Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk
Halkes PH, Gray L J, Bath PM, Diener HC, Gairaud-Chaumeil B, Yatsu FM, Algra A

CRD summary
This individual patient data review concluded that combination therapy with dipyridamole plus aspirin reduced vascular death/stroke and other vascular events when compared with aspirin alone in patients after a transient ischaemic attack or stroke. There is some uncertainty regarding this conclusion given potential biases and assumptions within the review.

Authors' objectives
To determine the efficacy of combination therapy with dipyridamole plus aspirin compared with aspirin alone for the secondary prevention of stroke in patients after transient ischaemic attack or minor stroke of presumed arterial origin (updating a previous review, see Other Publications of Related Interest). A secondary objective was to determine whether baseline risk or subgroups defined using patient characteristics would modify the efficacy of combination therapy.

Searching
The search updated that of a previous review in which MEDLINE (1966 to 2001), EMBASE (1980 to 2002), the Cochrane Library (2002, Issue 4), and the Web of Science (1981 to 2002) were searched; details of the new search were not provided. References from relevant articles and reviews were scanned. Trialists and the manufacturer of dipyridamole were contacted. No language restrictions were applied. Both published and unpublished trials were eligible.

Study selection
Randomised controlled trials (RCTs) that compared dipyridamole plus aspirin with aspirin alone were eligible for inclusion. Individuals with a previous history of ischaemic cerebrovascular disease or transient ischaemic attack were eligible for inclusion.

The primary outcome was a composite outcome of death from any vascular cause, non-fatal stroke and non-fatal myocardial infarction. The secondary outcomes included vascular death or non-fatal stroke, all death, vascular death, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction.

Pre-specified subgroup analyses for the primary outcome were: age (up to 65 years versus 65 years and over), gender, qualifying event (transient ischaemic attack versus stroke), type of vessel disease (small versus large), dose of aspirin (less than 75mg versus 75mg or more), formulation of dipyridamole (immediate versus extended release), time between event and randomisation (less than one week versus one week to one month versus one to six months) and history of hypertension, stroke, diabetes, or ischaemic heart disease. Subgroup analyses were also performed according to baseline risk with risk derived from two models based on different risk factors.

The included trials used conventional-release or modified-release dipyridamole (daily dose 150mg to 400 mg) plus aspirin (daily dose ranged from 50mg to 990mg). The average age of included patients was 65 years; almost two-thirds were male.

Two reviewers selected trials for inclusion. It was unclear whether this was completed independently or how disagreements were resolved.

Assessment of study quality
No details of validity assessment were provided in the paper. In the previous review, the methodological quality of the primary studies was assessed using method of randomisation, concealment of allocation, completeness of follow-up, and blinding of the outcome assessment. Trials satisfying at least three of the criteria listed were considered to be of a high quality. The authors sought to clarify differences between their analysis of the data according to methods used in...
trial publications and published results.

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
Trial authors were contacted to provide individual patient data (IPD) for their trial. The data requested included: demographics, clinical presentation, treatment assignment and outcome at the end of the trial. Data were re-coded and merged into a single dataset.

Methods of synthesis
Hazard ratios and associated 95% confidence intervals (CIs) were calculated for each outcome based on intention to treat, via Cox proportional hazard models, with trial as a stratification factor. Publication bias was assessed in the original meta-analysis using Egger's test for asymmetry. The analyses were conducted in duplicate and independently.

Results of the review
Six RCTs were eligible for inclusion in the review; IPD from five RCTs were included in the meta-analysis (n=7,612 patients).

The trial-adjusted hazard ratio for combination of vascular death, non-fatal stroke and non-fatal MI was 0.82 (95% CI 0.72 to 0.92), indicating that aspirin and dipyridamole were significantly more effective than aspirin alone. Hazard ratios did not differ in subgroup analyses or baseline risk strata.

Authors' conclusions
Dipyridamole given in combination with aspirin reduced vascular death/stroke and other vascular events when compared with aspirin alone.

CRD commentary
The review question was supported by clear inclusion criteria. Several databases were searched and attempts were made to minimise language and publication bias; publication bias was assessed using appropriate methods. While the study selection process was carried out in duplicate, the procedures used for the data extraction and quality assessment were not fully reported, so the possibility of error or bias being introduced at these stages could not be assessed.

The validity of the eligible trials was assessed by checking the raw data from each trial and resolving any problems with the trial investigators. The data appeared to have been analysed using appropriate techniques for the meta-analysis of IPD; heterogeneity was investigated using subgroup analyses and discussed in the text.

The evidence presented appeared to support the author's conclusions, but some uncertainties remain regarding the assessment of validity and construction of a multi-component outcome. There was also potential for bias, as the analysis updated an earlier meta-analysis adding a trial and modifying inclusion criteria with the objective of identifying patients who may benefit the most from the combination of aspirin and dipyridamole.

Several authors disclosed financial links with the pharmaceutical companies Boehringer Ingelheim (manufacturers of dipyridamole) and Sanofi/BMS. Some authors were involved in the primary trials of antiplatelet agents included in this review.

Implications of the review for practice and research
Practice: The authors stated that combination therapy with dipyridamole and aspirin should be preferred to aspirin alone in patients after a transient ischaemic attack or stroke.

Research: The authors did not state any implications for further research.

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