Collaborative overview of randomised trials of antiplatelet therapy - II: maintenance of vascular graft or arterial patency by antiplatelet therapy

Antiplatelet Trialists’ Collaboration

Authors’ objectives
To determine the efficacy of antiplatelet therapy in maintaining vascular patency in various categories of patients.

Searching
MEDLINE and Current Contents were searched by computer, and journals were manually searched. Additional material was obtained by examining reference lists of trials, review articles, abstracts and meeting proceedings, by collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, and by consulting colleagues and various manufacturers of antiplatelet agents.

Both published and unpublished studies, available for review by 30th March 1990, were included.

Study selection
Study designs of evaluations included in the review
Unconfounded randomised controlled trials comparing different antiplatelet therapies or comparing antiplatelet therapy with placebo.

Specific interventions included in the review
Treatment with agents which act on the vascular system by inhibition of platelet aggregation or adhesion, or both.

Cyclo-oxygenase inhibitors: aspirin, flurbiprofen, ibuprofen, indobufen, naproxen, sulphinpyrazone and triflusal.

Phosphodiesterase inhibitors: dipyridamole, E5510 and RA233.

Platelet calcium ion-channel inhibitors: suloctidil.

Phospholipase inhibitors: hydroxychloroquine.

Thromboxane synthetase inhibitors, receptor blockers, or both: dazoxiben, piracetam, picotamide, ridogrel, sulotroban, daltroban and GR32191.

Agents with direct effects on platelets: ticlopidine.

Participants included in the review
Coronary artery trials: patients having coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

Peripheral artery trials: patients with symptomatic peripheral vascular disease, those having non-coronary arterial grafting procedures, and those having transluminal angioplasty in the legs.

Haemodialysis access trials: patients with arteriovenous fistulas or shunts placed for haemodialysis.

Outcomes assessed in the review
Occurrence of any vascular graft or arterial occlusion (partial occlusions were excluded), assessed by angiography, doppler ultrasonography, limb plethysmography, systematic angiography and clinical examination. Data were also obtained on major bleeding complications, i.e. requiring transfusion, reported in the trials.

How were decisions on the relevance of primary studies made?
Studies were reviewed by the collaborative review group. Individual data were requested from investigators to judge patient recruitment and eligibility, duration of treatment and the classification of outcomes.

Assessment of study quality
Trials had to demonstrate they used concealed treatment allocation (randomisation method precluded prior knowledge of the next treatment), and were unconfounded (one treatment group differed from the other only in the treatment of interest). Trials were required to use the same method for assessing patency in both treatment and control groups. Information about the exact nature of randomisation, treatment allocation, placebos, and blinding procedures was requested from individual investigators and assessed by the collaborative review group.

Data extraction
Summary data for each study were requested from principal investigators for each trial, and checked for internal consistency and with published reports of the trials. Individual patient data were requested and intention to treat analyses were performed for most studies. When the data were not available, the study was included unless the number of exclusions was so extensive that the trial could not be considered properly randomised.

Methods of synthesis
How were the studies combined?
Summary statistics were calculated for each study by summing events and patients in each treatment group, after adjusting for differences in studies which were not evenly randomised. The results were combined using the Peto method of meta-analysis (see Other Publications of Related Interest no.1), the pooled effect sizes being described as a reduction in proportional odds, together with a 99% confidence interval.

How were differences between studies investigated?
Analyses were performed separately according to patients included in the trials (coronary grafts, coronary angioplasty, intermittent claudication, peripheral grafts, peripheral angioplasty, arteriovenous fistulas, arteriovenous shunts, fistulas and shunts). Analyses were also performed separately, according to whether the antiplatelet agent was started prior to, within 24 hours, or more than 24 hours after the procedure.

Results of the review
Twenty-three coronary artery studies involving 6,156 patients (adjusted figure);

14 peripheral artery studies involving 3,226 patients (adjusted figure); and

9 dialysis studies involving 418 patients (adjusted figure).

When combining all events, antiplatelet therapy produced an substantial reduction in vascular occlusion rates.

Coronary artery grafts: the odds of occlusion reduced from 30% (control) to 21% (antiplatelet group) benefiting 90 patients per 1,000 treated for 7 months.

After coronary angioplasty: the odds of occlusion reduced from 8% (control) to 4% (antiplatelet group) benefiting 40 patients per 1,000 treated for 6 months.

Peripheral artery procedures: the odds of occlusion reduced from 25% (control) to 16% (antiplatelet group) benefiting 90 patients per 1,000 treated for 19 months.

Patients with shunts or fistulas: the odds of occlusion reduced from 39% (control) to 17% (antiplatelet group) benefiting 200 patients per 1,000 treated for 2 months.

The data on haemorrhages was incomplete, but there was an excess of bleeds (1 per 1,000 fatal bleeds, 13 per 1,000 nonfatal bleeds, if antiplatelet therapy started before procedure) among the antiplatelet groups.
There was no evidence of differences between antiplatelet agents and regimens, or from indirect comparisons, according to when the antiplatelet treatment was commenced.

**Authors’ conclusions**

Antiplatelet therapy (chiefly aspirin alone, or aspirin plus dipyridamole) greatly reduces the risk of vascular occlusion in a wide range of patients at high risk of this complication. Further studies are required to determine exactly when treatment should start (to limit any perioperative bleeding while still preventing most early occlusion) and for how long it should be continued.

**CRD commentary**

The Antiplatelet Trialists’ Collaboration employed rigorous review methods, including the pursuit of individual patient data and thorough checking of individual study results, which ensure that the results of the review are valid. Recommendations on using the treatment rely on the benefits of reduced occlusion rates outweighing the risks of major bleeds. Whilst the data on haemorrhages is incomplete, the difference in rates and the note that most bleeds were nonfatal, suggests that the conclusions are robust. In some of the included trials, the outcome assessment was not performed blind which is a potential threat to validity. However, comparison with the results of a synthesis limited to only placebo-controlled trials, which are more likely to have had blind outcome assessment, suggests that the results are not materially affected by this potential bias.

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

Antiplatelet therapy should be considered for patients undergoing coronary artery bypass grafting or angioplasty, or leg artery bypass grafting or angioplasty, and for those with fistulas or shunts placed for haemodialysis access, unless there are contraindications. The timing of commencement of therapy and duration of therapy should be investigated in further randomised controlled trials.

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**Other publications of related interest**

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