Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal no.90): a systematic review and economic analysis


CRD summary
This review found that modified-release dipyridamole with aspirin was better than aspirin in people with a history of stroke or transient ischaemic attack. The review was well conducted. The reproducibility and generalisability of the results may be limited by the small number of trials and their differences in outcomes reported and treatments applied.

Authors’ objectives
To assess the effectiveness of clopidogrel or modified-release dipyridamole with or without aspirin, compared with aspirin alone or to each other, for the prevention of occlusive vascular events in people with a history of myocardial infarction, stroke or peripheral artery disease.

Searching
MEDLINE, EMBASE, Web of Science and The Cochrane Library were searched from 2003 to 2009. Manufacturer submissions to the National Institute of Health and Clinical Excellence were also considered. Full search strategies were presented.

Study selection
Only randomised controlled trials were eligible for inclusion. Trials had to assess either clopidogrel or modified-release dipyridamole with or without aspirin in comparison either with aspirin alone, or each other. Patients had to have a history of myocardial infarction, ischaemic stroke or established peripheral artery disease. Trials where clopidogrel was combined with aspirin, or used as an adjunct to percutaneous coronary intervention were excluded, as were patients with acute coronary syndrome or atrial fibrillation.

Mean follow-up time ranged from 1.9 to 3.5 years. Mean ages ranged from 62.5 to 66.7 years. Most patients were male (range: 58% to 72% male) and most were hypertensive (range: 51.5% to 74%). Numbers of current smokers ranged from 21% to 36.5% and patients with diabetes from 15.3% to 28%.

Two reviews performed the study selection independently; discrepancies were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
Trial quality was assessed in terms of randomisation, baseline comparability of trial arms, eligibility criteria, blinding, withdrawals and outcome reporting. Quality was assessed by two reviewers independently and checked by a third.

Data extraction
Data was extracted on a range of vascular outcomes, according to what was reported in each trial, including: all cause mortality; vascular mortality and incidence of stroke; transient ischaemic attack; and myocardial infarction. Data on the numbers of events in each arm were extracted and results reported as either a relative risk (RR), odds ratio (OR), relative risk reduction (RRR) or hazard ratio (HR) with corresponding 95% confidence intervals (CIs). Individual-level data on clopidogrel was made available by the manufacturer and included in the analysis.

Two reviewers independently extracted data. The process was checked by a third reviewer.

Methods of synthesis
Results from trials were reported in tables and a narrative description of the results undertaken. To compare treatments, pooled relative risks, odds ratios, relative risk reductions or hazard ratios (with 95% confidence intervals) were calculated using a Bayesian, fixed-effect, mixed treatment comparison model. Direct comparisons were not possible due to the differences in treatments used and outcomes reported across trials. Results from these indirect comparisons were compared with the results within individual trials. Separate analyses were performed in different populations.
(patients with prior stroke; patients with prior myocardial infarction or established peripheral artery disease).

**Results of the review**

Four trials were included with 48,855 patients. Trial size ranged from 2,736 to 20,332. Two trials assessed clopidogrel, one modified-release dipyridamole alone and three modified-release dipyridamole combined with aspirin. All trials were judged to be of good quality; one trial was open-label.

The CAPRIE trial found that clopidogrel was more effective than aspirin at preventing first vascular events (RRR 8.7, 95% CI 0.3 to 16.5), but found no significant results for any other outcomes.

The ESPS-2 trial found that modified-release dipyridamole with aspirin was more effective than aspirin alone (RR 0.76, 95% CI 0.63 to 0.93) and modified-release dipyridamole alone (RR 0.75, 95% CI 0.61 to 0.91) at preventing stroke. For some secondary outcomes, modified-release dipyridamole alone was no different to aspirin alone.

The ESPRIT trial found that modified-release dipyridamole with aspirin was more effective than aspirin alone at preventing first vascular events (HR 0.80, 95% CI 0.66 to 0.98) and composite outcomes where this was a component.

The PROFESS trial found no significant difference between clopidogrel and modified-release dipyridamole with aspirin for preventing recurrent stroke, but found a significant benefit of modified-release dipyridamole with aspirin for preventing new or worsening congestive heart failure, and a benefit of clopidogrel for incidence of intracranial haemorrhage. Analysis of individual-level data found that clopidogrel reduced the risk of vascular events in people with multivascular disease (RRR 14.9, 95% CI 0.3 to 27.3).

In patients with prior stroke/transient ischaemic attack, the mixed-treatment comparison models found no evidence of differences between any of the treatments for the prevention of first ischaemic stroke, myocardial infarction, vascular death or all-cause mortality. There was evidence that clopidogrel was more effective than aspirin at preventing recurrent stroke (RR 0.752, 95% CI 0.60 to 0.92). Modified-release dipyridamole with aspirin was similarly also more effective than aspirin alone (RR 0.764, 95% CI 0.62 to 0.92). Clopidogrel reduced the risk of major bleeding compared with aspirin (RR 0.596, 95% CI 0.36 to 0.89). No mixed-treatment analysis was performed in patients with myocardial infarction or established peripheral artery disease.

**Cost information**

A full systematic review of cost-effectiveness was undertaken, using a similar process to the review of clinical effectiveness. Cost-effectiveness models were fitted. The authors concluded that for patients with ischaemic stroke, clopidogrel was most cost-effective followed by modified-release dipyridamole with aspirin, then aspirin. For patients with peripheral artery disease or multivascular disease, clopidogrel then aspirin were most cost effective. For patients with myocardial infarction, aspirin was most cost-effective followed by clopidogrel.

**Authors' conclusions**

Modified-release dipyridamole with aspirin was better than modified-release dipyridamole alone or aspirin alone for patients with a history of ischaemic stroke/transient ischaemic attack. There was insufficient evidence to distinguish between clopidogrel and modified-release dipyridamole with aspirin in patients with a prior history of ischaemic stroke/transient ischaemic attack.

**CRD commentary**

The aims of the review and inclusion criteria were clearly stated. Relevant sources were searched for studies. Action was taken to identify unpublished data, including the use of manufacturer-supplied individual patient data. Appropriate action was taken to minimise reviewer error and bias throughout the review process. Quality assessment was undertaken using a standard checklist; results were reported but not used in the analysis. One trial (ESPRIT) was open-label which may have led to bias in its results; this was not considered in the analysis.

Results from all trials were fully and clearly presented and evaluated. The indirect mixed-treatment comparisons used in the analysis were less reliable and required more assumptions than direct comparisons of treatments so conclusions of these analyses should be taken with some caution. This approach was appropriate given the clinical diversity across the trials.
The review was well conducted and the authors' conclusions reflected the evidence presented. Conclusions should be interpreted with caution because of the limited numbers of trials and the different treatments used and outcomes presented across the trials.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors suggested that future trials should distinguish between single vascular bed and multivascular disease with pre-specified definitions of multivascular disease and should be sufficiently powered, with sufficient follow up to detect differences between patient subgroups. They also suggested that a well-audited clinical registry of patients using anti-platelet agents should be established.

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