Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis

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Authors' objectives
To compare the effectiveness and safety of adding dipyridamole or aspirin to warfarin among patients with prosthetic heart valves.

Searching
MEDLINE was searched from 1966 to November 1999 using the following search terms: 'heart-valve prosthesis', 'mechanical heart-valve', 'thromboembolism', 'anticoagulant', 'antiplatelet' and 'haemorrhage'. Reference lists of reports, reviews, meta-analyses and consensus statements were also searched. Reports published as manuscript or described in abstract form in any language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), blind and non-blind, were included. The minimum duration or follow-up periods were not specified. In practice, the follow-up varied from one to 2.5 years.

Specific interventions included in the review
Comparisons of oral anticoagulation (warfarin) and antiplatelet therapy (aspirin or dipyridamole) with warfarin alone. The actual doses of dipyridamole varied from daily doses of 225 to 400 mg, or up to 5 mg/kg body weight. The doses of aspirin varied from 100 mg daily to 500 mg twice daily.

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

Outcomes assessed in the review
The primary outcome measure was arterial thromboembolic event (TE). The other outcomes assessed were mortality and major bleeding.

How were decisions on the relevance of primary studies made?
Studies meeting the inclusion criteria as far as types of participants, interventions, random allocation and objective outcomes, were included. The paper states that the reviewers were not blinded to author, journal or type of publication. It is unclear how many of the reviewers were involved in this process.

Assessment of study quality
The authors state that study quality was not assessed. However, the sensitivity analyses performed assessed whether the studies were double-blind or not, abstract versus full publications, and English versus other languages. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two independent reviewers extracted data on the three major outcomes.

The categories of data extracted included: year of publication, mean duration of follow-up, type of antiplatelet (aspirin or dipyridamole), anticoagulation control/international normalised ratio (INR), target INR or prothrombin time ratio, whether the study was single- or double-blinded, and drug doses. The results of individual trials and meta-analyses were reported as odds ratios (ORs) along with 95% confidence intervals (CIs). The authors state that the data were extracted in an 'intention to treat' format. Some data on bleeding for two trials were extracted from unpublished data included in
other reviews or meta-analyses, but one study was later excluded due to discrepancies in the reported denominator.

**Methods of synthesis**

How were the studies combined?

All of the studies were combined in a statistical meta-analysis for each of the three major outcomes (TE, mortality and major bleeding). Both fixed-effect (Mantel-Haenszel) and random-effects models were used. Similar meta-analyses were performed on various subgroups: early trials (pre-1990) versus later trials; early trials using dipyridamole versus early trials using aspirin; early aspirin trials versus later aspirin trials; and double-blind compared with non-blinded studies. The numbers-needed-to-treat were also presented.

The number of 'missing and negative' trials required to nullify the results was estimated to assess the possibility of publication bias (Rosenthal and L'Abbe methods).

How were differences between studies investigated?

Tests of heterogeneity were carried out for each of the meta-analyses performed using the chi-squared statistic. These tests were not significant for any of the three major outcomes when combining all studies. Sensitivity analyses were also performed for each of the subgroup comparisons.

Each study was deleted in turn to assess the impact of the individual studies on the overall results. A cumulative meta-analysis, based on chronological order, was performed to assess the robustness of treatment effects over time.

**Results of the review**

Ten RCTs with a total of 2,199 participants were included in the review. Only 3 of the trials were double-blinded.

Addition of an antiplatelet to oral anticoagulation reduced the risk of TE (OR 0.41, 95% CI: 0.29, 0.58, p<0.001), and total mortality (OR 0.49, 95% CI: 0.35, 0.67, p<0.001). There was an increased risk of major bleeding (OR 1.5, 95% CI: 1.03, 2.18, p=0.033).

The risk of major bleeding was higher in studies performed before 1990, compared with two more recent trials using lower-dose aspirin (OR 2.23 versus 0.88, p=0.025). There was significant heterogeneity comparing the two later aspirin trials with either the early aspirin trials (p=0.068) or the early dipyridamole trials (p=0.066).

According to L'Abbe's method, 80 small negative trials (40 per group) or 11 larger trials (event rate 10%, 250 per group) would have to exist to nullify the results. Rosenthal's method suggested that 30 to 50 negative trials would be required to overturn the results for death and TE, respectively.

**Authors' conclusions**

Addition of antiplatelet therapy, especially low-dose aspirin, to warfarin reduces the risk of death and systemic TE in patients with prosthetic heart valves. The risk of major bleeding is slightly increased with antiplatelet therapy. Nonetheless, the risk of bleeding appears to have diminished with the lower doses of aspirin used in the more recent trials, resulting in a favourable risk-to-benefit ratio.

**CRD commentary**

The review question and the inclusion criteria were stated clearly. Details of the studies were presented in several tables and the results of the meta-analyses were clearly described, both graphically and in the text.

The search strategy was probably adequate since earlier reviews have been examined, but it could have been more extensive. Other databases, such as EMBASE, should have been searched. The search terms used were described, but it was unclear whether both MeSH terms and textwords were used.

The authors state that TE was well-defined. Similar definitions were used in each trial and these involved either transient or permanent cerebral ischaemic injury or ultrasound or surgically confirmed other systemic arterial...
embolism. Major bleeding was not consistently defined and 'major' versus 'minor' was not distinguished in all studies.

The validity assessment of the primary studies was limited to studies stating 'random allocation'. No attempt was made to ascertain the method of randomisation or whether the sequence was concealed. The authors state that 'objective methods' were used to assess the development of major clinical outcomes or adverse consequences, and the methods used to ascertain TE were described. However, there were differences between trials in defining 'major bleeding' events, and these are described in the text. A sensitivity analysis comparing double-blind with non-blinded trials was carried out, and it was stated that no differences in any of the outcomes were found. Such analyses, however, are hindered by the relatively small number of trials in the review. Some information is provided about the review process, but agreement between the reviewers was not reported. The authors acknowledge and discuss many of these limitations in the conclusions.

The authors describe in detail the two recent trials of low-dose aspirin, since their conclusions concerning the low risk of a major bleed are based on these studies. They also attempt to provide explanations for the differences between their results and those of earlier reviews.

The authors’ conclusions appear reasonable and clinically important with regard to the first two outcomes (reduction in risk of TE and mortality). The magnitude of the increased risk of a major bleed is less clear as the confidence intervals were wider, and of borderline significance (1.03 to 2.18). Heterogeneity between the studies appeared to be greater for this outcome, although it did not reach statistical significance. The authors acknowledge and discuss the lack of power for this outcome.

Implications of the review for practice and research
Practice: The authors state that low-dose aspirin can be safely added to anticoagulation with an acceptable risk of bleeding, and with reduced rates of death and TE expected.

Research: Large well-designed trials with clear methods of defining and measuring the outcome are required to resolve uncertainty concerning the increased risk of a major bleed with low-dose aspirin.

Bibliographic details

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http://content.onlinejacc.org/cgi/content/full/37/2/569

Other publications of related interest
This additional published commentary may also be of interest. Meisner JS, Hla A. Review: oral anticoagulants plus antiplatelet agents reduce thromboembolism and all cause mortality for heart valve prostheses. Evid Based Med 2001;6:147.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aspirin /administration & dosage /adverse effects; Dipyridamole /administration & dosage /adverse effects; Drug Therapy, Combination; Heart Valve Prosthesis; Humans; Platelet Aggregation Inhibitors /administration & dosage /adverse effects; Randomized Controlled Trials as Topic; Risk Factors; Thromboembolism /prevention & control; Treatment Outcome; Warfarin /administration & dosage /adverse effects
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.