Effectiveness of clopidogrel and MR-dipyridamole in the prevention of occlusive vascular events

Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation

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Executive summary

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Executive summary

It is widely accepted that atherothrombosis is the most important cause of occlusive vascular events. The clinical manifestations of atherothrombosis include transient ischaemic attack (TIA), ischaemic stroke, unstable angina, myocardial infarction (MI) and intermittent claudication. The importance of long-term secondary prevention in patients at high risk of recurrent vascular events is clear and aspirin and other oral antiplatelet agents have been shown to be protective in such patients. This review examined the clinical effectiveness and cost-effectiveness of two alternative antiplatelet agents, clopidogrel and modified-release (MR)-dipyridamole, relative to prophylactic doses of aspirin for the secondary prevention of occlusive vascular events.

Methods

Search strategy

Eleven databases were searched for randomised clinical trials (RCTs) and reviews for the assessment of the clinical effectiveness and cost-effectiveness of clopidogrel and MR-dipyridamole. Additional searches were conducted in five databases for systematic reviews of side effects associated with aspirin treatment. A further MEDLINE search was carried out to identify economic costs related to heart disease in the UK.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full paper of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness, RCTs that compared clopidogrel or dipyridamole alone, or in combination with aspirin, to aspirin were included. For the assessment of cost-effectiveness, a broader range of studies were considered. For the evaluation of adverse events associated with aspirin, only systematic reviews were included.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked by a second for accuracy.

Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness were presented in structured tables and as a narrative summary. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables. For analyses based on patient-level data, the validity of the studies was assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. For analyses based on decision models, the critical appraisal was based on a range of questions.

Handling the company submission

No additional clinical effectiveness data were presented in either of the two company submissions. All economic evaluations (including accompanying models) included in the company submission were assessed. Following this analysis, if the existing models (company or published) were not sufficient, modified versions of the models were developed.

Results

A total of 2906 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness and 441 studies were ordered as full papers and assessed in detail. Two RCTs were identified. The CAPRIE trial investigated clopidogrel compared with aspirin for the secondary prevention of ischaemic events in patients with MI, ischaemic stroke or peripheral arterial disease (PAD), and ESPS-2 investigated MR-dipyridamole alone and in combination with aspirin compared with aspirin alone and placebo for the secondary prevention of stroke in patients with prior stroke or transient ischaemic attack. For the assessment of the cost-effectiveness of clopidogrel and MR-dipyridamole, eight cost-effectiveness reviews were identified. ▶

A total of 5449 titles and abstracts were screened following the searches for adverse events associated with aspirin and 147 articles were ordered as full papers and assessed in detail. Five systematic reviews that primarily examined adverse events associated with long-term aspirin use were identified.

Clinical effectiveness

Clopidogrel

One RCT, the CAPRIE trial, was identified that investigated the use of clopidogrel for the secondary prevention of occlusive vascular events. In addition, 15 papers reporting on additional aspects of the CAPRIE trial were identified.

The point estimate for the primary outcome (ischaemic stroke, MI or vascular death) favoured clopidogrel over aspirin, but the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than aspirin. In terms of the secondary outcomes reported, there was a non-significant trend in favour of clopidogrel over aspirin but the boundaries of the confidence intervals on the relative risks all crossed unity.

There was no difference in the number of patients ever reporting any bleeding disorder in the clopidogrel group compared with the aspirin group. The incidences of rash and diarrhoea were statistically significantly higher in the clopidogrel group than the aspirin group. Patients in the aspirin group had a higher incidence of indigestion/nausea/vomiting than patients in the clopidogrel group. Haematological adverse events were rare in both the clopidogrel and aspirin groups. No cases of thrombotic thrombocytopenic purpura were reported in either group.

MR-dipyridamole

One RCT, ESPS-2, was identified which investigated the use of MR-dipyridamole and acetylsalicylic acid (ASA)–MR-dipyridamole for the secondary prevention of occlusive vascular events. In addition, four papers reporting on additional aspects of the trial were identified.

Treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2 compared with treatment with aspirin. ASA–MR-dipyridamole was significantly more effective than aspirin alone in patients with stroke or TIAs at reducing the outcome of stroke and marginally more effective at reducing stroke and/or death. Treatment with ASA–MR-dipyridamole did not statistically significantly reduce the risk of death compared to treatment with aspirin. The number of strokes was statistically significantly reduced in the ASA–MR-dipyridamole group compared with the MR-dipyridamole group. In terms of the other primary outcomes, stroke and/or death and death, the results favoured treatment with ASA–MR-dipyridamole but the findings were not statistically significant.

There was no difference in the number of bleeding complications between the ASA–MR-dipyridamole and aspirin groups. The incidence of bleeding complications (including severe and fatal bleeds) was significantly lower in the MR-dipyridamole treatment group. More patients in the MR-dipyridamole treatment groups experienced headaches compared to patients receiving treatment with aspirin alone.

Cost-effectiveness

The York model assessed the cost-effectiveness of differing combinations of treatment strategies in four patient subgroups, under a number of different scenarios. The results of the model were sensitive to the assumptions made in the alternative scenarios, in particular the impact of therapy on non-vascular deaths.

Summary of cost-effectiveness data in stroke patients

The results from the extended model developed by the University of York TAR team were sensitive to the scenario under consideration. The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional quality-adjusted life-year (QALY). ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in TIA patients

The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY. ASA–MR-dipyridamole would be the most ►

cost-effective therapy given a 2-year treatment duration. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.

Summary of cost-effectiveness data in MI patients

The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY. Clopidogrel would be considered cost-effective for treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Summary of cost-effectiveness data in PAD patients

The following conclusions are possible from the York model assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY. Clopidogrel would be considered cost-effective for treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Conclusions

Clinical effectiveness

- Clopidogrel was marginally more effective than aspirin at reducing the risk of ischaemic stroke, MI or vascular death in patients with atherosclerotic vascular disease. That is, the point estimate favoured treatment with clopidogrel but the lower boundary of the 95% confidence intervals suggests that the size of this benefit may be very small.
- Treatment with clopidogrel did not statistically significantly reduce the risk of vascular death or death from any cause compared with aspirin.
- There was no statistically significant difference in the number of bleeding complications experienced in the clopidogrel and aspirin groups.
- Compared with aspirin alone, treatment with MR-dipyridamole alone did not significantly reduce the risk of any of the primary outcomes reported in ESPS-2.
- MR-dipyridamole in combination with aspirin was superior to aspirin alone at reducing the risk of stroke and marginally more effective at reducing the risk of stroke and/or death. Compared with treatment with MR-dipyridamole alone, MR-dipyridamole in combination with aspirin significantly reduced the risk of stroke.
- Treatment with MR-dipyridamole in combination with aspirin did not statistically significantly reduce the risk of death compared with aspirin.
- Compared with treatment with MR-dipyridamole alone, bleeding complications were statistically significantly higher in patients treated with aspirin and MR-dipyridamole in combination with aspirin.
- Due to the assumptions that have to be made, no conclusions could be drawn about the relative effectiveness of MR-dipyridamole, alone or in combination with aspirin, and clopidogrel from the adjusted indirect comparison.

Cost-effectiveness

- The following conclusions are possible assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY.
- For the stroke and TIA subgroups, ASA–MR-dipyridamole would be the most cost-effective therapy given a 2-year treatment duration as long as all patients were not left disabled by their initial (qualifying) stroke. For a lifetime treatment duration, ASA–MR-dipyridamole would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered and all patients were not left disabled by their initial stroke. In patients left disabled by their initial stroke, aspirin is the most cost-effective therapy. Clopidogrel and MR-dipyridamole alone would not be considered cost-effective under any scenario.
- For the MI and PAD subgroups, clopidogrel would be considered cost-effective for a treatment duration of 2 years. For a lifetime treatment duration, clopidogrel would be considered more cost-effective than aspirin as long as treatment effects on non-vascular deaths are not considered.

Research recommendations

- The combination of clopidogrel and aspirin should be evaluated for the secondary prevention of occlusive vascular events. Two ongoing studies should provide evidence in this area.

►

- Randomised, direct comparisons of clopidogrel and MR-dipyridamole in combination with aspirin are required to inform the treatment of patients with a history of stroke and TIA.
- Trials are required which compare treatment with clopidogrel and MR-dipyridamole for the secondary prevention of vascular events in patients who demonstrate a genuine intolerance to aspirin.

Publication

Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al*. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**(38).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

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.

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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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