Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis

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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
Two alternative antiplatelet therapies, aspirin (325 mg orally per day) and clopidogrel (75 mg orally per day), were examined.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with peripheral arterial disease, a non-haemorrhagic stroke in the last 6 months, or a myocardial infarction (MI) in the last 35 days. Peripheral arterial disease was defined as symptomatic claudication in a patient with an ankle-brachial index of less than 0.85.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2000. Cost and resource use data came from sources published from 1994 to 2003. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to assess the clinical and economic impact of clopidogrel versus aspirin in a hypothetical 63-year-old patient in three main model sub-groups. The three sub-groups were peripheral arterial disease (as defined in 'Study Population'), stroke in the last 6 months, and MI in the last 35 days. The time horizon of the model was lifetime and 6-month cycles were considered. In each cycle, patients faced the risk of one or multiple vascular events (MI, stroke, amputation, or vascular death), one or multiple haemorrhagic events (gastrointestinal bleeding or intracranial haemorrhage), or another side effect (thrombotic thrombocytopenic purpura). The patients also faced a risk of age-related mortality. The structure of the tree was reported.

Outcomes assessed in the review
The outcomes estimated from the literature were annual event probability rates, the efficacy of clopidogrel, life expectancy, and utility values associated with model health states.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature was undertaken to identify primary studies. The efficacy of clopidogrel in comparison with aspirin was derived from a clinical trial (the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, CAPRIE, trial). Survival data came from life statistics. Other data were estimated from observational studies. The design of studies used for quality of life adjustments was not reported.

**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**
Eighteen primary studies provided evidence.

**Methods of combining primary studies**
The primary estimates were not combined as each source provided a single estimate. The data were then incorporated into the model using a narrative approach.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
Only the average relative risk reductions in vascular events with clopidogrel over aspirin and utility weights are reported in this abstract.

The relative risk reductions for peripheral arterial disease, stroke, and MI, respectively, were:

23.8% (95% confidence interval, CI: 8.9 - 36.2), 7.3% (95% CI: -5.7 - 18.7), and -3.7% (95% CI: -22.1 - 12) for total vascular events;

-37.5% (95% CI: -60.5 - -14.6), -4.9% (95% CI: -18.3 - 8.4), and 36.9% (95% CI: 27 - 46.8) for fatal stroke;

5.4% (95% CI: -10.4 - 21.1), 8.5% (95% CI: -3.1 - 20.2), and -9.9% (95% CI: -27 - 7.4) for nonfatal stroke;

33.4% (95% CI: 22.4 - 44.6), 22.4% (95% CI: 12.5 - 32.2), and 8.2% (95% CI: -6.2 - 22.6) for fatal MI;

38.2% (95% CI: 27.9 - 48.5), 11.9% (95% CI: 0.7 - 23.1), and 5% (95% CI: -9.9 - 19.9) for nonfatal MI;

-12.2% (95% CI: -30.9 - 6.5), 1.2% (95% CI: -11.3 - 13.8), and -1% (95% CI: -16.8 - 14.9) for amputation; and

24.1% (95% CI: 11.5 - 36.7), -1.5% (95% CI: -14.4 - 0.1), and -29.6% (95% CI: -49.9 - -9.3) for vascular death.
The relative risk reductions for bleeding events were the same for the three sub-groups of patients:

25.6% (95% CI: 12.8 - 51.2) for total bleeding events,

13.1% (95% CI: 6.5 - 26.3) for fatal intracerebral haemorrhage,

41.7% (95% CI: 20.8 - 83.4) for nonfatal intracerebral haemorrhage,

25.1% (95% CI: 12.5 - 50.2) for fatal gastrointestinal bleeding, and

31.3% (95% CI: 15.7 - 62.6) for nonfatal gastrointestinal bleeding.

The average utility weights were:

0.80 (range: 0.60 - 1) for peripheral arterial disease,

0.11 (range: 0 - 0.35) for severe stroke,

0.39 (range: 0.25 - 0.35) for moderate stroke,

0.76 (range: 0.55 - 0.95) for mild stroke,

0.87 (range: 0.80 - 0.95) for MI,

0.48 (range: 0.25 - 0.70) for amputation, and

0.30 (range: 0 - 0.60) for intracerebral haemorrhage.

Methods used to derive estimates of effectiveness
The authors made some key assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The rate of thrombotic thrombocytopenic purpura was 2 cases per 3 million patients monthly. The efficacy of clopidogrel was constant over time. The disutility tolls were 0.005 (range: 0 - 0.01) for gastrointestinal bleeding and 0.027 (range: 0 - 0.055) for thrombotic thrombocytopenic purpura.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were derived using a modelling approach, where survival and quality of life data were combined. The utility weights were obtained from published studies that used either time trade-off or standard gamble techniques. An annual discount rate of 3% was applied.

Direct costs
Discounting was relevant since the lifetime costs were estimated. An annual discount rate of 3% was applied. The unit costs were not presented separately from the quantities of resource used. Most of the costs were presented as macro-categories. The health services included in the economic evaluation were those associated with the treatment of acute events and the chronic care of disabled patients. Drug costs (including aspirin and clopidogrel) were also considered. The cost/resource boundary of the study was unclear. Although the authors stated that a societal perspective was applied, some categories of costs (e.g. non-medical direct costs) appear not to have been considered. The costs and resource use data were derived from published studies and Medicare diagnostic-related group data. The drug costs were based on average wholesale prices. Some economic data were also based on authors' assumptions. All costs were presented in 2002 values using a gross domestic product deflator.
Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered in the economic evaluation, probably because of the age of the hypothetical cohort of patients (63 years).

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were performed on all model inputs using published CIs and ranges of values, when appropriate, to examine the robustness of the estimated incremental cost-utility ratios to variations in baseline assumptions. A Monte Carlo probabilistic sensitivity analysis was performed using 1,000 simulations and a cost-effectiveness acceptability curve was also constructed. The scenario in which the efficacy of clopidogrel was identical to that of aspirin after 3 years' treatment (but clopidogrel maintained its advantage in the number of haemorrhagic events) was considered. In a supplementary analysis, the expected number of events prevented in a hypothetical cohort of 250,000 patients was calculated over a lifetime horizon.

Estimated benefits used in the economic analysis
The estimated QALYs were:

9.58 with clopidogrel and 9.03 with aspirin (difference 0.55) for patients with peripheral arterial disease;

8.66 with clopidogrel and 8.49 with aspirin (difference 0.17) for patients with stroke; and

10.83 with clopidogrel and 11.09 with aspirin (difference -0.26) for patients with MI.

Cost results
The estimated total costs per patient were:

$123,300 with clopidogrel and $109,500 with aspirin (difference $13,800) for patients with peripheral arterial disease;

$201,400 with clopidogrel and $196,000 with aspirin (difference $5,300) for patients with stroke; and

$98,500 with clopidogrel and $91,700 with aspirin (difference $6,800) for patients with MI.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and benefits of the two antiplatelet therapies. The incremental cost per QALY saved with clopidogrel relative to aspirin was $25,100 for patients with peripheral arterial disease and $31,200 for patients with stroke. However, for patients with MI, aspirin dominated clopidogrel, which was both more expensive and less effective. The supplemental analysis showed that in a cohort of 250,000 patients, the number of events prevented with clopidogrel relative to aspirin was 39,481 in patients with peripheral disease, 35,049 in patients with a prior stroke, and 10,521 in patients with a prior MI.

The univariate sensitivity analysis revealed that the estimated cost-utility ratios were sensitive to variations in clopidogrel efficacy (upper and lower bound of the 95% CI). For patients with peripheral arterial disease, the cost per QALY ranged from $13,500 to $86,400. For patients with stroke, the cost per QALY fell to $6,300 when the upper bound of clopidogrel efficacy was used. The cost of clopidogrel also had some effect on the base-case results.
Variation in clopidogrel price led to changes in the cost per QALY (for peripheral arterial disease) from $14,900 (lowest daily cost for clopidogrel) to $41,800 (highest daily cost for clopidogrel). In the scenario in which the efficacy of clopidogrel was identical to that of aspirin after 3 years' treatment, the cost per QALY increased to $53,200 for patients with peripheral arterial disease and to $111,800 for patients with stroke.

The probabilistic sensitivity analysis showed that the cost-effectiveness thresholds at which clopidogrel was cost-effective in 50% of simulations were $25,600 for patients with peripheral arterial disease and $30,300 for patients with stroke.

Authors' conclusions
Clopidogrel was a cost-effective alternative to aspirin for the secondary prevention of vascular events in patients with peripheral vascular disease or recent stroke, and the cost per quality-adjusted life-year (QALY) fell within traditional thresholds for cost-effectiveness. However, in the sample of patients with a recent myocardial infarction (MI), less clear conclusions could be drawn and aspirin appeared to be the most cost-effective preventive strategy.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparator was clear. Aspirin represents the current standard of care for the secondary prevention of vascular events. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
It was not stated whether a systematic review of the literature had been undertaken. Rather, primary studies appear to have been identified selectively. Limited information on the design and characteristics of the primary studies was provided. Similarly, the methods used to extract and combine the primary estimates were not reported. Some key assumptions were based on authors' opinions because of the lack of published data. However, the issue of uncertainty around all model inputs was satisfactorily addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as QALYs capture the impact of the intervention on both quality of life and survival, which are both affected by prevention strategies. Discounting was applied, as recommended in US guidelines. Little information on utility values was reported. Variations in the discount rate, as well as in quality of life weights, were carried out in the sensitivity analysis. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study. However, only the direct medical costs were included. A detailed breakdown of the cost items was not provided since most of the data were obtained from published studies. This reduces the possibility of replicating the study. The costs were treated deterministically in the base-case, but all cost inputs were varied in the deterministic and probabilistic sensitivity analyses. The price year was reported, which aids reflation exercises in other settings. The source of the data was provided.

Other issues
The authors reported the findings from other published economic evaluations on clopidogrel. However, differences in the time horizon and benefit measures limited the possibility of making clear comparisons of the results. The issue of the generalisability of the study results was not explicitly addressed, but extensive sensitivity analyses were carried out. These enhance the external validity of the analysis. The study referred to three groups of patients and this was reflected in the authors' conclusions. The authors noted some limitations to the validity of their analysis, mainly related to their use of assumptions.
Implications of the study
The study results suggested that clopidogrel could be a cost-effective strategy for the secondary prevention of vascular events in patients with peripheral vascular disease, or after a recent stroke. Further studies should be carried out to investigate the cost-effectiveness of clopidogrel in patients who have experienced a MI.

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