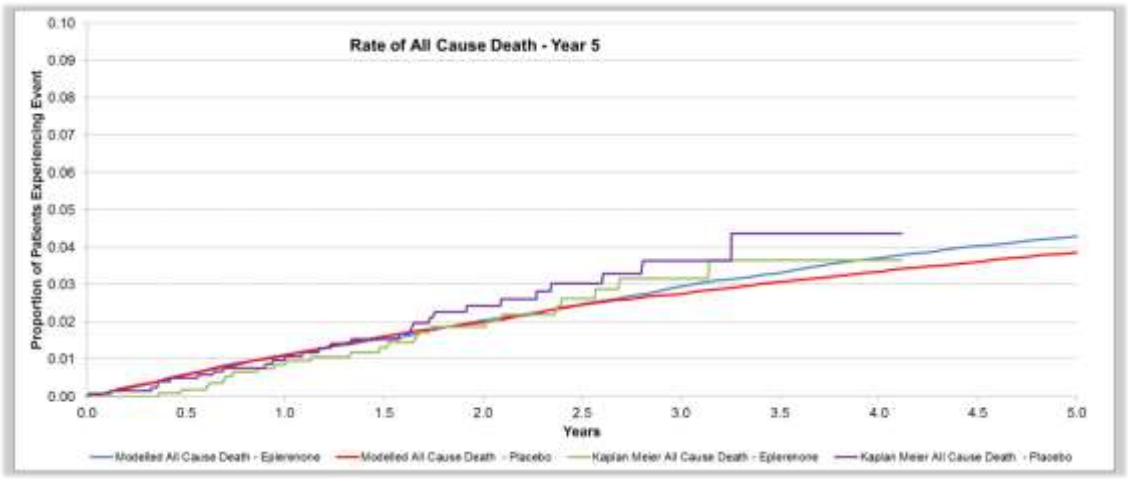


Figure S5: Comparison of modelled and EMPHASIS trial data, adverse events

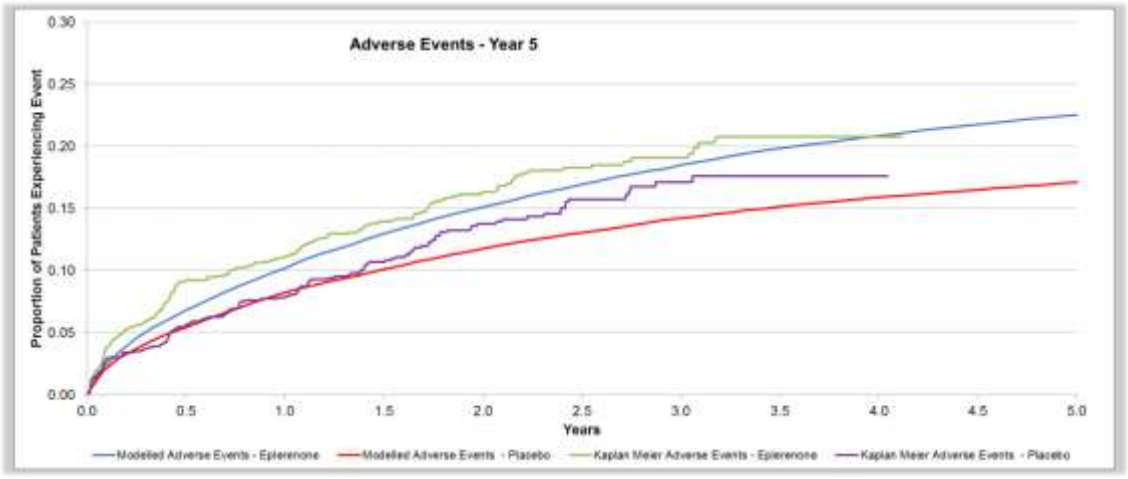
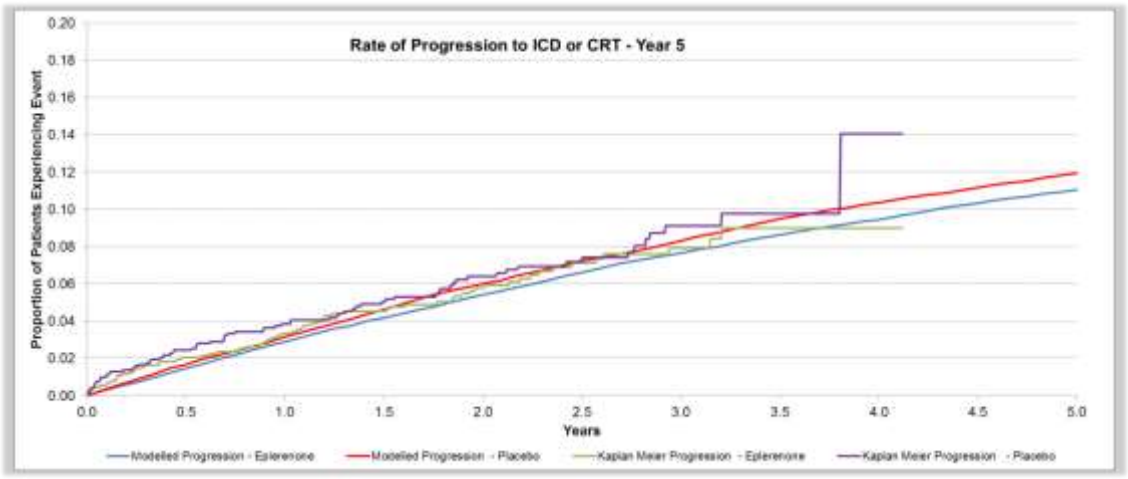


Figure S6: Comparison of modelled and EMPHASIS trial data, use of ICD or CRT



Legend: CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

Figure S7: Comparison of modelled and EMPHASIS trial data, discontinuation

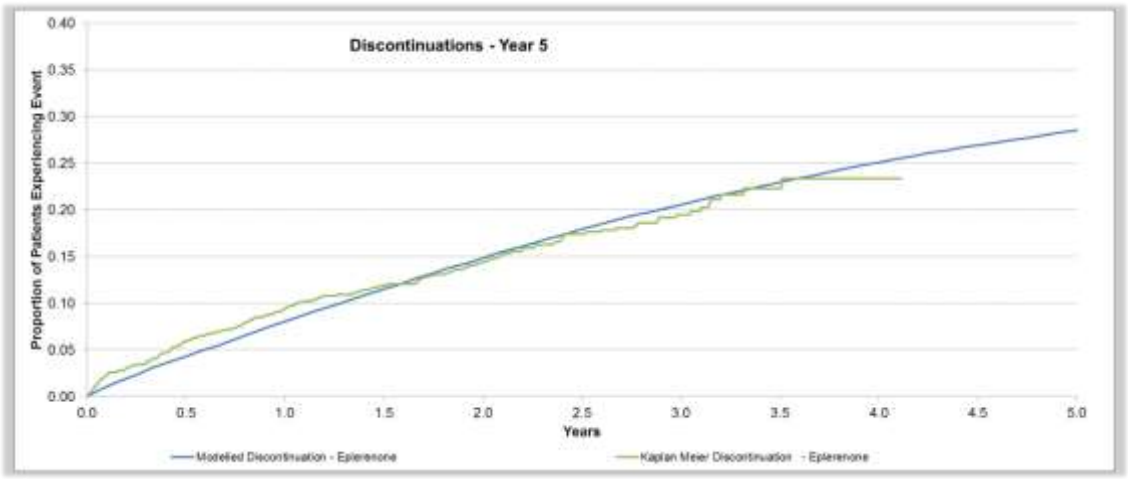
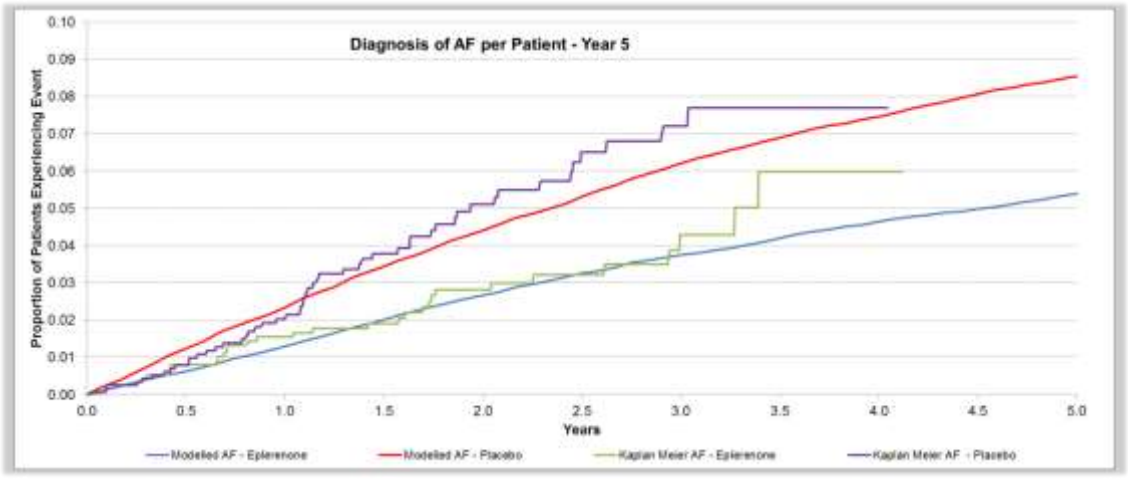


Figure S8: Comparison of modelled and EMPHASIS trial data, diagnosis of atrial fibrillation



Legend: AF = atrial fibrillation.

Rationale for Cost-effectiveness Analysis

When considering whether to fund any intervention, healthcare providers must assess if there is sufficient clinical benefit to be gained from the use of resources. Cost-effectiveness analysis is a useful tool in this process, attempting to quantify both clinical benefit and resource usage. By presenting data in terms applicable across interventions (i.e. cost per quality-adjusted life year) it allows stakeholders to make objective assessments about relative value. When combined with evaluation of numbers-needed-to-treat and budget impact analyses, cost-effectiveness data provides the payer with comprehensive evidence to inform decisions about allocation of resource. These analyses, coupled with the clinical findings from EMPHASIS-HF and other trials with mineralocorticoid receptor antagonists (MRAs) have clear implications for the management of patients with HF-REF. Not only do MRAs improve survival and reduce hospitalization, but they provide these benefits at modest additional cost to the healthcare system. There is little trade-off between the interest of the individual patient and the larger population served by the healthcare system.

Comparison of Published Information to Trial Based Estimates for Relationship between Mortality and CV Hospitalisation

Published information is available for a cohort of patients with HF in British Columbia by Setoguchi et al.[9] There are a few key differences between this population and the EMPHASIS trial population to which the decision problem relates:

- Older age – average age of 77 compared to EMPHASIS average age of 69
- HF population – all patients who have had a previous HF hospitalization compared to the specific EMPHASIS population of chronic systolic HF, New York Heart Association Class II and reduced left ventricular ejection fraction

In general, the data provided within the paper is supportive of the methodology used to estimate increased risk of CV mortality and shorter time to additional hospitalizations following first hospitalization within the modelling of the EMPHASIS trial data. The paper showed that, after adjusting for age, sex, and major comorbidities, the number of HF hospitalizations was a strong predictor of all-cause death.

Table S5 Comparison of Estimated Time to Death

	From 1st hospitalization	**From 2nd or more hospitalization**	**Hazard ratio from 1 hospitalization to 2 or more**
Setoguchi et al[9]	2.4 years	0.6 years	Between 1.22 and 1.84, adjusting for age and sex
EMPHASIS model*	8 years	4.5 years	1.75 (between 2 & 1 hospitalizations), 1.88 (between 3 or more & 1 hospitalizations)

* CV mortality, other cause mortality was not linked

Table S5 shows the comparison of the published information to that used within the trial. As would be expected, the trial hazard ratios are higher than the published information. This is because trial estimates are applied only to CV mortality with no impact assumed upon other mortality, whereas the estimates within the paper relate to all-cause mortality. The time to death from first hospitalization and second hospitalization within the two sources of information also make sense as the population within the published paper is 8 years older, meaning that death is likely to occur earlier.

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