Cost-effectiveness analysis of carvedilol for the treatment of chronic heart failure in Japan
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two treatments for the care of chronic heart failure (CHF) were under evaluation. The treatments compared were the addition of carvedilol to conventional therapies and conventional therapies alone. The conventional therapies included the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, diuretics and digitalis. The treatment regimes were low-dose (5 mg/day) and high-dose (20 mg/day) carvedilol and placebo.

Type of intervention

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 20 to 79 years (mean age 60), with New York Heart Association (NYHA) class II-III and a left ventricular ejection fraction of less than or equal to 40%. A baseline age of 60 years was assumed in the model.

Setting
The setting was secondary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from a clinical trial published in 2000. Hospitalisation costs and inpatient medical expenses were derived from hospital administrative data between April 1999 and March 2000. The dates and sources for the outpatient management and drug costs were not reported. Medical fees related to 2001. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study plus authors’ estimates.

Link between effectiveness and cost data
Resource use was not derived from the same patient sample as the effectiveness data, but was derived from secondary sources.

Study sample
The study sample was not described in detail, but further details can be obtained from the parent clinical study (see Other Publications of Related Interest). The final sample comprised 174 CHF patients randomised to the low-dose
group (5 mg/day), high-dose group (20 mg/day) or placebo.

**Study design**
The study design was not described in detail, but further details can be obtained from the parent clinical study (see Other Publications of Related Interest). The MUCHA study was a double-blind, placebo-controlled comparative trial that was carried in patients with CHF in Japan. It seems that the patients were followed up for 6 and 12 months. Eight per cent of the patients from the carvedilol groups dropped out because of adverse events of carvedilol.

**Analysis of effectiveness**
The effectiveness analysis was described in detail, but further details can be obtained from the parent clinical study, (see Other Publications of Related Interest). The primary outcomes appear to have been defined as the number of cardiovascular-related hospitalisations due to CHF.

**Effectiveness results**
Hospitalisation rates because of worsening of heart failure were 20.4% in the placebo group, 2.6% in the carvedilol high-dose group, and 2.1% in the carvedilol low-dose group. This amounted to a risk reduction of 88% for the high-dose group and 91% for the low-dose group. There were only 4 deaths, with no significant difference in mortality rates among the three groups.

**Clinical conclusions**
The results of the trial suggested that carvedilol treatment is associated with a significant reduction in hospitalisation rates due to worsening of heart failure.

**Modelling**
A Markov model (Data 3.5, TreeAge Software, Inc.) of outpatients with CHF was employed to simulate the remaining life expectancy and expected medical costs. In addition, a short-term simulation of 60 months was also modelled. The cycle length for the model was 1 month.

**Methods used to derive estimates of effectiveness**
State transition probabilities were estimated for the model. These were based on the MUCHA trial and other literature.

**Estimates of effectiveness and key assumptions**
The monthly hospitalisation rate due to worsening heart failure was 2.7% for patients in the conventional therapy group and 0.25% for patients in the carvedilol group.

The monthly heart failure mortality rate (for a Japanese population) was 0.8%.

The odds ratio for mortality of carvedilol therapy versus no carvedilol therapy was 0.51%.

The monthly mortality rate for the carvedilol group was 0.41%.

The dropout rate for carvedilol was 8% (first month only).

The authors also assumed that CHF patients received outpatient care, including testing, at regular intervals. In addition, heart failure was assumed to worsen a specific amount each month, leading to hospitalisation for a period of one month.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the expected number of occurrences of either death or hospitalisation during the expected life span of the patient and during a 5-year period.

**Direct costs**
Resource use and the costs were not reportedly separately. The direct health care costs included the outpatient treatment schedule received by both groups and any hospitalisation and inpatient medical expenses in the event of patients suffering from worsening of heart failure. The outpatient treatment comprised examination, medication and a variety of tests performed at regular intervals. The tests included chart X-ray (annual), 12-lead electrocardiogram (monthly), echocardiogram (annual), brain natriuretic peptide (monthly), weight (monthly), urine test, blood test, and biochemical assay I (annually).

The source of the outpatient treatment costs was not reported. Hospitalisation and inpatient medical expenses were taken from a sample of patients admitted for acute heart failure to the Kitasato University Hospital from April 1999 to March 2000. No further information on the unit charges was given. Critical treatment medical costs for cases of mortality because of worsening of heart failure were not included as the authors suggested that, in most cases, the patient dies before any treatment can be implemented. The costs were discounted at an annual rate of 3% after the second year of simulation. The costs were expressed in 2001 prices.

**Statistical analysis of costs**
The data were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
The indirect costs were not included.

**Currency**
Japanese yen (Y).

**Sensitivity analysis**
A one-way sensitivity analysis was performed on the carvedilol group. The variables investigated were the monthly hospitalisation rate and the dropout rate, using values 50% higher and lower than the actual figures used in the analysis, and the mortality rate, using a value estimated from the 95% confidence interval of the placebo group's relative risk. In addition, the impact of medical costs on the results was studied by using values from the 95% confidence interval of aggregated values. Finally, a sensitivity analysis was also conducted using a 70% resumption rate for carvedilol therapy after acute heart failure.

**Estimated benefits used in the economic analysis**
Over the expected life span of the patient, the expected number of occurrences of either death or hospitalisation, calculated from changes in patient states, was 1.27 for the carvedilol group and 3.68 for the conventional therapy group.

From the life-year analysis with 3% discount rate in effects, the remaining life expectancy was estimated to be 45 months for the conventional group and 49 months for the carvedilol group. From the 5-year analysis with a 3% discount rate, the remaining life expectancy was estimated to be 47 months for the conventional group and 52 months for the carvedilol groups.

**Cost results**
The outpatient medical costs were Y11,835 in the conventional group and Y12,365 in the carvedilol group. The monthly drug costs were Y3,435 in the conventional group and Y9,843 in the carvedilol group. The cost per hospitalisation because of worsening of CHF was estimated to be Y1,802,096 when using the sample of patients.
admitted for acute heart failure to the Kitasato University Hospital.

From the life-year analysis with 3% discount rate in costs, the total medical expenses were estimated to be Y2,764,769 in the conventional group and Y1,445,439 in the carvedilol group. From the 5-year analysis with a 3% discount rate for costs, the total medical expenses were estimated to be Y2,916,626 in the conventional group and Y1,526,986 in the carvedilol group.

Carvedilol treatment incurred higher outpatient costs and drug costs than conventional therapy. However, the cost of conventional therapy for acute care for CHF offset the previous costs incurred by the carvedilol treatment because patients in this group experienced fewer events.

**Synthesis of costs and benefits**

The costs and effects were not combined in an incremental analysis as carvedilol always dominated the conventional therapy. The sensitivity analysis showed that the baseline results were robust.

**Authors' conclusions**

Carvedilol treatment for chronic heart failure (CHF) is a highly cost-effective method of therapy in the Japanese setting.

**CRD COMMENTARY - Selection of comparators**

The authors provided sufficient and clear evidence for the comparator chosen. Treatment with beta-blockers seemed to be an effective alternative for mild and moderate patients with CHF in the USA and Europe. The authors aimed to provide evidence for the Japanese setting. Concomitant use of ACE inhibitors, diuretics and digitalis appear to represent current practice in the authors' setting. You should decide if this is widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The authors used a large, double-blind, placebo-controlled trial to obtain the effectiveness data and augmented this with estimates derived from other literature. The trial was not described in detail, but further information can be obtained from the published study. It is unclear whether this was the best source of evidence to obtain the parameters for the model, as the authors did not mention whether a relevant systematic review of the literature was available. This would have been a better source of evidence for the treatment effect parameters. The authors justified their selection of studies (e.g. monthly mortality rate) in terms of data relevant to the Japanese population.

**Validity of estimate of measure of benefit**

The estimation of benefits was obtained directly from the model. The authors stated that quality-adjusted life-years were not used as the utility values for Japanese patients at each stage of CHF were not available. The authors appear to have used the outcomes defined in the effectiveness paper as the measure of benefit, probably because they are the end points defined in other trials, thus allowing them to compare the results obtained.

**Validity of estimate of costs**

All the relevant categories of costs were included for the perspective adopted. However, the source of evidence for outpatient management was not stated and this may limit the generalisability of the results obtained. The fact that there was no detailed information on what exactly was included in each category makes the costing exercise somewhat difficult to understand and compare with other similar studies. The omission of critical treatment medical costs for cases of mortality because of worsening of heart failure seems unlikely to have affected the results, as the authors provided sufficient justification for the omission. Resource use was unclear and only one figure (for hospitalisation) was presented. This may well influence the generalisability of the results to other settings and also the comparison of this cost-effectiveness study with similar published evidence. The source of the unit costs was not clear, but was likely...
to have been the reimbursement rate set by the Japanese health care insurance system (as this was the chosen perspective).

**Other issues**
The authors did not compare the results of their study with published evidence, although they acknowledged that there were no studies that reported results for more than a 5-year period. The impact of the results on generalisability was partially addressed by the sensitivity analysis.

**Implications of the study**
The authors described and summarised the assumptions used in the model to validate their results. No further recommendations or suggestions for changes in practice were mentioned in the paper. However, the authors acknowledged that the impact on quality of life and productivity losses of patients are two issues where further research is needed, owing to the lack of published evidence.

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**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adrenergic beta-Antagonists /economics /therapeutic use; Adult; Aged; Angiotensin-Converting Enzyme Inhibitors /economics /therapeutic use; Carbazoles /economics /therapeutic use; Cost-Benefit Analysis; Diuretics /economics /therapeutic use; Dose-Response Relationship, Drug; Heart Failure /drug therapy /economics /mortality; Humans; Insurance, Health /economics; Japan; Markov Chains; Middle Aged; Propanolamines /economics /therapeutic use; Survival Analysis; Time Factors; Ventricular Dysfunction, Left /physiopathology

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