Effects of dipyridamole in combination with anticoagulant therapy on survival and thromboembolic events in patients with prosthetic heart valves: a meta-analysis of the randomized trials

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Authors' objectives
To assess the effects of dipyridamole in combination with anticoagulant therapy in patients with prosthetic heart valves.

Searching
MEDLINE was searched, and documentation submitted to the FDA (Food and Drug Administration) for approval of dipyridamole in the prevention of thromboembolism in patients with prosthetic heart valves, was examined.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled trials comparing the prevalence of thromboembolic events and deaths in groups treated with warfarin (or similar compound) plus dipyridamole, with control groups receiving the same anticoagulant therapy without dipyridamole.

Specific interventions included in the review
Dipyridamole (225 to 400 mg daily), with warfarin or similar anticoagulant drug; anticoagulants alone.

Participants included in the review
Patients with prosthetic heart valves were included.

Outcomes assessed in the review
All thromboembolic events, both fatal and non-fatal, including cerebral and other arterial emboli, myocardial infarction and strokes; haemorrhagic events, fatal and non-fatal; overall mortality.

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 authors performed the selection.

Assessment of study quality
The quality of the individual studies was not formally assessed.

Data extraction
Two independent individuals extracted summary data from published papers and from documentation submitted to the FDA. Any discrepancies were resolved by consensus after examining the original data. Analysis was on a strict intention to treat basis.

Methods of synthesis
How were the studies combined?
A meta-analysis was performed using standard modifications of the Mantel-Haenszel stratified analysis of contingency tables. Details of the individual studies are given in summary tables.

How were differences between studies investigated?
For each end point, the chi-squared statistic was calculated to test for heterogeneity.

**Results of the review**
Six studies involving 1,141 patients: anticoagulant therapy alone, n=582; anticoagulant plus dipyridamole, n=559.

The dipyridamole and anticoagulant combination reduced the risk of thromboembolic events (fatal or non-fatal) by 56% (95% confidence interval, CI: 33%, 71%) when compared with anticoagulants alone, and the overall mortality rate was reduced by 40% (95% CI: 10%, 60%) in the group receiving dipyridamole. However, for this end-point, there was significant heterogeneity between trials (p=0.046): most of the benefit in terms of overall mortality comes from a single trial (the largest in the series, with 385 patients), and includes a large peri-operative mortality difference between groups, which occurred before drug treatment started. The frequency of haemorrhagic events did not differ between treatment groups (risk reduction -1%, p=0.94).

**Cost information**
The costs are discussed but not specified.

**Authors' conclusions**
This meta-analysis supports the use of dipyridamole for patients with prosthetic heart valves.

**CRD commentary**
The review offers no formal quality assessment of individual studies.

**Implications of the review for practice and research**
The combination of antiplatelet and anticoagulant therapy should be considered after insertion of prosthetic heart valves. However, while the meta-analysis provides convincing evidence that dipyridamole in combination with anticoagulant therapy reduces thromboembolic events, the effect on overall mortality remains unclear; in particular, if fatal thromboembolism is significantly reduced overall, yet all-cause mortality is reduced only in a trial which includes confounding data, there is a possibility that dipyridamole has other adverse effects which could limit its value. The authors refer to 'unpleasant side effects', which should be considered, particularly when dipyridamole is compared with low-dose aspirin. Further trials are needed to establish which antiplatelet drug is most effective in combination with anticoagulant therapy.

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**Other publications of related interest**
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