Aspirin plus extended-release dipyridamole or clopidogrel compared with aspirin monotherapy for the prevention of recurrent ischemic stroke: a cost-effectiveness analysis

Shah H, Gondek K

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 antiplatelet therapy for the prevention of recurrent ischaemic stroke was studied. The antiplatelet agents considered were clopidogrel (75 mg/day), and aspirin (ASA; 50 mg/day) combined with modified-release dipyridamole (MRD; 400 mg/day).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of a hypothetical cohort of patients who had survived an initial ischaemic stroke.

Setting
The setting was secondary care. The economic analysis was carried out in the USA.

Dates to which data relate
The effectiveness data for clopidogrel and ASA-MRD related to 1996, while that for ASA monotherapy related to 1999. The price year was 1999.

Source of effectiveness data
The effectiveness data were obtained from two large trials, that is, the second European Stroke Prevention Study (ESPS-2) and the European trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costs were not determined from the same patient sample used to derive the effectiveness estimates. They were estimated from a sample of Medicare patients in the USA.

Modelling
A deterministic, decision-analytic model was used to estimate the incremental cost and cost-effectiveness of clopidogrel or ASA-MRD, compared with ASA monotherapy, in the two years following an ischaemic stroke. The model was simplistic and limited patients to only one recurrent stroke over the 2-year period following the initial event. The baseline risk of events in the model was derived from a hypothetical prospective cohort study carried out in the UK.
Outcomes assessed in the review
The model parameters assessed in the review were the relative risk reductions (RRRs) of ASA versus placebo, ASA plus extended-release dipyridamole (ERD) versus ASA, and clopidogrel versus ASA. The actuarial risk of suffering a recurrent stroke within one or two years was also reported.

Study designs and other criteria for inclusion in the review
This was a non-systematic review. The major sources are described in the 'Source of Effectiveness Data” section.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
Four primary studies were included in the review.

Methods of combining primary studies
The parameter estimates were selectively obtained from the literature.

Investigation of differences between primary studies
Not applicable.

Results of the review
The RRR of ASA versus placebo was 25%. The RRR of ASA-ERD versus ASA was 23.1%, (p=0.006). The RRR of clopidogrel versus ASA was 8%.

Methods used to derive estimates of effectiveness
The authors made assumptions in the model.

Estimates of effectiveness and key assumptions
The authors assumed:

- each patient in the cohort could only have one recurrent stroke during the 2-year timeframe;
- all deaths that occurred during the 2-year timeframe were assigned to the midpoint of the analysis;
- the patients were assumed to be 100% compliant with their drug therapy;
- the withdrawal rates and switch rates were considered to be equal across all treatment arms; and
adverse events were considered mild and transient.

**Measure of benefits used in the economic analysis**
The main outcome measure was the number of strokes averted.

**Direct costs**
Resource use was not reported separately from the costs. The costs included were the direct health service costs, as reimbursed by the Medicare programme. The cost data included acute-care hospitalisations, rehabilitation hospitalisations, outpatient care, physician services, home care, nursing home care, durable medical equipment and outpatient drug expenditures. The costs associated with hospitalisation for the initial stroke were not included. Discounting was relevant, as the model extended to two years, but was not conducted. The stroke cost data related to 1991. These were adjusted to 1999 prices using an inflation rate of 3% per annum. The price year was 1999.

**Statistical analysis of costs**
The costs were treated in a deterministic manner, and no indication was given of the level of variation in the cost sample.

**Indirect Costs**
The indirect costs were not included in the model.

**Currency**
US dollars ($).

**Sensitivity analysis**
Several univariate sensitivity analyses were conducted. The variables investigated were the cost of stroke (+/- 20%), the baseline risk of recurrent stroke (+/-20 %), the relative risk of stroke for ASA-MRD compared to ASA (+/- 10%), and the relative risk of stroke for ASA compared to placebo (+/- 10%).

**Estimated benefits used in the economic analysis**
In the base-case 2-year analysis, compared with ASA monotherapy, ASA-MRD was estimated to prevent an additional 33 strokes per 1,000 patients while clopidogrel was estimated to prevent an additional 11 strokes per 1,000 patients. This did not extend beyond the duration of the clinical trials used to inform the effectiveness data. Side effects of treatment were not considered in the analysis.

**Cost results**
The estimated costs associated with each treatment (from the model) were not reported.

**Synthesis of costs and benefits**
The costs and benefits were synthesised as a cost per stroke averted.

Compared with treatment with ASA monotherapy, the incremental cost per stroke averted was $28,472 with ASA-MRD and $161,316 with clopidogrel.

In each of the univariate sensitivity analyses considered, the incremental cost per stroke averted with ASA-MRD compared with ASA did not rise above $50,000. Likewise, the incremental cost per stroke averted with clopidogrel compared with ASA did not fall below $100,000.
Authors' conclusions
The combined treatment of aspirin plus modified-release dipyridamole (ASA-MRD) was a cost-effective alternative to treatment with aspirin (ASA) monotherapy for the secondary prevention of stroke. The authors concluded that treatment with clopidogrel was not cost-effective in comparison with ASA, but that it might be useful for patients who are sensitive to ASA.

CRD COMMENTARY - Selection of comparators
ASA monotherapy was the chosen comparator as it was current, standard practice in the US health-care setting. The dosage for the comparator could have been clarified. You should decide if ASA is a widely used health technology for the secondary prevention of strokes in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness model parameters were derived from a non-systematic review of the literature. Normally this would raise questions about their validity. However, the two main sources of data were large, multi-centre, randomised controlled trials, which provide a strong source of evidence for clinical effectiveness. There was little commentary on the similarity of the clinical trials used to inform the effectiveness data, except that the data were extracted from the stroke-qualifying sub-group in the effectiveness trial for clopidogrel.

Validity of estimate of measure of benefit
The choice of benefit was the number of strokes averted over a 2-year timeframe. This was modelled using the RRRs taken directly from the clinical trials. The choice of benefit was justified in this study of the secondary prevention of stroke. However, the limited time period should be taken into consideration.

Validity of estimate of costs
Given that the study was conducted from the perspective of the third-party payer, the relevant cost categories were evaluated. The authors acknowledged that the costs associated with disability following stroke were not included and, as such, the costs associated with each therapy are likely to have been underestimated. Again, the limited timeframe should be taken into account, as recurrent strokes may have been postponed. The price year was reported, but the costs and the quantities were not reported separately.

The price of ASA-MRD was obtained directly from the manufacturer, rather than from published pricing lists from which the costs of ASA and clopidogrel were obtained. This brings the cost-effectiveness results into question if the true cost of ASA-MRD does not match the manufacturer's estimate. The other prices were based on the charges reimbursed by Medicare. This indicates that the results are not generalisable to other health care payers.

Other issues
The structure and the parameters (both costs and effects) of the model could have been reported better. This limits the reproducibility of the model in different settings. The authors confined their conclusions to patients with ischaemic stroke, although the clinical trial results for ASA-MRD contained patients who had experienced a transient ischaemic attack (TIA). No comment was made about the implications of including these patients with a milder event. However, TIA is very similar to minor ischaemic stroke and so the implications may be small. This study perspective was very narrow, both in terms of the time horizon and in the scope of disease considered. The authors noted some limitations to their model, which have been discussed already. The authors did not compare their results with other studies and they do not appear to have presented their results selectively.

Implications of the study
The authors suggest that ASA-MRD should be used, instead of ASA monotherapy, in the secondary prevention of stroke. In addition, that clopidogrel should only be considered for ASA-intolerant patients.
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Other publications of related interest


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