A cost-effectiveness analysis of combination antiplatelet therapy for high-risk acute coronary syndromes: clopidogrel plus aspirin versus aspirin alone

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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
A combination antiplatelet therapy for the prevention of subsequent coronary events in patients with acute coronary syndrome (ACS) was examined. The combination therapy comprised clopidogrel (75 mg/day) plus aspirin (325 mg/day).

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with unstable angina or non-Q wave MI. The patients included in the analysis were suffering from an ACS characterised by electrocardiographic changes or elevated serum cardiac markers in association with chest pain. Patients who had prolonged ST-segment elevation, or who had undergone revascularisation in the last 3 months were excluded. Also excluded were those at risk for severe bleeding or heart failure, and those who had been treated with oral anticoagulants or glycoprotein IIb/IIIa inhibitors in the preceding 3 days.

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 2001. The resource use and cost data were derived from studies published from 1990 to 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A Markov model was constructed to examine the costs and benefits of combination therapy versus monotherapy in a hypothetical 64-year-old patient with an ACS. The time horizon of the model was lifetime. Patients moved between health states at monthly intervals. The model considered several vascular events. More specifically, MI, stroke, vascular death and revascularisation, intracerebral and gastrointestinal (GI) haemorrhagic events, and clopidogrel-associated thrombotic thrombocytopenic purpura (TTP). Patients could die at any stage of the model due to age-related mortality. A structure of the tree was reported in the paper. The impact of procedures and outcomes, such as congestive heart
failure, were indirectly considered using adjusted annual health care costs for such events.

Outcomes assessed in the review
The outcomes estimated from the literature were:

- the probabilities of fatal MI, nonfatal MI, revascularisation, vascular death, and bleeding for patients treated with aspirin during the first month and from months 2 to 12;
- the probabilities of fatal stroke, nonfatal stroke, fatal intracerebral haemorrhage, and nonfatal intracerebral haemorrhage for all patients treated with aspirin (monthly);
- the probabilities of fatal TTP (during the first month on therapy and after the first month) and nonfatal TTP (during the first month on therapy and after the first month) for all patients treated with clopidogrel;
- the relative risk reduction with clopidogrel relative to aspirin for thrombosis prevention, bleeding, and revascularisation (first month); and
- utility values for severe, moderate, and mild stroke, coronary artery disease and intracerebral haemorrhage.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature had been undertaken to identify the primary studies. Age-specific mortality rates were derived from life tables. Most of the clinical data were derived from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trials. The other data were obtained from 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
Thirteen primary studies provided the evidence.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
For patients treated with aspirin, the probabilities values during the first month were 0.0079 (range: 0.0059 - 0.014) for fatal MI, 0.024 (range: 0.020 - 0.028) for nonfatal MI, 0.227 (range: 0.217 - 0.237) for revascularisation, 0.016 (range: 0.013 - 0.019) for vascular death, and 0.015 (range: 0.012 - 0.018) for bleeding.
The corresponding values from months 2 to 12 were 0.0011 (range: 0.00081 - 0.0014) for fatal MI, 0.0036 (range: 0.0031 - 0.0041) for nonfatal MI, 0.018 (range: 0.017 - 0.019) for revascularisation, 0.0023 (range: 0.0019 - 0.0027) for vascular death, and 0.011 (range: 0.009 - 0.014) for bleeding.

For all patients treated with aspirin (monthly), the probability values were 0.00049 (range: 0.00033 - 0.00069) for fatal stroke, 0.0010 (range: 0.00079 - 0.0013) for nonfatal stroke, 0.0001 (range: 0.00089 - 0.0018) for fatal intracerebral haemorrhage, and 0.0001 (range: 0.00094 - 0.0018) for nonfatal intracerebral haemorrhage.

For all patients treated with clopidogrel, the probability values were 0.000001 for fatal TTP (during the first month on therapy and after the first month), 0.000006 for nonfatal TTP during the first month on therapy, and 0.000007 for nonfatal TTP after the first month.

The relative risk reduction with clopidogrel relative to aspirin was 20 (range: 10 - 28) for thrombosis prevention, -38 (range: -67 - 0) for bleeding, and 9 (range: 0 - 18) for revascularisation (first month).

The utility values were 0.11 (range: 0 - 0.35) for severe stroke, 0.39 (range: 0.25 - 0.55) for moderate stroke, 0.76 (range: 0.55 - 0.95) for mild stroke, 0.87 (range: 0.80 - 0.90) for coronary artery disease, and 0.30 (range: 0 - 0.60) for intracerebral haemorrhage.

Methods used to derive estimates of effectiveness
The authors made some assumptions when literature-based estimates were not available.

Estimates of effectiveness and key assumptions
The disutility tolls for the calculation of quality-adjusted life-years (QALYs) were 0.005 (range: 0 - 0.01) for GI bleeding and 0.027 (range: 0 - 0.055) for TTP.

Measure of benefits used in the economic analysis
The summary benefit measure was the expected number of QALYs. This was derived combining survival data and utility values in the decision model. The utility values were obtained from published population-based values through time trade-off or standard-gamble techniques. A discount rate of 3% was applied.

Direct costs
An annual discount rate of 3% was applied because discounting was relevant (lifetime horizon). A detailed breakdown of the costs was not provided since the costs were presented as macro-categories (health states). The unit costs were not presented separately from the quantities of resources used. The economic evaluation considered all inpatient costs associated with the treatment of acute clinical events, as well as medications, procedures and nursing care specific to each health state. The cost/resource boundary of the study was unclear, although the authors stated that a societal perspective had been used. The costs for events and chronic care of disabled patients were derived from the literature, while medication costs came from average wholesale prices. The resource use data were derived from published sources and authors’ opinions. All the costs were expressed in 2002 values using the gross domestic product deflator.

Statistical analysis of costs
The costs were assigned stochastic distributions that were used in the probabilistic sensitivity analysis.

Indirect Costs
The indirect costs were not included in the economic evaluation, probably because of the age (64 years or older) of the patient population considered.
Currency
US dollars ($).

Sensitivity analysis
A one-way sensitivity analysis was carried out on all model inputs to examine the robustness of the base-case results. The ranges of values used were generally derived from the literature. A probabilistic sensitivity analysis was also performed, using 1,000 simulations and determining a cost-effectiveness acceptability curve. In an alternative scenario, the duration of clopidogrel therapy was varied from one month to one year. A two-way sensitivity analysis was carried out on the annual probability of vascular events and the proportion of events that were cerebrovascular.

Estimated benefits used in the economic analysis
The discounted QALYs were 9.51 with aspirin monotherapy and 9.61 with clopidogrel-aspirin combination therapy. The QALY gain with clopidogrel-aspirin therapy was 0.10.

Cost results
The discounted costs were $127,700 with aspirin monotherapy and $129,300 with clopidogrel-aspirin combination therapy. The difference in costs was $1,600.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the preventive strategies. The incremental cost per QALY gained with clopidogrel-aspirin combination therapy relative to aspirin monotherapy was $15,400.

The sensitivity analysis showed that the base-case cost per QALY was quite robust to variations in the model inputs. In general, even under unfavourable scenarios, the incremental cost-utility ratio remained below the threshold of $50,000 per QALY. The probabilistic sensitivity analysis suggested that, at a threshold of $14,600 per QALY, clopidogrel-aspirin combined therapy was cost-effective in 50% of simulations. At a threshold of $50,000 per QALY, combination therapy was the optimal strategy in 97.2% of simulations.

Treatment with clopidogrel was progressively less cost-effective the longer the duration of therapy. After the third year of therapy, the cost per QALY increased above the threshold of $50,000 per QALY ($61,300 in the third year, $136,500 in the fourth year, and $730,000 in the fifth year).

The two-way sensitivity analysis showed that in populations with a low risk for vascular events, aspirin monotherapy was more effective than clopidogrel-aspirin combination therapy. Finally, it was estimated that in the USA approximately 250,000 individuals would meet the inclusion criteria of the study population considered in this analysis, and that adding clopidogrel to aspirin for 1 year would result in a societal gain of 25,500 QALYs at a cost of $392 million over the cohort lifetime.

Authors' conclusions
In patients with high-risk unstable angina or non-Q-wave myocardial infarction (MI), the addition of one year of clopidogrel therapy to aspirin therapy improved quality-adjusted life expectancy at a cost that was comparable to other accepted therapies. However, the authors pointed out that longer courses of combination treatment, particularly, beyond 2 years, were less likely to be cost-effective. In general, combination therapy should maintain a threshold for absolute risk reduction to overcome the risk for bleeding and the increased cost of adding clopidogrel to aspirin.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (aspirin monotherapy) was based on the comparison carried out in the main clinical trial (the CURE study). You should decide whether this is a valid comparator in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness evidence came mainly from published studies, but it was not stated whether a systematic review of the literature had been undertaken to identify the primary studies. Most of the evidence came from a clinical trial, while other studies appear to have been identified selectively. The issue of comparability of the sources used was not addressed. In addition, it was unclear whether the primary estimates were combined using a narrative approach. Some assumptions were also made. The impact of changes in the model inputs was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as it incorporated the impact of the interventions on survival and quality of life. The utility values were derived from published studies. QALYs are comparable with the benefits of other health care interventions. Discounting was applied, as recommended by US guidelines.

Validity of estimate of costs
The authors stated that a societal perspective was adopted, but it appears that the indirect costs have been excluded from the analysis because of the age of the patient population (average 64 years). Most of the costs were derived from published studies and were not broken down into single-item categories. This reduces the possibility of replicating the study results. The costs were treated deterministically in the base-case, but statistical analyses were carried out in the sensitivity analysis. Discounting was carried out on account of the lifetime horizon of the study. The price year was reported, which will facilitate reflation exercises in other settings. Overall, limited information on the cost analysis was provided.

Other issues
The authors did not make direct comparisons of their findings with those from other studies, but stated that the cost-effectiveness of combination therapy was comparable to that of therapy with glycoprotein IIb/IIIa inhibitors for a similar population receiving a coronary stent. In terms of the issue of the generalisability of the study results, the authors noted that caution is required when applying their findings to other groups of patients, owing to the strict inclusion and exclusion criteria of the study population (which reflected the sample of patients enrolled into the CURE trial). The authors noted that their analysis shared the limitations of the CURE trial, which represented the main source of clinical evidence.

Implications of the study
The study results supported the use of clopidogrel-aspirin combination therapy in patients with high-risk unstable angina or non-Q-wave MI. However, before definitive recommendations can be made, reliable long-term data will be necessary to better assess the benefits and risk of clopidogrel treatment beyond one year.

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Other publications of related interest


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