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Cost-effectiveness of spironolactone in patients with severe heart failure

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Abstract:

Background Management of heart failure is estimated to consume 1% to 2% of total healthcare resources with hospital admissions accounting for up to 70% of this. The ability of the aldosterone antagonist spironolactone to reduce hospital admission rates by 35% would be expected to prove cost-effective.

Aim To determine the cost effectiveness of spironolactone when added to standard therapy in patients with severe chronic heart failure.

Methods A Markov model of chronic heart failure was constructed using "Treeage®" software. Irish cost data were incorporated into the model.

Results The incremental cost-effectiveness ratio (ICER) for spironolactone therapy was €466 per life year gained (LYG). Sensitivity analysis demonstrated an ICER range of €75 to €1136 per LYG.

Conclusion This economic evaluation suggests that the addition of spironolactone to standard therapy for patients with severe chronic heart failure is not only safe and effective but is highly cost-effective in the Irish healthcare setting.

Introduction

Chronic heart failure is a disease associated with high morbidity and mortality, and is now acknowledged as a major contributor to increasing healthcare expenditure in the western world. The addition of spironolactone to standard therapy in patients with severe heart failure has been proven to reduce mortality and hospital readmission rates.

In the Randomised Aldactone Evaluation (RALES) study patients with severe heart failure (defined as New York Heart Association (NYHA) class III and IV, left ventricular ejection fraction $\leq 35\%$) were randomised to receive spironolactone 25mg daily (n=822) or placebo (n=841) in addition to standard therapy which might include loop diuretic, ACE inhibitor, digoxin , β blocker or a combination of these[1]. The mean age of the patient cohort was 65 years.. The trial was stopped early, after a mean follow up of 24 months, when a significant reduction in death from any cause was found. Spironolactone reduced mortality by 30% and reduced hospitalisation rate for heart failure by 35%. It was well tolerated and the incidence of serious hyperkalaemia was minimal in both study groups.

Heart failure consumes between 1-2% of the total healthcare budget in developed countries, and hospital costs account for at least two thirds of this. The readmission rates within six months of discharge with a primary diagnosis of heart failure is up to 50%[2, 3]. Reducing admission rates should be cost-effective. Spironolactone is relatively inexpensive, costing €0.12 daily on the General Medical Services (GMS) scheme), and the RALES study demonstrates its clinical effectiveness.

In the present study, we determined the incremental costs and effects of spironolactone plus standard therapy compared with standard therapy alone.

Method

This study was performed through the design of a Markov model using "Treeage®", a health economic tool for conducting economic evaluations. Economic modelling is a technique which is used to extrapolate cost and effectiveness estimates over a longer time period than that obtained from clinical trial data. Markov models are particularly suited to modelling the progression of chronic disease, as they represent random processes that evolve over time[4].

The first task in constructing a Markov model is to define the disease in terms of different health states, which represent clinically and economically important events in the disease process. In this model three health states were defined; severe heart failure, severe heart failure with hospitalisation and death. Transition probabilities were then assigned for movement between these states over a discrete time period of one year (Figure 1).

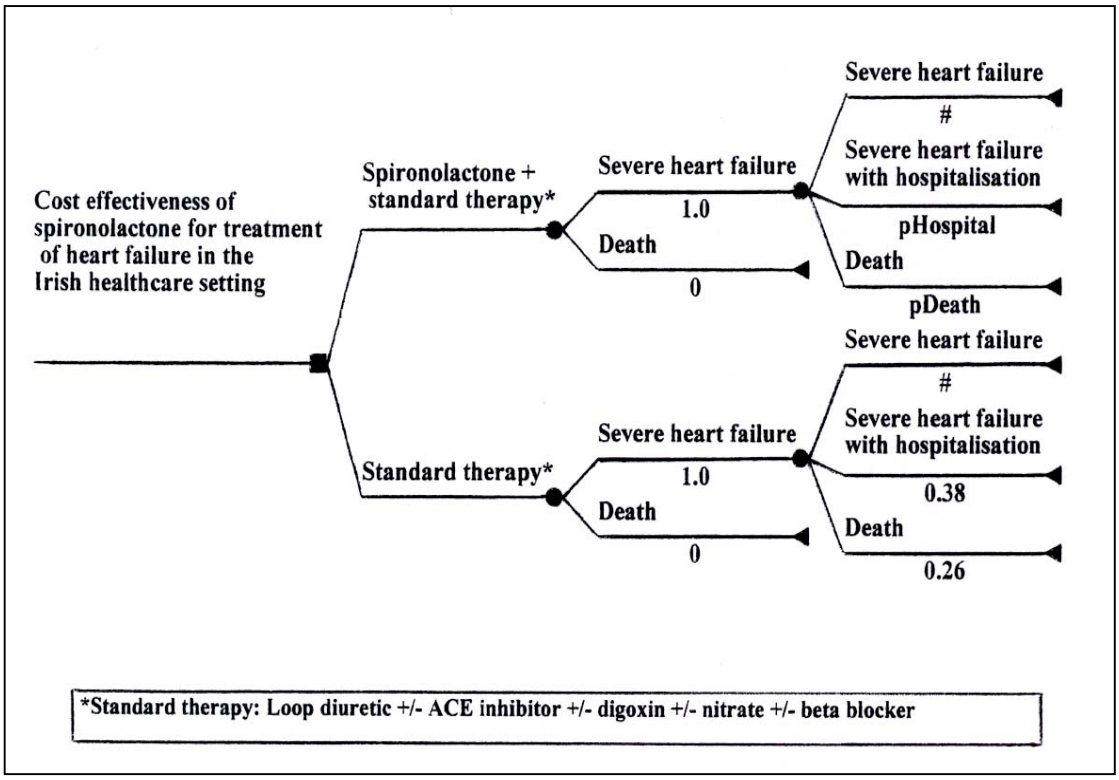

Figure 1. Markov Model – cost-effectiveness of spironolactone for the treatment of severe heart failure in the Irish healthcare setting.

The probabilities for death and hospitalisation for patients on standard therapy were obtained from a cohort of patients attending our teaching hospital over a 12 month period[5]. Differences in the probabilities of mortality and hospitalisation for patients treated with spironolactone plus standard therapy were obtained from the RALES study[1]. We assumed that the probabilities of hospitalisation and death for severe heart failure among patients on spironolactone would revert to those of patients receiving standard therapy after the trial period of 2 years i.e. the mean follow up period for the RALES study. However, the model was designed to enable alteration in the rates of hospitalisation (pHospital) and mortality (pDeath) in the spironolactone arm to facilitate sensitivity analysis. The model was run over a 10 year period to reflect patient survival rates. The incremental cost effectiveness ratio (ICER) can be calculated as (Cost A- Cost B) / (Effect A – Effect B).

Resource use was estimated as follows: The mean dose of spironolactone prescribed in the RALES study was 25 mg daily. The drug acquisition cost, of €45 per annum,

was obtained from the July 2002 edition of the *Irish Monthly Index of Medical Specialities* (MIMS). The cost of hospitalisation for the treatment of severe heart failure was established previously by this centre (£2,146)[3]. This cost was calculated in Irish pounds in 2000, converted to euro and inflated using the annual consumer price index for 2000-2001 and 2001-2002 as provided by the Central Statistics Office i.e. 5.6% and 4.9% respectively to give a hospitalisation cost estimate of €3,019. The cost of one hospital outpatient clinic visit was calculated using the same method and was estimated at €83 per patient[5]. Both costs and outcomes were discounted at 5% and 1.5% respectively.

Results

In this model, the ICER of spironolactone in patients with severe heart failure was €466/LYG. Sensitivity analysis demonstrates the influence of hospitalisation and mortality rates, based on 95% confidence intervals from the RALES study, on this figure (Table 1). The effect of number of outpatient visits required when initiating spironolactone and the cost of hospitalisation was also examined. The costs of hospitalisation employed in the sensitivity analysis were based on the range obtained from a cost of illness study undertaken in our hospital previously[3]. The model is sensitive to changes in hospitalisation and mortality rates and to variations in cost of hospitalisation and outpatient visits. If the cost of hospitalisation is €3019 the ICER is €466/LYG, but if the cost of hospitalisation is increased to €9319 the spironolactone arm dominates standard therapy, that is, spironolactone therapy results in savings.

Two way sensitivity analysis demonstrating the relationship between probability of death or hospitalisation on the incremental cost effectiveness ratio (ICER) of spironolactone in patients with severe heart failure.		
Probability of Hospitalisation (pHospital)	**Probability of Death (pDeath)**	**ICER**
0.21	0.16	€309/LYG
0.25	0.18	€466/LYG
0.29	0.21	€624/LYG
One way sensitivity analysis demonstrating the relationship between costs of hospitalisation and number of outpatient visits on the ICER		
Additional outpatient visits required to initiate spironolactone	**Number of visits**	**ICER**
	1	€466/LYG
	2	€815/LYG
	4	€1136/LYG
Cost of hospitalisation	**Cost**	**ICER**
	€1060	€728/LYG
	€3019	€466/LYG
	€9319	Dominated*
* Dominated means that at this cost of hospitalisation the use of spironolactone is both more effective and less costly than standard therapy.		

Table 1. Cost effectiveness of spironolactone - sensitivity analysis.

Discussion

The results of this study demonstrate that the addition of spironolactone to standard therapy for the management of chronic severe heart failure is a highly cost effective intervention. The spironolactone treatment arm had an ICER of €466/LYG. Sensitivity analysis demonstrated an ICER range of €75/LYG to €1136/LYG. Although the model is sensitive to changes in costs and effects the use of spironolactone remains cost effective under all scenarios. An ICER of €20,000 per life year gained (LYG) would be considered very cost effective.

It is recommended that patients receiving spironolactone should have their blood biochemistry checked at 1, 4, 8 and 12 weeks, then at 6, 9 and 12 months and 6 monthly thereafter[6]. For the model used in this study, we estimated patients on spironolactone would require one extra outpatient visit compared with patients receiving standard therapy (estimated at 4 outpatient visits per year). If 4 additional outpatient visits were required initially the ICER would be €974/LYG, which is still highly cost effective. The RALES study demonstrated that, as well as substantially reducing the risk of both hospitalisation and death among patients with severe heart failure, spironolactone significantly improves patients symptoms of heart failure. For the purpose of this study effectiveness of spironolactone was measured in terms of changes of life expectancy rather than quality adjusted life years, because data to estimate the latter were unavailable. Whilst the average age of Irish outpatient populations with CCF may be higher than those in the RALES study (76 versus 65 years) the aetiology of the CCF was similar[3].

A cost effectiveness study from Spain also using data from the RALES study, demonstrated an ICER of €3555/LYG[7]. The result differs from our study due in part

to differing methodologies employed in the cost effectiveness analysis. Firstly, a societal perspective was taken for the Spanish study. Pension payments for those who survived were included, as well as direct medical costs. In the Spanish study future costs and benefits were discounted at a rate of 3%, compared to a rate of 5% for costs and 1.5% for benefits in our study. A similar study investigating the cost effectiveness of the beta blocker carvedilol for patients with chronic severe heart failure in Ireland reported an ICER of €1560/LYG[8]. Carvedilol has a higher drug acquisition cost than spironolactone and initially requires additional outpatient visits to titrate the dose. However, current European guidelines recommend β blockers in combination with ACE inhibitors as first-line therapy for patients with stable heart failure, unless contraindicated. Spironolactone is recommended as second-line therapy for patients in whom there are persisting symptoms and signs of heart failure[6].

Conclusion

The RALES study demonstrated the benefits of spironolactone in reducing morbidity and mortality in patients with severe heart failure. The addition of spironolactone to standard therapy would be expected to be a highly cost effective intervention in the management of patients with severe heart failure, as it has a low drug acquisition cost combined with significant clinical benefits. In this study, the incremental cost effectiveness ratio for spironolactone when added to standard therapy was €466/LYG. This demonstrates that the prescribing of spironolactone for patients with severe chronic heart failure is a highly cost effective intervention in the Irish healthcare setting.

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