Cost-Effectiveness Analysis of Carvedilol for the Treatment of Chronic Heart Failure in Japan

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Background The cost-effectiveness of ß-blocker use in patients with chronic heart failure (CHF) has never been elucidated in a Japanese study.

Methods and Results A Markov model for outpatients with CHF was constructed to simulate remaining life expectancy and expected medical costs for each patient. Each patient was assumed that they received either carvedilol in addition to conventional therapies (ie, diuretics, diuretics, and angiotensin-converting enzyme inhibitors) or conventional therapies alone. Analyses were conducted both for each patient’s remaining lifetime and for a period of 5 years. Analyses were performed from the perspective of Japanese healthcare insurance. Analysis for treatment over the course of each patient’s expected life span with carvedilol plus conventional therapies versus conventional therapies alone yielded expected medical costs of ¥3.5 million and ¥3.5 million respectively, and a life expectancy of 121 months and 88 months, respectively. The analysis of a 5-year period yielded ¥1.4 million and ¥2.8 million in expected medical costs and 49 and 45 months life expectancy, respectively, for carvedilol versus conventional therapy.

Conclusions Carvedilol treatment for CHF patients is a highly cost-effective method of therapy in the Japanese medical environment. (Circ J 2004; 68: 35–40)

Key Words: Beta-blocker; Carvedilol; Cost-effectiveness; Heart failure

Traditionally, ß-blockers have been contraindicated for patients with chronic heart failure (CHF), but large-scale clinical trials for carvedilol and a number of other ß-blockers have shown that they reduce mortality and morbidity rates1–6 establishing the usefulness of ß-blocker therapy for patients with CHF. In the treatment guidelines for CHF in the USA and Europe, active ß-blockers are recommended for mild to moderate CHF7–9. Further, in a double-blind, placebo-controlled comparative trial in Japan (Multicenter Carvedilol Heart Failure Dose Assessment: MUCHA) with CHF patients with ischemic or non-ischemic dilated cardiomyopathy, carvedilol was found to lead to a marked reduction in cardiovascular-related hospitalization rates compared with the placebo10. The present study uses the results from the MUCHA trial to perform a cost-effectiveness analysis of carvedilol in patients with CHF.

Methods

MUCHA Trial Summary

The subjects in the MUCHA trial were 174 CHF patients aged 20–79 years (mean age, 60.3) with New York Heart Association (NYHA) class of II–III and a left ventricular ejection fraction of less than or equal to 40%. Patients who were shown to tolerate 2.5 mg or 5 mg per day of carvedilol orally were divided into a low-dosage group (5 mg/day), a high-dosage group (20 mg/day), and a placebo group, and then administered the test drug for 6–12 months (mean, 10.3 months). Concomitant use of angiotensin converting enzyme (ACE) inhibitors, diuretics, and digitalis was permitted during the trial period. Results showed that hospitalization rates because of worsening of heart failure were 20.4% for the placebo group, 2.6% for the carvedilol high-dosage group, and 2.1% for the carvedilol low-dosage group, amounting to a risk reduction of 88% for the high-dosage group and 91% for the low-dosage group. There were only 4 cases of death, with no significant difference in mortality rates among the 3 groups.

Model

A Markov model showing the long-term changes in status of the CHF patients was constructed to investigate the medical economics of conventional therapy alone (ie, diuretics, ACE inhibitors, and digitalis) as opposed to carvedilol combined with conventional therapy.

A Markov model similar to that shown in Fig 1 was constructed to express the status of CHF outpatients. For this analysis, we performed a long-term simulation wherein state transitions were calculated monthly over the expected life span of the CHF patient; however, because the prognosis for CHF patients being treated with carvedilol beyond 5 years is unknown, we also performed a sub-analysis using a short-term simulation period of 60 months (5 years)11. Analyses were performed from the perspective of Japanese healthcare insurance in Japan, and loss of productivity in the workplace arising from either outpatient treatment or hospitalization was not taken into account. Costs and effectiveness after the second year were discounted by an annual rate of 3% in the calculations.

Some assumptions were established as follows.
Patients were assumed to be 60-year-old CHF patients with an NYHA class of II–III, as per the MUCHA trial.

The CHF patients were assumed to receive outpatient care, including testing, at regular intervals. The conventional treatment group was assumed to receive treatment with diuretics, ACE inhibitors, and digitalis at the same ratio as the patients in the MUCHA trial: 77% were administered diuretics, 86% ACE inhibitors, and 65% digitalis. Based on the drug price in Japan for each type of drug and the administration ratios described, the additional daily drug costs for each patient was set at ¥14.5 per day (Table 1).

For the carvedilol group, patients were assumed to be administered the 3 conventional medications as well as one 10 mg tablet of carvedilol twice a day (daily cost: ¥213.6).

Heart failure was assumed to worsen a specific amount each month, leading to hospitalization for a period of 1 month (S1 → S2). During the hospitalization period, the patient was assumed to receive acute treatment, with their previous treatment of conventional therapy or conventional therapy plus carvedilol temporarily curtailed. The appropriate chronic treatment was then resumed once the patient was discharged from the hospital (S2 → S1).

Mortality, both from worsening of heart failure and natural causes, was assumed to occur. Because mortality arising from worsening of heart failure resembles sudden death, in that the patient often dies before there is a chance to receive acute care at a medical facility, critical treatment medical costs for cases of mortality because of worsening heart failure were not taken into account.

Probabilities

1. Worsening Heart Failure The probability for worsening of heart failure was set according to the results of the MUCHA trial.

Because the analysis cycle for the Markov model is 1 month, the state transition probabilities used in the model must be on a monthly basis. For the probability of worsening of heart failure, the yearly hospitalization rate for the high-dosage carvedilol group and the placebo group because of worsening of heart failure in the MUCHA trial was used to calculate the monthly hospitalization rates: it was 2.7% for patients in the conventional therapy group and 0.25% for patients in the carvedilol group.

2. Mortality Rate Two types of mortality were considered for the purposes of this study: from worsening of heart failure and mortality from all other causes.

In the MUCHA trial, there were only 4 cases of death, so no reliable mortality rates for heart failure worsening were obtained. Therefore, it was decided to instead adopt mortality rates obtained from other long-term follow-up studies. The cumulative yearly mortality rate in the well-known SOLVD study\textsuperscript{12} on enalapril (mean follow-up period, 41.4 months) is reported at 12.4%. Tsuchihashi et al reported in their domestic Japanese research (mean follow-up period, 2.4 years) a cumulative yearly mortality rate of 9.1%\textsuperscript{13}.

Because the subjects of the present analysis are Japanese, it was decided to use the latter study’s data on mortality among Japanese, so the monthly heart failure mortality rate was calculated to be 0.8%.

It was decided that the mortality rate from worsening of heart failure for the carvedilol group would be calculated...
relative to the mortality rate of the conventional therapy group. According to a meta-analysis of β-blockers, it is reported that the overall odds ratio for mortality of carvedilol therapy versus non-carvedilol therapy is 0.51 (95% confidence interval: 0.33–0.77). Thus the relative risk was considered to be 0.51, and the monthly mortality rate for the carvedilol treatment group was set at 0.41%.

The natural mortality rate according to age for a Japanese population was used for the non-CHF-related mortality rate.

3. Dropout Rate The MUCHA trial was designed such that patients were administered a dose of 2.5 mg/day of carvedilol at the outset, then received gradually increasing dosage levels up to 20 mg/day. This gradually increasing dosage schedule was not adopted in this model for analysis, but the dropout rate at the initial treatment stage was 3%. The dropout rate during the initial dosage increase period in the MUCHA trial was 8%, and this figure was used as the dropout rate because of adverse events in the carvedilol group in our analysis model. However, in the model, dropouts are assumed to occur only in the first month, with good response to medication continuing thereafter. Patients who have dropped out are assumed to undergo conventional therapy as outpatients.

Costs

CHF treatment was assumed to take place in a hospital with 200 beds or more with full separation of pharmacy and clinic functions. An outpatient treatment schedule was constructed and treatment costs estimated. Medical fees used in the treatment cost estimate were those current for April 2001. Patients in both the carvedilol treatment group and the conventional treatment group were assumed to receive outpatient care at the hospital at a frequency of once per month. Outpatient examination fees and medication fees for medications newly prescribed at each visit were calculated each time. Medical insurance points for dispensing fees incurred for outpatients (excluding drug costs) were set at ¥11,835 for the conventional therapy group and ¥12,635 for the carvedilol group. The carvedilol-dispensing fee accounts for the additional fee for digitalis, so this was weighted in the calculations in the ratio in which digitalis medication was used (0.65). Using the conditions just described, medical costs incurred for outpatients (excluding drug costs) were set at ¥11,835 for the conventional therapy group and ¥12,635 for the carvedilol group. The carvedilol-dispensing fee accounts for the additional fee for digitalis.

Hospitalization costs and inpatient medical expenses in the event of patients suffering from worsening of heart failure and requiring acute treatment were culled from the medical receipt analysis. Among patients who were newly admitted to Kitasato University Hospital for acute heart failure in the 1 year period between 1 April 1999 and 31 March 2000, there were 26 patients who were NYHA II or III. Mean values for days hospitalized and general medical fees incurred during hospitalization are 42 days (29.3 days: 54.8 days) and ¥1,802,096 (¥1,149,467: ¥2,454,725), respectively (figures in parentheses are 95% confidence intervals). The median values were 32 days and ¥1,267,900, respectively. For our analysis we used the mean values for medical fees incurred for worsening of heart failure.

The parameters used in our analysis are listed in Table 2.

Sensitivity Analysis

Sensitivity analyses were performed with the parameters used in our analysis model. Sensitivity analyses were performed for the carvedilol group’s monthly hospitalization rate and the dropout rate by using values 50% higher and lower than the actual figures used in the analysis, and, for the mortality rate, by using a value estimated from the 95% confidence interval of the placebo group’s relative risk. Sensitivity analysis was also performed for medical costs incurred because of heart failure worsening by using the 95% confidence interval of aggregated values. Finally, sensitivity analysis was also performed using a 70% resumption rate for carvedilol therapy after acute heart failure.

Software

Markov model calculations were made using DATA 3.5.8 decision analysis software from TreeAge Software, Inc. Analysis of inpatient medical costs in the event of worsening of heart failure was made with SPSS Inc, Chicago, IL, USA.

Results

Changes in Patient Status

A Markov model was used to simulate changes in patient states over the course of their expected life span. The patient survival curve (per patient) is drawn by plotting the ratio of surviving patients along the time axis (Fig 1: S1, S2). The survival curves for both groups are shown in Fig 2. The expected number of occurrences of either death or hospitalization calculated from changes in patient states is 1.27 and 3.68 for the carvedilol group and the conventional therapy group, respectively.
Cost-Effectiveness

Total expected medical fees and remaining life expectancy for patients in both groups were estimated with the Markov model (Fig 3a–d).

Total expected medical fees over the period of each patient’s life yielded in the analysis, when discounted by an annual rate of 3%, were ¥3.5 million for the carvedilol group and ¥5.5 million for the conventional therapy group. The remaining life expectancy calculated was 121 months and 88 months for the carvedilol group and the conventional therapy group, respectively. These results show that the carvedilol group can expect medical fees that are lower by approximately ¥2 million and a life expectancy longer by approximately 33 months than the conventional therapy group.
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Fig 4. Estimated Costs by Items (lifetime analysis). (Black boxes) Carvedilol group, (white boxes) conventional group.


tively, for the carvedilol group and the conventional therapy group, yielding an additional life expectancy of 4 years for the carvedilol group.

Results for the 5-year analysis period also showed lower expected medical fees and a longer life expectancy for the carvedilol group than for the conventional therapy group.

When examining itemized costs, we see that the carvedilol group incurred higher fees than the conventional therapy group in terms of outpatient fees, carvedilol medication costs because of prolonged life months by carvedilol, and conventional medication costs; however, the carvedilol group incurs much lower fees related to hospitalization because of worsening of heart failure than the conventional medication group. This effect more than makes up for the other fees, and results in lower fees overall for the carvedilol group (Fig 4).

Sensitivity Analysis

Sensitivity analyses were performed on the values used in the expected lifetime analysis (with 3% discounting) for the carvedilol group’s hospitalization rate because of heart failure worsening, dropout rates, the carvedilol group’s mortality rate, and medical costs incurred by heart failure worsening. Results showed that for all parameters fees were lower and effects greater in the carvedilol group than for the conventional therapy group. The same results were obtained when the resumption rate for carvedilol use after acute heart failure treatment was set at 70%.

Discussion

In this analysis we constructed a Markov model of treatments and prognoses for patients with CHF in order to compare costs and effectiveness of treatment with the \( \beta \)-blocker carvedilol versus treatment with conventional therapy. We performed both a lifetime analysis covering patient life expectancy and a sub-analysis using a shorter period of 5 years. In both analyses, it was clearly shown that chronic treatment with carvedilol yields a vastly superior cost-effectiveness for patients with CHF when compared with conventional therapy.

Conventional therapy was assumed to consist of concomitant use of diuretics, ACE inhibitors, and digitalis, costing a total of ¥3,435 per month. Despite the fact that treatment with carvedilol required an additional ¥6,408 per month in medication fees, because it was so effective in reducing hospitalization rates because of worsening of heart failure, its use still resulted in a 23% cost reduction in the lifetime analysis and a 38% reduction in the 5-year analysis. Whereas life expectancy for the conventional therapy group was 108 months (9 years), it was 157 months (13 years) for the carvedilol group, an extension of 4 years. Therefore, it can be concluded that carvedilol treatment for CHF patients is a highly cost-effective method of therapy in the Japanese medical environment.

Beta-blockers have traditionally been contraindicated for patients with CHF, but in the USA and Europe they are already an established therapy for chronic heart failure, together with ACE inhibitors, diuretics, and digitalis. Several analyses of the cost-effectiveness of \( \beta \)-blockers for CHF have already been reported, and they may be divided into 2 categories: analyses that collect medical resource expenditure data in actual clinical trials and the like\(^{14-17}\) and those that, as in the present analysis, model prognoses for CHF and study the cost-effectiveness of \( \beta \)-blockers within a simulation\(^{18,19}\). Because clinical trials are conducted within a strictly managed experimental setting to evaluate the efficacy of a given treatment, using data on costs collected within this process is actually likely to introduce a bias into the analysis. The model analysis, on the other hand, simulates CHF patient prognoses to construct a model, which is in turn used to make various estimations. However, the modeling process invariably involves making both simplifications and numerous assumptions in the construction of the model itself, making a certain level of uncertainty inevitable. In order to measure this uncertainty, the parameters used in the model are altered and the results re-evaluated in a process known as sensitivity analysis. In the present study, sensitivity analyses were performed on the parameters of hospitalization rates of patients in the CHF group because of worsening of heart failure, mortality rates, and dropout rates, in addition to the carvedilol therapy resumption rate after acute heart failure when set at 70%. Results were that in all cases
analyzed, costs were lower and benefits greater in the carvedilol group.

Next, we would like to comment on the assumptions made in the construction of the Markov model of chronic CHF management used in our analysis.

For this analysis, we assumed that carvedilol’s effects on CHF continued throughout the dosage period, which amounted to patient life expectancy as set in the simulation. However, the mean dosage period in the MUCHA trial was approximately 10 months, and it is unknown whether or not carvedilol shows the same effects over a longer period of time. Similarly, there have not been any reported studies in the USA or Europe with a follow-up period of longer than 5 years. In order to evaluate the effects of a medication over a period longer than that of the original clinical trial being used as a base, one must make assumptions, such as whether the medication’s effects are maintained over a certain period of time or whether they will start diminishing after a certain point. However, because there is no basis for either of these assumptions, they were both avoided in this analysis. Therefore, in place of assuming a certain degree of long-term effectiveness for carvedilol, we conducted a sub-analysis with a period of only 5 years to estimate what effects may be expected of carvedilol over this shorter time period.

Hospitalization on account of worsening of heart failure was assumed to occur at a given frequency during the analysis period. Some analyses from the USA adjust their hospitalization rate depending on actual hospitalization frequencies, but as no such information is available in Japan with which to carry out such adjustments, a constant hospitalization rate was adopted for this analysis.

We applied Japanese natural mortality data to the Markov model as death probabilities from other than CHF because of a lack of CHF patients’ natural mortality data. Although, this might lead to underestimation on costs and length of life, we thought the impact on the results was very small. Actually, we conducted an additional analysis in which the death probabilities from other than CHF was weighted and confirmed that the impact of this setting is very small (results not presented).

Because epidemiological data is scarcer in Japan than in Europe and the USA, both in terms of CHF and other conditions, a number of assumptions had to be made in the process of constructing our model. If an applicable large-scale, long-term clinical trial is conducted in the future, we will be able to use the results to refine our model further.

Analyses were performed from the perspective of the payer of medical costs. Patients were assumed to be the general retirement age in Japan of 60 years, so indirect costs such as loss of productivity in the workplace were not taken into account. Further, because utility values for Japanese patients at each stage of CHF were not obtainable, estimates were not made of quality-adjusted life-years. Although CHF afflicts mostly the elderly, it is presumed to cause losses of productivity on a large scale because the symptom of breathlessness becomes a heavy burden for workers by limiting daily physical activities. This limiting of daily activities naturally negatively influences patient quality of life (QOL) as well. It may be presumed that treatment with carvedilol both reduces productivity losses and improves patient QOL by reducing the frequency of hospitalization because of worsening heart failure. A further study of these factors is warranted.

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References