Analysis of trials evaluating combinations of acetylsalicylic acid and dipyridamole in the secondary prevention of stroke

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Authors' objectives
To investigate whether the addition of dipyridamole to aspirin further reduces the risk of stroke recurrence.

Searching
MEDLINE, International Pharmaceutical Abstracts, EMBASE and BIOSIS Previews were searched from 1966 to May 2001 for articles in the English language. The search terms used were 'dipyridamole', 'aspirin', 'acetylsalicylic acid', 'ischaemic stroke' and 'cerebrovascular disorders'.

Study selection
Study designs of evaluations included in the review
The authors aimed to identify clinical trials. Four of the identified studies were reported to be randomised double-blind trials, 3 of which were placebo-controlled. The design of one study was not fully described.

Specific interventions included in the review
Studies of the combined use of aspirin and dipyridamole were eligible for inclusion in the review. In the included studies, a range of doses and dose frequencies of aspirin and dipyridamole were used: aspirin 25 mg twice daily (bid) to 325 mg four times daily, plus dipyridamole 75 mg three times daily (tds) to 200 mg bid. This combination was compared with aspirin alone, dipyridamole alone or placebo.

Participants included in the review
Studies of patients who had suffered a first stroke or transient ischaemic attack (TIA) were to be included. In the 5 included studies, the mean age of the participants ranged from 55.5 to 66.7 years and the proportion of males ranged from 58 to 76.3%. Ninety-one per cent of the patients in one trial were white; the race was unspecified in the other studies. The mean blood-pressure was reported in 2 studies as 150 (plus or minus 20)/90 (plus or minus 12) mmHg and 157.2/92.4 mmHg. Where reported, alcohol use occurred in 5.6 to 43.0% of the patients and cigarette smoking in 24.1 to 64.1%. The qualifying event was a complete stroke in 60.1 to 83.9% of the patients, TIA in 16.1 to 94.0%, and 2 studies reported reversible ischaemic neurological deficit (RIND) in 6.5 and 47.3% of the patients. The time from the qualifying event to study enrolment varied from less than 1 month to 1 year. The participants had one or more of the following concurrent diseases: arrhythmias, cardiac failure, diabetes, hypercholesterolaemia, hypertension, ischaemic heart disease and peripheral vascular disease.

Outcomes assessed in the review
The outcome specified by the inclusion criteria was recurrent stroke. In the review, the studies reported on fatal and nonfatal stroke, death from other causes, stroke, retinal infarction, TIA and RIND.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed. However, in reporting the individual trials, the authors comment on whether or not intention-to-treat analysis was used. Where this was not used, they reanalysed the results using the intention-to-treat principle.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
A narrative summary of each study was presented with a brief overall summary.

How were differences between studies investigated?
The authors noted that the different studies used different doses of aspirin and dipyridamole and different methods of assessing compliance, but they did not explore the differences further.

Results of the review
Five randomised studies with a total of 10,782 participants were included in the review.

Three of the earlier studies detected no differences in recurrent stroke when dipyridamole was added to aspirin for stroke prophylaxis. However, the two more recent trials found that the combination provided further reduction in the risk of recurrent cerebrovascular events when compared with aspirin alone, dipyridamole alone or placebo. In the first of the more recent trials (ESPS1), compared with placebo, aspirin 300 mg tds plus dipyridamole 75 mg tds reduced the stroke rate by 38.1% and all-cause mortality by 30.6%. In the second of the recent trials (ESPS2), aspirin 25 mg bid plus modified-release dipyridamole 200 mg bid reduced the risk of stroke by 37.0% compared with placebo, by 23.1% compared with aspirin alone, and by 24.7% compared with dipyridamole alone.

Aspirin given alone or combined with dipyridamole showed a higher risk of bleeding and gastrointestinal adverse effects than placebo. In one study, dipyridamole alone or combined with aspirin caused more neurological adverse effects compared with placebo.

Authors’ conclusions
Differences in the aspirin and dipyridamole doses and the methodology used may explain why the addition of dipyridamole to aspirin has only recently been demonstrated to provide benefit in the secondary prevention of stroke. Further studies are needed to confirm the long-term benefit.

CRD commentary
The topic of the review addressed a common and important medical problem. The objective was stated in clear terms but the inclusion and exclusion criteria were not particularly stated in terms of the study design. The major data sources were searched but other useful sources such as the reference lists and bibliographies of retrieved studies, unpublished data, data from drug companies and contact with experts, were not explored. The fact that the review was restricted to English language articles and that there was no apparent attempt to identify unpublished data introduces language bias and publication bias. Details of the key steps of selecting the studies, assessing validity and extracting the data were not provided; this makes it impossible to judge the validity and reproducibility of the review.

Given the clinical diversity of the five studies, particularly in terms of the drug regimens, it would appear appropriate that the results were not combined in a meta-analysis. The narrative pooling of the results presented was limited; a more thorough analysis could have been presented.

The authors’ conclusions are supported by the review but are rather too general given the available data.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors state that further studies are needed to confirm the long-term benefits of aspirin and dipyridamole in secondary stroke prevention.

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