Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction
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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
The use of 200 mg/day cilostazol for the secondary prevention of cerebral infarction.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 65-year-old men with first-ever ischaemic stroke (Barthel Index, BI=100).

Setting
The study setting was not explicitly stated, but it might have been both secondary care and primary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1991 and 2004. The price year was not explicitly reported, but it appears to have been 2004.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Modelling
A Markov model was developed to estimate the health outcomes and costs. The model comprised four stages:

- prophylactic treatment after first stroke;
- acute stage of recurrent cerebral infarction;
- chronic stage after recurrence of cerebral infarction; and
- death.

The time horizon was not specified, although it would appear to relate to the patient’s lifetime.
Outcomes assessed in the review
The outcomes assessed were:

the rate of cerebral infarction recurrence without prophylaxis,
the relative risk of cerebral infarction recurrence,
the rate of intra- and extra-cranial bleeding,
mortality due to cerebral infarction,
all other causes of mortality, and
the relative risk of mortality after recurrence by different levels of severity, as determined by the BI.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately six studies were included in the review of the literature. The authors used a meta-analysis and a double-blind randomised controlled trial to derive the recurrence rates for stroke and adverse events, and the results from one trial to derive the rates of haemorrhagic adverse events. The natural death rate at each stage was derived from Japanese life tables, while mortality rates after cerebral infarction recurrence were derived from data from a Japanese prefecture.

Methods of combining primary studies
Not relevant.

Investigation of differences between primary studies
Not relevant.

Results of the review
The rate of cerebral infarction recurrence without prophylaxis was 0.0578. The relative risk of cerebral infarction recurrence was 0.77 with aspirin and 0.583 with cilostazol.

The rate of intracranial bleeding was 0.0041 with aspirin and 0 with cilostazol.

The rate of extracranial bleeding was 0.0034 with aspirin and 0 with cilostazol.

The relative risk of mortality after recurrence ranged from 1.2 (BI=81) to 13 (BI=0).
Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). As no utility values have been estimated in Japan, the authors used the representative BI value (adding the minimum and maximum values for each BI category and dividing by 2) as the respective utility value. The utility values the authors used were 1 (BI=100), 0.9 (BI of 81 - 99), 0.705 (BI of 61 - 80), 0.49 (BI of 38 - 60), 0.19 (BI of 1 - 37) and 0.1 (BI=0).

Direct costs
The direct costs included in the analysis were those of the health care system. Such costs were for drugs, treatment for gastrointestinal bleeding, treatment for recurrence of cerebral infarction, and long-term care following recurrence. The costs of the drugs were derived from official reimbursement price lists. The costs of treating intracranial haemorrhage due to recurrence were derived from a published study. The costs of long-term care were derived from the Japanese Ministry of Health, Labour, and Welfare. Since the costs were incurred over the lifetime of the patient, the costs were appropriately discounted at an annual rate of 3%. The study reported the average costs per patient. The price year was not explicitly reported, but it appears to have been 2004.

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

Indirect Costs
The indirect costs were not included.

Currency
Japanese yen (JPY).

Sensitivity analysis
One-way sensitivity analyses were performed on all of the main parameters of the analysis, except utility values. The parameters were varied within a 50% decrease or increase from the base values. For utility values, the effect of varying the estimates was determined using Monte Carlo simulation, which randomly extracted the utility value for each BI category from a uniform distribution and had the range of each BI category as the upper and lower limit.

Estimated benefits used in the economic analysis
The QALYs gained were 11.15 with aspirin, 10.8 with no prophylaxis, and 11.79 with cilostazol.

Cost results
The average cost per patient was JPY 2,891,063 with aspirin, JPY 3,343,401 with no prophylaxis, and JPY 4,038,081 with cilostazol.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained). Both the cilostazol and no prophylaxis strategies were compared with aspirin. No prophylaxis was found to be dominated by the aspirin strategy (i.e. the aspirin strategy was both cheaper and more effective than no prophylaxis). Compared with aspirin, the additional cost per QALY gained was JPY 1,792,216 using the cilostazol strategy.

The results of the one-way sensitivity analyses showed that varying the relative risk for recurrence of cerebral infarction in the cilostazol and aspirin groups had the greatest effect on cost-effectiveness. The monthly cost of treatment in the cilostazol group and the recurrence rate of cerebral infarction in the untreated groups were the next most influential
parameters.

The results of the Monte Carlo simulation on utility values showed that the minimum incremental cost-utility ratio was JPY 1.78 million and the maximum was JPY 2.05 million for cilostazol compared with aspirin.

Authors’ conclusions
The use of cilostazol to prevent cerebral infarction recurrence would appear to be cost-effective. The authors reported that an incremental cost-utility ratio of JPY 1.79 million was not unreasonable if one took into account the willingness to pay for an additional quality-adjusted life-year (QALY) from agencies such as the National Institute for Clinical Excellence in the UK, which has an implicit threshold of approximately 30,000 (JPY 5.6 million).

CRD COMMENTARY - Selection of comparators
An explicit justification was given for using aspirin as the comparator. It represented an effective strategy in preventing the recurrence of cerebral infarction. You should decide whether the use of aspirin for the secondary prevention of cerebral infarction is current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature had been undertaken to identify relevant research and minimise biases. However, the authors appear to have made use of a meta-analysis and randomised controlled trial to derive most of the parameters for their model. The authors also appear not to have used many assumptions in their model. As reported, there was an imbalance in the quantity of information used to populate the model parameters relating to different treatments, since only one trial assessed cilostazol for the prevention of cerebral infarction recurrences. In addition, the influence of bleeding might have been underestimated in the study since some types of bleeding were not considered.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The authors reported that there were no utility measures for cerebral infarction in Japan, thus they converted the BI scores to utility values. Although the authors described the method used, they did not refer the reader to any literature and it was therefore unclear whether the method they used is common practice or valid. However, the authors appropriately varied the utility estimates in their sensitivity analysis.

Validity of estimate of costs
All the categories of cost relevant to the health care perspective adopted were included in the analysis. No major relevant costs appear to have been omitted from the analysis. The costs and the quantities were not reported separately, which will limit reflation exercises to other settings. The costs were derived from published sources. All costs were appropriately varied in a one-way sensitivity analysis using wide ranges (+/-50%). As the costs were incurred over the lifetime of the patient, all future costs were appropriately discounted. The price year was not explicitly reported, which will hamper future inflation exercises.

Other issues
The authors made appropriate comparisons of their findings with those from other studies that had also found secondary prophylaxis for cerebral infarction to be cost-effective. Although it was not explicitly stated in the paper, the issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The main limitation reported by the authors was that they found no estimates of utility values applicable in Japan.

Implications of the study
The authors recommended that the results of their analysis be re-examined within a certain period of time, as changes
in the drug prices and in medical treatment fees may vary in the future.

**Source of funding**
Supported by Otsuka Pharmaceutical Co. Ltd, Otsuka, Japan.

**Bibliographic details**

**PubMedID**
16565564

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Aspirin /economics /therapeutic use; Case-Control Studies; Cerebral Infarction /drug therapy /economics /prevention & control; Cost-Benefit Analysis; Health Care Costs; Humans; Male; Markov Chains; Models, Econometric; Models, Statistical; Platelet Aggregation Inhibitors /economics /therapeutic use; Quality-Adjusted Life Years; Tetrazoles /economics /therapeutic use; Time Factors

**AccessionNumber**
22006000765

**Date bibliographic record published**
31/08/2006

**Date abstract record published**
31/08/2006