Cost-effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial
Annemans L, Lamotte M, Levy E, Lenne X

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 clopidogrel, an antiplatelet agent, in patients with atherothrombosis.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with vascular disease with recent stroke, myocardial infarction (MI) or symptomatic peripheral arterial disease (PAD).

Setting
The setting was primary care. The study was carried out in Belgium.

Dates to which data relate
The effectiveness data and the quantity of drugs used were derived from a study published in 1996. Diagnosis-related group (DRG)-derived costs were from the year 1997. All of the costs were reported in 2002 prices.

Source of effectiveness data
The effectiveness data were taken from a single study, the CAPRIE trial (see Other Publications of Related Interest).

Link between effectiveness and cost data
With the exception of the quantity of drugs used, the costing was not carried out on the same sample used in the effectiveness study. The levels of resource use were derived from expert opinion.

Study sample
The sample size was planned at the start of the study to ensure a 90% power to detect an overall relative risk reduction of 11.6%. The effectiveness trial consisted of 19,185 patients with recent MI, recent ischaemic stroke, or symptomatic PAD. The mean age was 62.5 years. There were 9,553 patients in the clopidogrel group and 9,546 in the aspirin group. Additional information was taken from the CAPRIE study.

Study design
The study was an international, multi-centre, randomised controlled trial, with an average follow-up of 1.91 years. A total of 384 clinical centres from 16 countries participated. The patients were randomised to either 75-mg tablets of clopidogrel plus aspirin placebo or 325-mg tablets of aspirin plus clopidogrel placebo. The randomisation was conducted independently with computer-generated allocations, stratified by clinical centre and three disease groups (stroke, MI and PAD). The patients and the outcome assessors were blinded. Eight-six patients (46 clopidogrel and 40 aspirin) did not receive treatment as allocated. Twenty-two were lost to follow-up in the clopidogrel group versus 20 in the aspirin group.

Analysis of effectiveness
The basis of the primary analysis was intention to treat. The primary outcome of the trial was the composite mean risk reduction across all disease sub-groups. Event rates for vascular death, ischaemic stroke and MI with aspirin, clopidogrel and events avoided were the outcome measures from the trial that was used to derive the event rates in the model. The baseline characteristics for the aspirin and clopidogrel groups were comparable within each disease sub-group.

Effectiveness results
The results of the trial indicated that patients receiving clopidogrel experienced a mean 8.7% risk reduction, (p=0.043), in the primary composite end point of MI (fatal or nonfatal), ischaemic stroke (fatal or nonfatal) or vascular death in comparison with patients receiving aspirin.

For the aspirin group at 2 years, the event rates were 34.01 for vascular death, 50.28 for ischaemic stroke and 34.11 for MI.

For the clopidogrel group at 2 years, the event rates were 31.04 for vascular death, 46.15 for ischaemic stroke and 27.92 for MI.

For events avoided, the rates were 2.96 for vascular death, 4.13 for ischaemic stroke and 6.19 for MI.

Clinical conclusions
The study revealed that clopidogrel was superior to aspirin in the primary composite end point of MI (fatal or nonfatal), ischaemic stroke (fatal or nonfatal) or vascular death.

Modelling
A Markov model with a cycle length of 6 months was used to reproduce the trial results. The length of the model was 2 years. After this, the benefits were translated into life-years saved by applying estimates of life expectancy according to the events recorded in the model (the patient could also die during the model timeframe). The model was used to estimate the costs and benefits of 2-year treatment. The costs after 2 years were not considered, although the benefits were extrapolated to a lifetime perspective.

Measure of benefits used in the economic analysis
The measure of benefit used was the number of life-years gained (LYG) with clopidogrel in comparison with aspirin. The benefits were discounted at a rate of 3% per annum.

Direct costs
The direct costs of the health service were evaluated. These costs were for acute events (MI and stroke), the initial diagnosis of PAD, follow-up (MI, stroke and PAD), amputation in PAD patients, concomitant medication, and adverse events expected to differ between patients receiving clopidogrel and those receiving aspirin.

The costs were discounted at a rate of 3% per annum. Resource use was not presented separately from the costs. The
quantity of drugs used was derived from the effectiveness trial. The costs of the drugs were determined according to the level of reimbursement by the public health care payer in Belgium, using public pricing lists. Other resource use data were derived from expert opinion, and were translated into costs by applying DRG-derived costs from 1997. Some adverse events were costed by assuming that they would incur at least one visit to a general practitioner. The costs were updated to a 2002 price year using an inflation rate of 3% per annum. The costs were those of the health service. The study reported the average and incremental cost per patient. The costs incurred after the 2-year treatment had finished were not considered.

**Statistical analysis of costs**
The costs were treated in a stochastic way. The uncertainty in the cost data was characterised with a triangular distribution, the minimal and maximal values of which were derived from expert opinion.

**Indirect Costs**
Consistent with a health service perspective, the indirect costs were not taken into account.

**Currency**
Euro (Euro).

**Sensitivity analysis**
Several univariate sensitivity analyses were conducted. The parameters examined were the discount rate (0 - 6% per annum), the costs of adverse events (+/- 50%) and ischaemic events (+/- 50%), and life expectancy (+/- 50%). A probabilistic sensitivity analysis was also undertaken using a Monte Carlo simulation method, where the uncertainty in the effects was described using a beta-distribution and the uncertainty in the costs was described using a triangular distribution. The uncertainty under investigation was variability in the data.

**Estimated benefits used in the economic analysis**
In the base-case lifetime analysis, with life-years discounted at 3% per annum, patients receiving clopidogrel gained on average 64.13 life-years per 1,000 patients in comparison with those receiving aspirin. The total years for clopidogrel were 12,158 and for aspirin, 12,084. The adverse events of treatment were included in the analysis, but were assumed to only affect the costs.

**Cost results**
The total cost of patients receiving clopidogrel over two years, with a discount rate of 3% per annum, was Euro12,612 per patient. The corresponding total cost of patients treated with aspirin was Euro11,753 per patient. The incremental cost was Euro859. This included the cost of adverse events.

**Synthesis of costs and benefits**
The costs and benefits were synthesised as the cost per LYG. Both the costs and benefits were discounted at a rate of 3% per annum.

The incremental cost-effectiveness ratio of clopidogrel, compared with aspirin, was Euro13,390 per LYG in the base-case lifetime analysis.

The probabilistic sensitivity analysis indicated that, in the base-case analysis, the cost per LYG with clopidogrel in comparison with aspirin was Euro14,320 (95% confidence interval: 6,990 - 26,470).

If the willingness-to-pay threshold was Euro20,000 per life-year, the probability that clopidogrel was cost-effective in comparison with aspirin was estimated 86%.
When no discounting was applied, the cost per LYG with clopidogrel in comparison with aspirin was Euro7,720.

When the discount rate was 6% per annum for both the costs and benefits, the cost per LYG with clopidogrel in comparison with aspirin was Euro19,640.

Authors' conclusions
Clopidogrel represented a cost-effective alternative to treatment with aspirin for the secondary prevention of ischaemic events in patients with myocardial infarction (MI), stroke or symptomatic peripheral artery disease (PAD). Life expectancy data from a Saskatchewan database were a key driver of these results.

CRD COMMENTARY - Selection of comparators
Aspirin was chosen as the comparator since it is the current practice. You must decide whether aspirin is a widely used health care technology for the secondary prevention of ischaemic events in your own setting.

Validity of estimate of measure of effectiveness
The analysis used data from a randomised controlled trial, which is a strong source of evidence. The overall internal validity of the trial was very high. However, the study did not quote the actual effectiveness parameters entered into the model. The authors provided predicted event rates to indicate that the model closely recreated the trial. The usefulness of the model was reduced by the deficiency in reporting the actual point estimates and variance used. The model was designed to recreate the trial.

Validity of estimate of measure of benefit
The application of Saskatchewan life expectancy to a hypothetical Belgian population may be unsuitable if the case-mix and treatment profile differ between the two countries. The event rate in the model was derived from the clinical trial used to obtain the effectiveness data. Since the trial was not based solely in Belgium, the results may or may not be generalisable to the Belgian setting.

Validity of estimate of costs
The cost categories included were appropriate given the study perspective. It appears that most of the relevant cost items have been included. The majority of the resource use was derived from expert opinion. The methods used to obtain these estimates and to select the experts were not stated. The use of expert opinion introduces increased uncertainty into the results of the model. There was little sensitivity analysis around the estimates provided by the expert opinion. Appropriate reflation and discounting was performed and the price year was reported. These factors will help the results to be reproduced.

Other issues
The authors compared their results with a range of results from other analyses in the same disease area. The authors attempted to translate the avoidance of nonfatal events during the 2-year timeframe of the model to a gain in life expectancy. However, they did not attempt to estimate the impact on the costs after 2 years. The authors stated that a possible criticism of their model was the lack of quality of life data. The authors noted that the results are not generalisable to countries other than Belgium. The results were not reported selectively. The conclusions were appropriate for the scope of the analysis.

Implications of the study
Treatment with clopidogrel represents good value in Belgium in relation to treatment with aspirin.

Source of funding
Supported by a grant from Sanofi-Synthelabo and Bristol-Myers Squibb.

**Bibliographic details**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Aged; Aspirin /administration & dosage /therapeutic use; Cost-Benefit Analysis; Female; Humans; Male; Myocardial Infarction /complications /prevention & control; Platelet Aggregation Inhibitors /administration & dosage /therapeutic use /economics; Stroke; Thrombosis /complications /prevention & control; Ticlopidine /administration & dosage /therapeutic use /economics; Treatment Outcome

**AccessionNumber**
22003008271

**Date bibliographic record published**
31/01/2004

**Date abstract record published**
31/01/2004