Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease

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 aspirin and clopidogrel (a thienopyridine derivative) for secondary prevention in patients with coronary heart disease (CHD).

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients over 35 years of age who had survived an initial CHD.

Setting
The setting was the community. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and resource use data were derived from studies published between 1994 and 2001. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, plus estimates made by the authors.

Modelling
The Coronary Heart Disease Policy model, a state-transition computer simulation that predicts the incidence of coronary disease and mortality from noncoronary causes, was used in the analysis. This modelled patients aged 35 to 84 years in which CHD developed in the period 2003 to 2027. In each one-year cycle, patients with CHD could develop cardiac arrest, acute myocardial infarction (MI), coronary revascularisation, or any combination of these events, depending on the condition in which the person started that year. Each patient was assigned an annual cost on the basis of the history and additional costs related to any new events.

Outcomes assessed in the review
The outcomes assessed from the published studies and used as the inputs for the model were:
the reduction in the rate of CHD events (MI, cardiac arrest and death) with aspirin and/or clopidogrel;
the reduction in mortality from non-coronary causes with aspirin, and/or clopidogrel;

the reduction in the rate of revascularisation;

the current use of aspirin; and

the annual incidence of stroke per 100,000 persons.

**Study designs and other criteria for inclusion in the review**
The effectiveness data were derived from official statistics, clinical trials and observational studies.

**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**
The effectiveness evidence was mainly obtained from 5 studies.

**Methods of combining primary studies**
Narrative methods were used to combine the studies.

**Investigation of differences between primary studies**
Not carried out.

**Results of the review**
The reduction in the rate of CHD events was 31% (range: 21 - 41) with aspirin, 33.7% (range: 0.3 - 16.5) with clopidogrel relative to aspirin, and 37.2% (range: 10 - 28) with the combination of aspirin plus clopidogrel relative to aspirin.

The reduction in mortality from non-coronary causes was 2.8% with aspirin, 2.9% with clopidogrel relative to aspirin, and 2.9% with the combination relative to aspirin.

The reduction in the rate of revascularisation was 0 in the base-case, but was identical to the reduction in the event rate in the range reported.

The current use of aspirin was 85% (range: 42 - 85).

The annual incidence of stroke was 135 per 100,000 persons.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to support the data used in the decision model.
Estimates of effectiveness and key assumptions
The assumptions were used to select the average value of the outcomes assessed in the effectiveness analysis, since the ranges of values were found in the literature and then used in the sensitivity analyses.

Measure of benefits used in the economic analysis
Several outcome measures were obtained from the decision model. These included the number of deaths from CHD or from non-CHD, the number of MIs and the quality-adjusted life-years (QALYs). However, the benefit measure used in the economic analysis was the number of QALYs gained with the four strategies, and in the alternative strategy of the current use of aspirin. The health-related quality-of-life weights for both CHD and non-CHD were derived from published data.

Direct costs
A 3% discount rate was used in the economic analysis since the time horizon of the analysis was 25 years. The unit costs and the quantities of resources were not reported separately. The analysis included the drug acquisition costs, the annual costs of non-CHD according to age, and the annual costs of CHD (including rehabilitation services and home care). The cost/resource boundary adopted in the study was not stated. The costs and the resource use were estimated on the basis of published data and were derived using the decision model. All the costs were converted into 2000 prices using the medical component of the Consumer Price Index.

Statistical analysis of costs
Statistical analyses of the costs were not carried out.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were performed to assess the robustness of the study conclusions to variations in the assumptions and inputs used in the model. The model inputs and discount rate were varied using the ranges reported earlier. In particular, the costs of non-CHD were varied up to 100%, and the effect of excluding them from the analysis was assessed. The impact of limiting the benefits of the interventions to 3 years, as reported in some studies, was also assessed. Finally, some subgroup analyses were carried out. The type of sensitivity analysis conducted was not stated.

Estimated benefits used in the economic analysis
The number of deaths from CHD was 11,079,000 with no treatment, 9,570,000 with the current use of aspirin, 9,405,000 with strategy 1, 9,294,000 with strategy 2, 9,132,000 with strategy 3, and 8,916,000 with strategy 4.

The number of deaths from non-CHD was 4,019,000 with no treatment, 4,268,000 with the current use of aspirin, 4,295,000 with strategy 1, 4,314,000 with strategy 2, 4,343,000 with strategy 3, and 4,389,000 with strategy 4.

The number of MIs was 16,508,000 with no treatment, 15,075,000 with the current use of aspirin, 14,919,000 with strategy 1, 14,813,000 with strategy 2, 14,664,000 with strategy 3, and 14,466,000 with strategy 4.

The number of QALYs was 115,535,000 with no treatment, 121,768,000 with the current use of aspirin, 122,450,000 with strategy 1, 122,906,000 with strategy 2, 123,538,000 with strategy 3, and 124,343,000 with strategy 4.
The incremental QALYs gained were 6,233,000 with the current use of aspirin over no treatment, 682,000 with strategy 1 over current use of aspirin, 456,000 with strategy 2 over strategy 1, 632,000 with strategy 3 over strategy 2, and 1,437,000 with strategy 4 over strategy 2.

Cost results
The total costs (in millions of dollars) were $1,797,000 for no treatment, $1,867,000 with the current use of aspirin, $1,874,000 with strategy 1, $1,888,000 with strategy 2, $2,045,000 with strategy 3, and $2,071,000 with strategy 4.

The incremental costs (in millions of dollars) were $69,000 with the current use of aspirin over no treatment, $8,000 with strategy 1 over current use of aspirin, $14,000 with strategy 2 over strategy 1, $156,000 with strategy 3 over strategy 2, and $182,000 with strategy 4 over strategy 2.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility analysis. The additional costs per incremental QALY gained were $11,000 with the current use of aspirin over no treatment, $11,000 with strategy 1 over current use of aspirin, $31,000 with strategy 2 over strategy 1, $250,000 with strategy 3 over strategy 2, and $150,000 with strategy 4 over strategy 2. The ranking of the cost-utility ratios was unaffected by the variations examined in the sensitivity analyses.

Authors' conclusions
Aspirin offered the most convenient cost-utility ratio under a wide range of assumptions. Clopidogrel was attractive only for patients with contraindications to aspirin. The authors noted that although favourable, the cost-utility ratio of aspirin was quite low given the very low cost of the drug. However, this was due to the fact that the costs for the care of non-coronary events increased substantially, due to the increased survival of the patients.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. No treatment was selected in order to assess the active value of the other interventions, while the current use of aspirin was chosen because it represented the current practice. The four strategies represented possible alternatives for the treatment of patients with CHD. You should assess whether these interventions represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness measures were derived from published studies. However, although the authors stated that a review of the literature was carried out, no details of the search strategy were provided. In addition, the methods to ensure the validity of the studies and to combine the evidence from the primary studies were not reported, and would appear to have been based on the authors' assumptions. Sensitivity analyses, however, were carried out to explore the impact of the assumptions on the study results. It was unclear whether the authors considered the impact of differences in the primary studies when estimating the effectiveness.

Validity of estimate of measure of benefit
The main benefit measure used in the economic analysis was the QALYs. These were obtained from an appropriate decision model. Values of the quality weights were obtained from the literature.

Validity of estimate of costs
The perspective of the analysis was not stated. A societal perspective would have been appropriate for the study population considered, the main implication of this being the inclusion of productivity losses and other indirect costs. The unit costs and the quantities of resources used were not reported. The costs were estimated using data derived from the literature. Statistical analyses were not carried out, but sensitivity analyses were performed on the key cost inputs.
Appropriate discounting was carried out and the price year was reported.

**Other issues**
The authors made some comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not addressed. However, the study results were fairly robust to variations in both the cost and effectiveness data. The conclusions of the analysis appear valid for the general population of patients with CHD. The authors reported their results in detail, especially the sensitivity analyses.

**Implications of the study**
The study results imply that an aspirin-based strategy for the secondary prevention of CHD represented the most cost-effective intervention, with clopidogrel being restricted to patients with contraindications to aspirin. The authors note an important caveat to the results in that "The gap between proven effectiveness and unattractive projected cost effectiveness could be eliminated by reductions in the price of clopidogrel".

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