

**Cost effectiveness of beta blocker therapy for patients
with chronic severe heart failure
in Ireland**

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Abstract:

Management of heart failure is estimated to consume 1% to 2% of total healthcare resources and recent data from the UK suggests this may be as high as 4% with hospital admissions accounting for approximately 70% of this expenditure. The safety and efficacy of β -blockers when added to standard therapy i.e. ACE inhibitors in chronic heart failure has recently been demonstrated in large placebo controlled trials. The ability of β -blockers to reduce hospital admission rates would be expected to prove cost effective. In this study the cost effectiveness of the β -blocker carvedilol when added to standard therapy in patients with severe heart failure was determined. Using economic modelling techniques and Irish cost data the incremental cost effectiveness ratio (ICER) for carvedilol therapy was €1560 per life year gained (LYG). Sensitivity analysis demonstrated an ICER range of €1560/LYG to €7322/LYG under a variety of assumptions. This suggests that carvedilol 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:

Three major placebo controlled clinical trials reported in the late 1990's demonstrated the beneficial effects of β -adrenergic receptor blockers when added to standard therapy in patients with mild to moderate heart failure.⁽¹⁻³⁾ Beta blocker therapy (carvedilol, bisoprolol, metoprolol) was well tolerated and resulted in a significant reduction in morbidity and mortality as well as reducing hospital admissions. Further evidence has confirmed the benefit of carvedilol in patients with severe chronic heart failure i.e. breathless at rest or minimal exertion. Carvedilol reduced mortality by 35% and the combined risk of death or hospitalisation by 24%.⁽⁴⁾ From an economic perspective between 1% and 2% of total healthcare resources are consumed in the management of heart failure therefore the introduction of drugs such as carvedilol with significant acquisition costs does raise the issue of cost effectiveness. The important issue for resource allocation is how much additional benefit is achieved for the extra cost incurred i.e. the incremental cost effectiveness ratio (ICER) of one therapy over another which is calculated as $\text{Cost A} - \text{Cost B} / \text{Effect A} - \text{Effect B}$. When costs are measured in monetary units and effect in natural units e.g. life years gained (LYG) an ICER less than €20,000 per LYG would be considered very cost

effective. In this study we determined the cost effectiveness of carvedilol for the treatment of patients with severe heart failure using economic modelling techniques incorporating Irish cost data.

Methods:

Markov modelling is used to determine the cost effectiveness of interventions used in chronic diseases as it represents random processes that evolve over time.⁽⁵⁾ The disease process is divided into distinct health states with transition probabilities assigned for movement between these states. Estimates of resource use are attached to each state and transition within the model. Running the model over a large number of cycles enables the estimation of long-term costs and outcomes associated with a disease and a particular healthcare intervention. In this model we used Treeage®, a health economic tool for conducting economic evaluations. Two health states were defined i.e. severe heart failure and death with transition probabilities as shown in Figure 1. Differences in the probabilities of death and hospitalisation in patients treated with carvedilol plus standard therapy (ACE inhibitor plus loop diuretic) were taken from the COPERNICUS study where mortality was reduced by 35% and hospitalisation for worsening heart failure by approximately 33%.⁽⁴⁾ The probabilities for patients treated with standard therapy were obtained from the patient cohort attending our hospital over a 12-month period, where readmission and mortality rates were 38% and 19% respectively. The model enables alteration in the rates of hospitalisation (pHosp) and mortality (pDeath) in the carvedilol arm to facilitate sensitivity analysis. Resource utilisation was estimated as follows: drug acquisition cost plus additional outpatient visits for the up-titration of carvedilol to the target dose of 25mg twice daily was estimated at €10 for the first year and €482 per annum thereafter. The cost of hospitalisation for the treatment of heart failure was determined by this centre in 2000 (£2,146).⁽⁶⁾ This cost was converted to euro and inflated using the annual consumer price index for 2000-2001, provided by central statistics office (5.6%), to give a hospitalisation cost estimate of €2,877. The model was run over a 10 year period with cost effectiveness expressed as cost per life year gained (LYG). Data were extrapolated on the basis that there was no additional benefit from carvedilol after the trial period. Both costs and outcomes were discounted at 5% and 1.5% respectively. Results were subject to sensitivity analysis.

Results:

In this economic model the incremental cost effectiveness of carvedilol in patients with severe heart failure was €1560/LYG. Sensitivity analysis demonstrates the influence of mortality and hospitalisation rates on this figure. The ICER increases with decreasing efficacy of carvedilol therapy e.g. €7322/LYG when mortality is reduced by just 5%. Similarly hospitalisation rates affect the ICER value e.g. a reduction in hospitalisation rate of 5% (as compared with 33%) increases the ICER to €2801/LYG. If the efficacy of carvedilol therapy in reducing mortality and hospitalisation was 50% of that obtained in the COPERNICUS study the ICER value would be €3545/LYG. It is seen that drug cost has a significant influence on cost effectiveness with an ICER of €98 when carvedilol cost is reduced by 50%. If the economic model is run for 5 years (rather than 10 years) the ICER is €2,275/LYG.

Discussion:

Morbidity and mortality for all grades of symptomatic heart failure are high with a one-year mortality of 20-30% for mild to moderate heart failure and up to 50% for severe heart failure.⁽⁷⁾ The prevalence of heart failure is 3 to 20 per 1,000 population but exceeds 100 per 1,000 in patients over 65 years. In developed countries the prevalence is increasing due in part to the increasing elderly population and success in the treatment of conditions such as myocardial infarction and hypertension. Management of heart failure is estimated to consume 1 to 2% of total healthcare resources and recent figures from the UK suggest this may exceed 4% with hospital admission accounting for 70% of this expenditure.^(8,9)

Whilst ACE inhibitors represent the cornerstone of heart failure treatment recent prospective, placebo-controlled studies of the addition of β -blockers to standard therapy in patients with chronic heart failure have confirmed a significant beneficial effect in terms of morbidity and mortality. This benefit extends to patients with severe heart failure where carvedilol produced a 35% reduction in mortality and a 24% decrease in the combined risk of death or hospitalisation. Current guidelines suggest β -blockers in combination with ACE inhibitors are first line therapy for patients with stable class I to IV heart failure.⁽¹⁰⁾ The ability of β -blocker therapy to reduce hospital

admission rates by approximately 30% suggests the potential for this therapy to be cost effective. In this study a Markov economic model is used to estimate the cost effectiveness of the β -blocker carvedilol for the treatment of patients with severe heart failure in the Irish healthcare setting. The carvedilol treatment arm had an incremental cost effectiveness ratio (ICER) of €1,560/LYG. A therapeutic intervention with an ICER less than €58,000 is frequently considered cost effective. Therefore carvedilol therapy for heart failure patients in Ireland is a highly cost effective intervention. When the probability of death or hospitalisation was varied in a one-way sensitivity analysis the ICER remained within the range €1560/LYG to €7,322/LYG. Even the assumption that the beneficial effect of carvedilol would be just 50% of that achieved in the COPERNICUS study the ICER was €3,545/LYG.

These results are consistent with other pharmacoeconomic analyses of β -blocker therapy in heart failure. A UK cost effectiveness model constructed using data from the CIBIS I and II trials and extrapolating data over a 5-year period demonstrated an ICER of £2761/LYG (€4526/LYG) under the worst case scenario.⁽¹¹⁾ The best-case scenario was a UK£771 saving per LYG. Similarly an economic evaluation of CIBIS for Germany indicated bisoprolol therapy resulted in overall savings due mainly to a reduction in hospitalisation.⁽¹²⁾ The results of these studies will differ from this study due in part to differing healthcare costs and the fact that the majority of patients in the CIBIS study had mild to moderate heart failure. It is unclear as to whether carvedilol is more or less cost effective than other β -blockers used for the treatment of heart failure i.e. metoprolol, bisoprolol. A head to head comparison of metoprolol and carvedilol on mortality and hospitalisation, the Carvedilol or Metoprolol Evaluation Trial (COMET) is ongoing and should provide definitive answers to these questions.

Conclusion:

The concept of using β -blockers for the treatment of heart failure was introduced in the 1970's. However, clinicians have been sceptical and β -blockers were widely regarded as contraindicated in heart failure. Over the past 7 years large randomised, placebo-controlled trials have demonstrated the beneficial effects of β -blockade in

reducing morbidity and mortality from heart failure. The significant reduction in hospital admission rates would be expected to prove cost effective. In this study, an economic model for severe chronic heart failure indicates an incremental cost effectiveness ratio of €1560/LYG for carvedilol when added to standard therapy. This suggests that carvedilol therapy for patients with severe chronic heart failure is not only safe and effective but is highly cost-effective in the Irish healthcare setting.

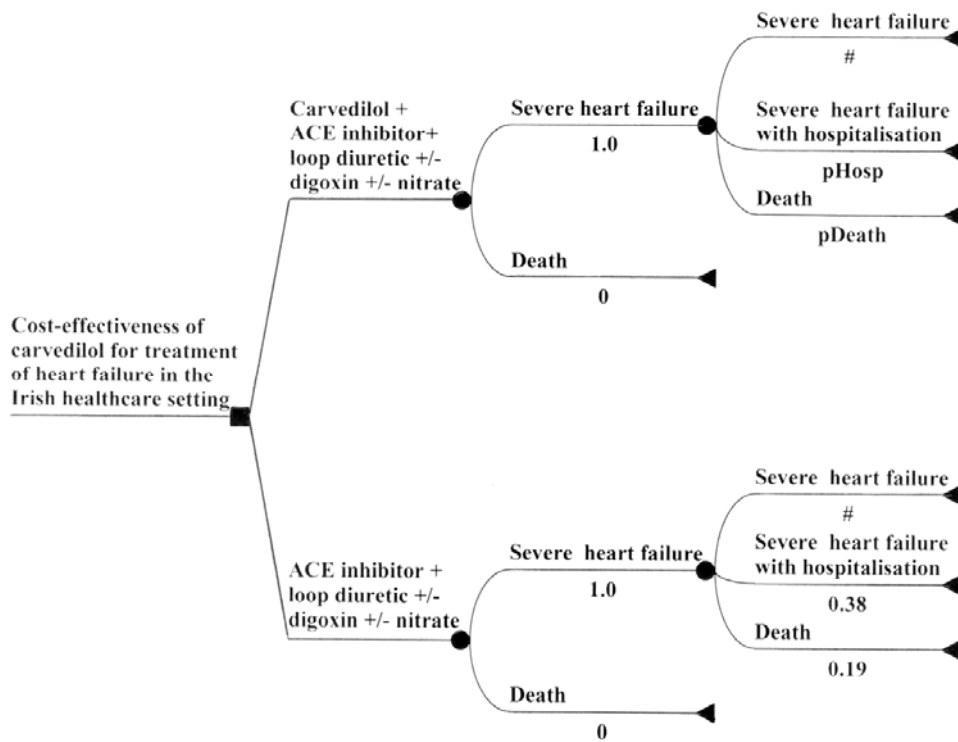


Figure 1

Markov Model – cost effectiveness of carvedilol for the treatment of severe heart failure in the Irish healthcare setting.

Table 1 One way sensitivity analysis demonstrating the relationship between probability of death or hospitalisation and drug cost on the incremental cost effectiveness ratio (ICER) of carvedilol therapy in patients with severe heart failure.

| | Probability | ICER |
|------------------------|--------------------|-------------|
| Death | 0.12 | €1,560/LYG |
| | 0.14 | €1,835/LYG |
| | 0.16 | €2,522/LYG |
| | 0.18 | €7,322/LYG |
| Hospitalisation | 0.26 | €1,560/LYG |
| | 0.29 | €1,974/LYG |
| | 0.33 | €2,388/LYG |
| | 0.36 | €2,801/LYG |
| Drug Cost | 100% | €1,560/LYG |
| | ↓ 20% | €1,185/LYG |
| | ↓ 50% | €98/LYG |

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