Pharmacoeconomic Analysis of Cilostazol for the Secondary Prevention of Cerebral Infarction

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Background  The antiplatelet agent, cilostazol, is known to reduce the risk of subsequent cerebral infarction. However, the cost effectiveness of such treatment in comparison to aspirin has not been studied.

Methods and Results  A Markov model was developed to calculate the health outcomes and associated costs for 65-year-old patients with cerebral infarction who were treated with 200 mg/day cilostazol or 81 mg/day aspirin. Cilostazol was more effective, but also more expensive than aspirin. Cilostazol would extend quality-adjusted life years (QALY) by 0.64, while increasing life-time costs by approximately ¥1.1 million. The incremental cost-effectiveness ratio of cilostazol in comparison with aspirin was estimated to be ¥1.8 million per QALY.

Conclusions  The use of cilostazol to prevent recurrence of cerebral infarction appears to be cost effective. (Circ J 2006; 70: 453–458)

Key Words: Aspirin; Cerebral infarction; Cilostazol; Pharmacoeconomics; Quality-adjusted life years

Stroke (cerebrovascular disease) has attracted increased concern in terms of clinical importance in Japan where it is now the third most common cause of death. According to the National Medical Care Expenditure, the annual medical expenses for cerebrovascular disease in Japan reached ¥1.8 trillion and accounted for 7.3% of all medical expenses in 2001. This condition is clearly of major medical economic importance. Cerebral infarction, which accounts for approximately 75% of all strokes in Japan, must be assigned a prominent position in any consideration of countermeasures for cerebrovascular disease in the Japanese population. Recently, there are also some reports indicating the relationships between abdominal visceral fat and serum cholesterol and cerebral infarction. It is known that the recurrence rate is high in patients with first-ever cerebral infarction, and prognoses for physical function and lifespan are poorer after recurrence than after the initial stroke. Therefore, it is very important both for the patient and for the patient’s family to prevent recurrence of cerebral infarction.

Antiplatelet drugs such as aspirin are considered to be effective in preventing the recurrence of cerebral infarction. However, the use of aspirin is associated with elevated risk for hemorrhagic complications such as gastrointestinal bleeding, making it necessary to consider the risk/benefit ratio specific for each patient’s condition. Results from a placebo-controlled, double-blind, comparative study (the Cilostazol Stroke Prevention Study; CSPS), have indicated that the antiplatelet drug, cilostazol, can be highly effective in reducing the risk of subsequent cerebral infarction. In addition to the previous approval for the indication of peripheral arterial disease, cilostazol has recently been approved for the indication of cerebral infarction recurrence. The hemorrhagic events commonly associated with aspirin occur only rarely with cilostazol, and this drug promises to be highly effective for the prevention of cerebral infarction in a clinical setting. However, cilostazol is more expensive than aspirin.

In Europe and North America, this type of drug is assessed from a pharmacoeconomic perspective as well as in terms of clinical usefulness. Pharmacoeconomic analysis is not based exclusively on the cost of the drug but also takes into consideration the ‘value-for-money’ concept, so that in some cases, additional expenses may be acceptable for a drug that is worthwhile for the cost. In the United Kingdom, the National Institute for Clinical Excellence (NICE) recommends specific drugs to physicians based on pharmacoeconomic findings for each drug. The threshold value for NICE assessment of drug cost effectiveness is estimated as £30,000 (approximately ¥5.7 million) per 1 quality-adjusted life year (QALY).

In the present study analysis, we used a Markov model and studied the medical economics of cilostazol by estimating per-patient cost and QALYs for this drug in comparison with aspirin.

Methods

Analytic Model

The patients who were our subjects for analysis were 65-year-old men with first-ever ischemic stroke (Barthel Index (BI)=100). We estimated lifetime QALYs, medical costs, and long-term care costs. For the purposes of this analysis, we constructed a Markov model as shown in Fig 1, which was comprised of 4 stages: (1) prophylactic treatment after first stroke; (2) acute stage of recurrent cerebral infarction;
(3) chronic stage after recurrence of cerebral infarction; and (4) death. After the initial cerebral infarction, patients were assumed to have been treated prophylactically with either cilostazol (200 mg/day) or aspirin (81 mg/day), which is considered the standard dose used in Japan. Patients were predicted to develop from the stage of prophylactic treatment to prevent recurrence to second cerebral infarction or death in a specified probability.

The rate of recurrence in patients receiving no prophylactic treatment was considered to be 5.78%, which was the recurrence rate in the CSPS placebo group. For recurrence rates in the aspirin and cilostazol groups, we multiplied the recurrence rate in the untreated group by the relative risk for recurrence. In the aspirin group, the relative risk for the recurrence of cerebral infarction was calculated to be 77% based on the results of the meta-analysis by the Antithrombotic Trialist Collaboration (ATT). That relative risk in the cilostazol group was calculated to be 58.3% on the basis of CSPS results. This analysis, however, does not refer to the other effects of aspirin other than inhibition of the recurrence of cerebral infarction, because the focus of this present study is on the cost-effectiveness for prevention of the recurrence of cerebral infarction.

We considered adverse drug reactions occurring during prophylactic treatment to be defined by the ATT meta-analysis as any hemorrhagic adverse event requiring hospitalization or transfusion (gastrointestinal, intracranial, or extracranial bleeding). For our estimates of intracranial and gastrointestinal bleeding in the aspirin group (excess risk in comparison to the untreated group), we used data from patients in the Swedish Aspirin Low-Dose Trial (SALT), who had characteristics similar to our patient model and who developed severe bleeding or bleeding that required transfusion (gastrointestinal, intracranial, or extracranial). For the cost of treating intracranial hemorrhage, we estimated the annual excess risk for the aspirin group. From the ATT results, we also estimated a mortality rate of 20% for extracranial bleeding. No difference was indicated between cilostazol and placebo groups with regard to hemorrhagic adverse drug reactions according to the CSPS results, so we set the excess risk level for cilostazol at 0.

For prognosis after recurrent cerebral infarction, we determined the mortality rate for each of the 6 categories according to the BI as reported by Iino (BI100, BI99-81, BI80-61, BI60-38, BI37-1, and BI0).12 The distribution of BI category after recurrence was set based on the condition of the distribution on day 28 after recurrence in the CSPS.

The natural death rate at each stage was established by sex and age from the 2002 Abridged Life Table13 For the mortality rate after recurrence of cerebral infarction, we used data from Akita Prefecture, stratified by sex, age, and subtype.14 We assumed mortality in all patients after a second recurrence of cerebral infarction to make the model simple. Parameters used in the analysis are shown in Table 1.

Analysis was performed from the perspective of publicly financed health insurance. In doing this analysis, we focused on medical treatment costs and long-term care costs. QALY figures were used as indicators of effectiveness, and were subtracted by 3% annually for both costs and effects.

Cost Estimation

The cost for treatment per day, according to the official National Health Insurance (NHI) reimbursement price list for April 2004, was ¥6.4 for aspirin and ¥475.2 for cilostazol. For the costs of treating intracranial hemorrhage associated with recurrence of cerebral infarction and prophylactic aspirin administration, we used the estimation of ¥2,413,270 in patients aged 70 years or less, as reported by Fukuda et al.15

For the cost of treating extracranial hemorrhage caused by prophylactic aspirin administration, we compared the incidence of gastrointestinal bleeding as reported in the SALT study and the incidence of extracranial hemorrhage estimated from the ATT meta-analysis. This comparison led us to conclude that gastrointestinal bleeding accounts for the majority of instances of extracranial hemorrhage, so we considered it appropriate to use the cost of treating gastrointestinal bleeding as the treatment cost for extracranial hemorrhage. We assumed that gastrointestinal bleeding would require hospitalization for 1 week, and that the treatment cost would be ¥133,390.

For long-term care costs, we used the representative values for BI categories, determined by calculating from the formula of (maximum value + minimum value for that BI category)/2. Then, we determined the long-term care period required for each representative BI category, on the basis of functional independence measures (FIM) and BI,16 as well as the regression formula by using the long-term care period and FIM%.17 To calculate the level of long-term care required for each long-term care period, we finally determined the monthly monetary cost for each level of long-term care required, according to tabulated results in the monthly survey of long-term care expenses published by the Japanese Ministry of Health, Labor, and Welfare (May 2002 through April 2003 survey) (Table 2).

Utility Value

QALYs, which combine the patient’s quality of life...
(QOL) and number of years of survival, are widely used as a pharmacoeconomic indicator, with 1 QALY considered equivalent to 1 year of perfect health. To calculate QALYs, one must apply a relative numerical value for QOL on a linear scale, where death is assigned a value of 0 and perfect health a value of 1. This numerical value is called the utility value. For this analysis, it is necessary to determine the utility value for each representative BI value to estimate the QALYs. Because the utility value for this purpose has not yet been estimated in Japan, we used each representative BI value (adding the minimum and maximum values for that BI category and dividing by 2) as the respective utility value.

**Base Case Analysis and Sensitivity Analysis**

We determined total cost (medical treatment cost + long-term care cost), QALYs, and incremental cost-effectiveness ratio (ICER) in the base case analysis, using a discount rate of 3% to evaluate future value from the present value. For reference purposes, we also estimated the number of years of survival.

Sensitivity analysis was performed for the main parameters used in these analyses other than the utility value, using values within a 50% increase or decrease from the base values. The results were assessed using ICER as an evaluation index.

For the utility value, we determined the effect for the result by implementing a Monte Carlo simulation, which randomly extracted the utility value of each BI category from a uniform distribution and had the range of each BI category as the upper and lower limit.

All analysis was performed by using DATA Professional software (TreeAge Software, Inc, Williamstown, MA, USA).

**Results**

**Base Case Analysis**

Lifetime costs were lowest for aspirin (¥3.34 million for the group that received no prophylactic treatment, ¥2.89 million for the group that received prophylactic treatment) compared to cilostazol (¥3.5 million for the group that received no prophylactic treatment, ¥3.9 million for the group that received prophylactic treatment). The QALYs were highest for aspirin (1.0583 years) compared to cilostazol (1.0578 years). The ICER for aspirin vs. cilostazol was ¥322,240 per QALY gained.
million for the aspirin prophylaxis group, and ¥4.04 million for the cilostazol prophylaxis group) (Fig 2). Cilostazol was associated with the highest figure for QALYs (10.80 QALYs for the untreated group, 11.15 QALYs for the aspirin group, and 11.79 QALYs for the cilostazol group) (Table 3).

When we compared cost and QALYs for the aspirin group and the untreated group, the aspirin strategy was clearly dominant (low cost and high effectiveness). For this reason, the untreated group was excluded from further assessment. Next, we compared the aspirin and cilostazol groups. QALY values were higher in the cilostazol group, but so were treatment costs. In a situation such as this, it is necessary to calculate the ICER, which is the additional cost of extending the QALY value by 1, and to use that value for the assessment of the medical economics of cilostazol prophylaxis. In this study, the ICER was ¥1.79 million for the cilostazol group in comparison to the aspirin group. According to the criteria used by NICE in the UK (£30,000, or approximately ¥5,600,000), an ICER of ¥1.79 million is not unreasonable.

**Sensitivity Analysis**

Results for variation within a range of 50% increase or decrease of the base case analysis are shown in Fig 3. Sensitivity analysis revealed the factors that would influence the ICER. The results showed that the ICER of cilostazol prophylaxis over aspirin prophylaxis was ¥1.79 million (Table 3). In all scenarios, cilostazol prophylaxis was dominant (lower cost and higher QALY). The results showed that the ICER of cilostazol prophylaxis over aspirin prophylaxis was ¥1.79 million (Table 3). In all scenarios, cilostazol prophylaxis was dominant (lower cost and higher QALY).

![Fig 3. Results of sensitivity analysis using a tornado diagram.](image)

Table 3 Results of Base Case Analysis Comparing Aspirin and Cilostazol for Secondary Prevention of Stroke Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Cost (¥)</th>
<th>ΔCost*</th>
<th>QALY</th>
<th>ΔQALY</th>
<th>ICER (QALY)</th>
<th>Life expectancy (years)</th>
<th>ΔLife expectancy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2,891,063</td>
<td>–</td>
<td>11.15</td>
<td>–</td>
<td>–</td>
<td>11.57</td>
<td>–</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>3,343,401</td>
<td>452,338</td>
<td>10.8</td>
<td>–0.35</td>
<td>(Dominated)</td>
<td>11.31</td>
<td>–0.26</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>4,038,081</td>
<td>1,147,018</td>
<td>11.79</td>
<td>0.64</td>
<td>1,792,216</td>
<td>12.13</td>
<td>0.56</td>
</tr>
</tbody>
</table>

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

*In comparison to aspirin.
Discussion

In this analysis, we used a Markov model to investigate the medical economics of cilostazol in comparison to aspirin for the prevention of the recurrence of cerebral infarction. This type of analysis evaluating medical economics is called pharmacoeconomics, with an increasing number of studies carried out each year. There have been a number of overseas reports on the pharmacoeconomic analysis for the prevention of recurrence of cerebral infarction. For example, QALY values, as we have defined them here, have also been used as a pharmacoeconomic indicator by Sarasin et al in comparing the effects of treatment with aspirin monotherapy, aspirin + dipyridamole, and clopidogrel for the prevention of stroke and transient ischemic attack in 65-year-old patients. Of these 3 groups, aspirin + dipyridamole showed the highest value for QALYs and also the lowest cost, indicating that this was the most desirable method of prophylaxis in terms of cost-effectiveness. Clopidogrel showed higher QALY values and higher costs than aspirin, with an ICER of $26,580 (approximately ¥2,900,000) in comparison to aspirin. The results of sensitivity analysis provide a basis of discussion for individual values used in the present study. Cilostazol findings are from the CSPS, a study performed in Japanese patients, while findings for aspirin come from the ATT meta-analysis. This is due to the fact that no direct comparative study has been conducted so far between cilostazol and aspirin. A number of sources are available regarding the effects of aspirin on the rate of cerebral infarction recurrence, but most of those studies were performed in patients of a single nationality or from a narrow range of nationalities, and we consider it problematic to treat those findings as equivalent to data from Japanese patients. We chose to use the ATT meta-analysis because it covered a wide range of nationalities, including Japanese, and we considered its findings to be more applicable to this study than the results of researches performed in a single country.

In the present study, we had to carry out the analysis based on the results of a single study, CSPS, because it was only available clinical trial that cilostazol was evaluated for the prevention of recurrence of cerebral infarction. However, comparing this to the case of aspirin, the results of a meta-analysis is used as the basis; there is an imbalance of the quantity of information used, therefore, we have to take this into consideration. Also, the confidence interval of relative risk for recurrence overlaps between 2 groups; therefore, there would be a case that the recurrence rate of cilostazol exceeds that of aspirin depending upon the value used. In that case, ICER would increase further.

Because bleeding is a major problem associated with the prophylactic use of aspirin, we decided to use ATT and SALT as our sources for the probability of bleeding. ATT results are based on cumulative researches involving multiple nationalities, while SALT is a Swedish study. Although it would have been ideal to use data from Japanese subjects, the results of sensitivity analysis indicated that bleeding did not greatly influence our results in terms of cost-effectiveness. This is because we adopted the ATT definition of bleeding (‘any hemorrhagic adverse event requiring hospitalization or transfusion’), which excludes outpatient visits to the hospital and drug treatment. It is thus possible that our findings have underestimated the influence of bleeding.

Medical costs for the recurrence of cerebral infarction have been presented. The establishment of appropriate ICER values in Japan will have to wait for further research, but for reference, the threshold level in the USA is approximately $50,000 (approximately ¥5,000,000). With allowances for the differences in medical systems, this figure can provide a useful additional criterion when using the NICE standards for assessment of cost-effectiveness.
are taken from a report by Fukuda et al. That report, which covers not only cerebral infarction but all types of stroke, includes the cost of rehabilitation as well as the acute stage of treatment. This ensures that none of the medical costs associated with the treatment of cerebral infarction are missed.

Utility value is an important parameter for estimating QALYs. However, there are only a few published studies on utility in Japan, whereas there are some reports on the QALYs. However, there are only a few published studies on the treatment of cerebral infarction are of treatment. This ensures that none of the medical costs includes the cost of rehabilitation as well as the acute stage covers not only cerebral infarction but all types of stroke, fees and in the insurance system for long-term care. The occurrence, not only in drug prices, but also in medical treatment moreover, the primary end-point is set on the ICER, we however, as the same condition is set for both groups and, furthermore, the primary end-point is set on the ICER, we therefore have considered that there would only be relatively minor effects on the results by this setting of the BI distribution.

The prices for cilostazol and aspirin were specified as the NHI prices in April 2004. If we had used the NHI prices prior to April 2004 (¥496.6/day for cilostazol, no change for aspirin), the ICER for cilostazol would have been higher than the current value. The NHI price list is revised every 2 years, and at each revision, many drug prices are reduced. The NHI price of cilostazol may change again in a few years, and although there are too many other variables to predict the outcome of such a change at present, the medical economics of cilostazol could become even more favorable as a result.

The considerations and conclusions of medical economics depend on a range of economic conditions. Changes will occur, not only in drug prices, but also in medical treatment fees and in the insurance system for long-term care. The results of the present analysis should be also re-examined within a certain period of time.

Acknowledgment
The present study was supported by the Otsuka Pharmaceutical Co Ltd, Otsuka, Japan.

References

Circulation Journal Vol. 70, April 2006