Collaborative overview of randomised trials of antiplatelet therapy - III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients

Antiplatelet Trialists’ Collaboration

Authors’ objectives
To determine the efficacy of antiplatelet therapy as prophylaxis against deep venous thrombosis or pulmonary embolism in surgical and high-risk medical 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Both published and unpublished studies, available for review by 30th March 1990, were included.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
At least 1-month 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, sulphipyrazone and triflusal.

Phosphodiesterase inhibitors: dipyridamole, E5510 and RA233.

Platelet calcium ion-channel inhibitors: sulodcital.

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
Patients undergoing general, traumatic orthopaedic and selective orthopaedic surgery, and high-risk medical patients.

Outcomes assessed in the review
The occurrence of deep venous thrombosis, as identified prospectively by systematic venography or systematic radiolabelled fibrinogen-uptake tests. The occurrence of pulmonary embolism, as identified in all trials systematically looking for deep venous thrombosis regardless of method. Overall mortality and the occurrence of major bleeds which required transfusion.

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). 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?
Data from patients undergoing general, traumatic orthopaedic and elective orthopaedic surgery, and high-risk medical patients were analysed separately. Analyses were also performed separately for trials in which patients did or did not receive heparin. Results were reported separately for deep venous thrombosis, pulmonary embolism and major bleeds.

Results of the review
For deep venous thrombosis:

- general surgery, 22 studies with 2,893 patients (adjusted total);
- traumatic orthopaedic surgery, 10 studies with 898 patients (adjusted total);
- elective orthopaedic surgery, 13 studies with 863 patients (adjusted total);
- high-risk medical patients, 8 studies with 527 patients (adjusted total).

For pulmonary embolism:

- general surgery, 26 studies with 6,827 patients (adjusted total);
- traumatic orthopaedic surgery, 11 studies with 998 patients (adjusted total);
- elective orthopaedic surgery, 16 studies with 1,066 patients (adjusted total);
- high-risk medical patients, 9 studies with 555 patients (adjusted total).

Antiplatelet therapy led to reductions in the rates of deep venous thrombosis and pulmonary embolism, which were similar in most groups, and overall, were statistically significant.

The odds of deep vein thrombosis were reduced from 33.6% (control) to 24.8% (antiplatelet groups), benefiting 90 patients per 1,000 treated. The odds of pulmonary embolism were reduced from 2.7% (control) to 1.0% (antiplatelet groups) benefiting 17 patients per 1,000 treated. The proportional reductions for both deep venous thrombosis and pulmonary embolism were similar in general, traumatic orthopaedic and elective orthopaedic surgery, and high-risk
medical patients.

Antiplatelet therapy led to lower death rates from pulmonary embolism (0.9% on control compared to 0.2% on antiplatelet, p=0.0001), but non significant higher rates of fatal bleeds and other deaths. Overall, there were fewer deaths on antiplatelet treatment (1.0% on control compared to 0.7% on antiplatelet, p>0.05), but this difference is not statistically significant. There was an excess of nonfatal major bleeds (3 per 1,000 patients) and other complications (reoperations, wound haematomas, or infections due to bleeding; 22 per 1,000 patients) among surgical patients treated with antiplatelet agents.

A comparison between aspirin alone and aspirin plus dipyridamole for treatment of deep venous thrombosis was noted to be statistically significant, but given the large numbers of comparisons made in these studies the importance of this result is questionable.

There was little information on the benefit of using antiplatelet agents in addition to heparin, but the available evidence suggested that the effects may be additive for the prevention of pulmonary embolism. The additional benefit for deep venous thrombosis was unclear.

Authors' conclusions
It had previously been supposed that antiplatelet therapy did not influence venous thromboembolism, and consequently many surgeons and physicians do not use it routinely for thromboprophylaxis, even for patients who are at substantial risk of deep venous thrombosis or pulmonary embolism. These results indicate that antiplatelet therapy, either alone or in addition to other proven forms of thromboprophylaxis (such as subcutaneous heparin) for greater effect, should be considered.

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. The authors' conclusions are supported by the results presented.

Implications of the review for practice and research
Prophylactic antiplatelet therapy should be considered in surgical and medical patients who are at high risk of venous thrombosis and pulmonary embolism.

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