Clopidogrel and aspirin in the treatment of non-ST-segment-elevation acute coronary syndromes

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Most of the mortality and morbidity associated with non-ST-segment elevation acute coronary syndromes (ACS) arises from disruption of atheromatous plaques, followed by platelet aggregation and thrombus formation. Aspirin is the most commonly prescribed antiplatelet agent, which is known to reduce the risk of fatal and non-fatal myocardial infarction in patients with unstable angina. Clopidogrel, a different antiplatelet agent, inhibits platelet aggregation induced by adenosine diphosphate, thereby reducing ischaemic events. Combining clopidogrel with aspirin may therefore have an additive effect as each acts via a different inhibitory pathway.

Aim of the review

To review systematically the clinical effectiveness and the cost-effectiveness of clopidogrel used in combination with standard therapy including aspirin, compared with standard therapy alone for the treatment of non-ST-segment elevation ACS.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Eleven electronic databases were searched from inception to April 2003 for the clinical effectiveness and cost-effectiveness sections. In addition, the manufacturers' submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria:

- Intervention: studies in which clopidogrel was used in combination with standard therapy (including aspirin) compared with standard therapy alone.
- Participants: individuals with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). Trials that only included participants with ACS who had undergone angioplasty were excluded.
- Outcome measures: studies that reported on cardiovascular death, myocardial infarction, stroke, refractory ischaemia, severe ischaemia, heart failure, revascularisation, unstable angina, other vascular events and death were included. Bleeding complications and haematological parameters were the adverse events assessed. Studies that reported on the quality of life and costs from all reported perspectives were also included.
- Design: randomised controlled trials (RCTs) that compared clopidogrel in combination with standard therapy, including aspirin, with standard therapy alone were included in the assessment of clinical effectiveness. For the evaluation of adverse events associated with combined aspirin and clopidogrel therapy, RCTs and post-marketing surveillance studies with a clearly defined protocol and denominator were included. For aspirin therapy, as its safety profile is well established, only systematic reviews and meta-analyses were included.
- A broader range of studies were considered in the assessment of cost effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses) were included.

Data extraction and quality assessment

Both data extraction and quality assessment were undertaken by one reviewer and independently checked by a second reviewer, with any disagreements being resolved through discussion. The quality of RCTs was assessed according to criteria based on NHS CRD Report No. 4, and the quality of systematic reviews was assessed according to the guidelines for the Database of Reviews of Effect (DARE) criteria. The quality of economic evaluations was assessed according to a checklist updated from one developed by Drummond and colleagues.

Data synthesis

The clinical effectiveness and cost-effectiveness of clopidogrel in combination with standard therapy

compared with standard therapy alone were synthesised through a narrative review with full tabulation of the results of the included studies. In the economic evaluations, a cost-effectiveness model was constructed using the best available evidence to determine cost-effectiveness in a UK setting.

Results

Clinical effectiveness

One RCT (the CURE trial) was included in the review of the clinical effectiveness of clopidogrel in combination with aspirin. The study was a randomised, double-blind, placebo-controlled trial of high quality. A further five systematic reviews of varying quality examined the adverse events associated with long-term aspirin use. The results of the trial showed that clopidogrel in addition to aspirin was significantly more effective than placebo plus aspirin in patients with non-ST-segment elevation ACS for the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or stroke over the 9-month treatment period. However, clopidogrel was associated with a significantly higher number of episodes of both major and minor bleeding. The results from the systematic reviews that assessed the adverse events associated with long-term aspirin use showed that aspirin was associated with a significantly higher incidence of haemorrhagic stroke, extracranial haemorrhage and gastrointestinal haemorrhage compared with placebo.

Cost-effectiveness

The systematic literature search identified only one study that met the criteria for inclusion in the cost-effectiveness review. A separate cost-effectiveness model and accompanying report were submitted by the manufacturers (Sanofi-Synthelabo Ltd and Bristol-Myers Squibb).

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered relevant from the perspective of the NHS. The review of this evidence highlighted potential limitations within the submission in its use of data and in the model structure used. These limitations led to the development of a new model with the aim of providing a more reliable estimate of the cost-effectiveness from the perspective of the UK NHS. This model indicated that clopidogrel appears cost-effective compared with standard care alone in patients with non-ST-elevation ACS as long as the NHS is willing to pay £6078 per quality-adjusted life-year (QALY). The results were most sensitive to the inclusion of additional strategies which assessed alternative treatment durations with clopidogrel. Although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.

Conclusions

Clinical effectiveness

The results of the CURE trial indicate that clopidogrel in combination with aspirin was significantly more effective than placebo combined with aspirin in a wide range of patients with ACS. This benefit was largely related to a reduction in Q-wave mycardial infarction. There was no statistically significant benefit in relation to mortality. The trial data suggested that a substantial part of the benefit derived from clopidogrel is achieved by 3 months, with a further small benefit over the remaining 9 months of chronic treatment.

Cost-effectiveness

The results from the base-case model suggest that treatment with clopidogrel as an adjunct to standard therapy (including aspirin) for 12 months, compared with standard therapy alone, is cost-effective in non-ST elevation ACS patients as long as the health service is willing to pay £6078 per additional QALY. However, although treatment with clopidogrel for 12 months remained cost-effective for the overall cohort, provisional findings indicate that the shorter treatment durations may be more cost-effective in patients at low risk.

Recommendations for future research

To estimate the exact length of time that clopidogrel in addition to standard therapy should be prescribed for patients with non-ST-segment ACS would require a prospective trial that randomised patients to various durations of therapy. This would accurately assess whether a 'rebound' phenomenon occurs in patients if clopidogrel were stopped after 3 months of treatment.

Publication

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NHS R&D HTA Programme

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The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

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Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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