Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

Authors' objectives
To determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events.

Searching
MEDLINE, EMBASE, a Derwent database, SciSearch and BIOSIS Previews were searched up to September 1997. Trial registers of the Cochrane Stroke and Peripheral Vascular Disease Groups were also searched. Trials were also identified through manual searches of journals, abstracts and proceedings of meetings, by examining the reference lists of trials and reviews, and through contact with colleagues (including those in the pharmaceutical industry). The search terms were not provided in this paper, but are available from the authors on request.

Study selection
Study designs of evaluations included in the review
Individual patient data (IPD) or tabular data from randomised controlled trials were included.

Specific interventions included in the review
One or more antiplatelet regimes versus a control or versus another antiplatelet regime. In the included studies, the main treatments were: aspirin (less than 75 mg); clopidogrel; aspirin and dipyridamole; aspirin and glycoprotein IIb/IIIa antagonist. Trials of oral antiplatelet regimes were eligible only if they assessed more than one day of treatment, but trials of parenteral antiplatelet regimes of any duration were included.

Participants included in the review
Patients considered to be at high annual risk (e.g. over 3% per year) of vascular diseases because of evidence of pre-existing disease (previous occlusive event or predisposing condition). This included patients with acute myocardial infarction (MI) or ischaemic stroke, stable or unstable angina, previous MI, stroke or cerebral ischaemia, peripheral arterial disease, atrial fibrillation, diabetes, carotid disease, cardiac valve disease, patients undergoing coronary or non-coronary revascularisation, haemodialysis.

Outcomes assessed in the review
The primary outcome was 'serious vascular event', i.e. nonfatal MI, nonfatal stroke or death from a vascular cause, including any death from an unknown cause as this was mostly likely to be vascular. The individual trialist's definition of each event was used.

How were decisions on the relevance of primary studies made?
The coordinators of all potentially eligible trials were asked for details of methods of randomisation, blinding of treatment allocation, scheduled duration of treatment, and if different, scheduled duration of follow-up. The trials had to use a method of randomisation that precluded prior knowledge of the next treatment to be allocated and have comparisons that were unconfounded (study arms differed only in terms of the antiplatelet regimes).

Assessment of study quality
Data on all the patients originally randomised were collected. These included details of randomisation and baseline characteristics, which enabled checking for balance across the groups. The data were checked for both internal consistency and for consistency with relevant published reports, and any queries were referred back to the trial coordinators. The authors do not state how judgements of validity were made, or how many of the reviewers performed the validity assessment.
**Data extraction**

Investigators of trials that had contributed at least 200 patients provided, for each patient originally randomised, data on the baseline characteristics (age, gender, blood-pressure, medical history) and dates of randomisation, follow-up, and any vascular events that had occurred. They also provided a tabular summary of the number of patients originally allocated to each treatment group and the numbers experiencing outcomes of interest over the scheduled follow-up period. Investigators responsible for smaller trials (fewer than 200 patients) were asked only for the tabular summary.

**Methods of synthesis**

**How were the studies combined?**

The analyses were stratified by trial (to avoid direct comparisons between individuals in different studies). Trials that had unequal randomisation ratios, and therefore imbalances in the number of patients in the treatment and control groups, were adjusted by an appropriate integer.

**How were differences between studies investigated?**

Different trials or groups of trials were compared using standard chi-squared tests for heterogeneity or tests for trend between the observed effects on vascular events.

**Results of the review**

There were 197 trials comparing antiplatelet therapy with control, of which 195 provided vascular event data (135,640 patients), and 90 trials (77,000 patients) comparing different antiplatelet regimens.

**Overall results on vascular events.**

Overall, 7,705 (10.7%) vascular events were recorded among 71,912 on antiplatelet treatment versus 9,502 (13.2%) of 72,139 allocated controls (adjusted totals), (p<0.0001), a reduction of about one-quarter. These benefits were observed among all patient groups (previous MI, acute MI, previous stroke or transient ischaemic attack, acute stroke, other high risk). The absolute reductions in events were: 36 (standard error, SE=5) per 1,000 treated for two years among patients with previous MI; 38 (SE=5) per 1,000 patients treated for one month among those with acute MI; 36 (SE=6) per 1,000 treated for two years among those with previous stroke or transient ischaemic attack; 9 (SE=3) per 1,000 treated for three weeks among those with acute stroke; and 22 (SE=3) per 1,000 treated for two years among other high-risk patients, with separately significant results for those with stable angina (P=0.0005), peripheral arterial disease (p=0.004), and atrial fibrillation (p=0.01). Although the benefit for acute stroke patients appeared smaller, this may reflect the shorter treatment period (less than one month) among acute stroke patients, compared with an average of 29 months for patients with a previous stroke or transient ischaemic attack. Overall, antiplatelets produced a proportional 34% reduction in nonfatal MI, a 26% reduction in nonfatal MI or death from coronary heart disease (p<0.0001), a 25% reduction in nonfatal strokes (p<0.0001), a 15% reduction in vascular deaths (p<0.0001), and a 26% reduction in the odds of fatal or nonfatal pulmonary embolism (p<0.01).

**Risk of bleeding.**

The proportional increase in risk of a major extracranial bleed with antiplatelet therapy was about 60% (odds ratio 1.6, 95% confidence interval, CI: 1.4, 1.8), with similar proportional increases in each of the 5 categories of patient.

**Dose of aspirin.**

There was no significant differences in reductions in vascular events between different aspirin regimens (e.g. less than 75 mg daily versus at least 75 mg daily), although doses of less than 75 mg have not been widely assessed. The evidence from trials of higher doses indicates that the proportional increase in risk of a major extracranial bleed was similar with daily aspirin dose of less than 325 mg but, since gastrotoxicity is known to be dose-dependent, a dose of 75 mg to 150 mg daily is appropriate for long term protection.

**Effects of other antiplatelet drugs.**

Indirect comparisons of different antiplatelets provided no clear evidence of differences in the effects on serious
vascular events. Direct randomised comparisons suggested a possible reduction in risk with clopidogrel of 10% compared with aspirin, but the size of any additional benefit was statistically uncertain.

Effect of adding another antiplatelet drug to aspirin.

Among 10,404 patients in 25 trials comparing dipyridamole plus aspirin versus aspirin alone, the addition was associated with a non significant further 6% reduction in serious vascular events. Among 24,802 patients in 15 trials, the addition of an intravenous glycoprotein IIb/IIIa antagonist with aspirin alone produced a highly significant 19% proportional reduction in serious vascular events, preventing 20 events per 1,000 patients treated (p<0.0001). This reduction was larger among patients undergoing percutaneous coronary interventions (32%) than among patients not having such interventions (12%), (p<0.003), but the absolute benefit among patients with acute coronary syndromes was still significant. However, the benefits were offset by an increase in cranial bleeds (23 per 1,000 patients).

Full details of the results are provided in the paper and additional figures are available on the BMJ website. See Web Address at end of abstract.

Authors’ conclusions

Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute MI or ischaemic stroke, stable or unstable angina, previous MI, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation. Low-dose aspirin (75 to 150 mg daily) is an effective antiplatelet regimen for long-term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed.

CRD commentary

This review updates a previous IPD meta-analysis (see Other Publications of Related Interest), but includes patients with a wider range of occlusive vascular disease. In particular, there is considerably more information on the benefits of antiplatelet therapies among patients having coronary procedures, and in patients with acute stroke, stable angina, atrial fibrillation, peripheral arterial disease and diabetes mellitus.

This was a very large and comprehensive study. The review question and inclusion criteria were clearly stated; appropriate information was obtained from trialists; and the data were checked for consistency. The searches appear to be comprehensive, with attempts made to identify unpublished literature, but it is not stated whether any language restrictions were applied. Some methodological details (such as search terms) were not published, but are available from the authors on request. Additional information on the trials included is available on the BMJ website. See Web Address at end of abstract. The statistical methods used and the authors’ conclusions appear appropriate.

A correction (BMJ 2002;324:71) was noted in the last sentence of the article: ‘For most healthy individuals, however, for whom the risk of a vascular event is likely to be substantially less than 1% a year, daily aspirin may well be inappropriate.’ The online text therefore differs from the text in the print version of the journal, which incorrectly ended ‘...may well be appropriate’.

Implications of the review for practice and research

Practice: Individuals at high risk of occlusive vascular disease should receive antiplatelet therapy, unless some contraindication exists. Clopidogrel is an appropriate alternative for patients with a contraindication to aspirin. In high-risk patients the benefits of antiplatelet therapy outweigh hazards of bleeding unless this risk is extremely high (such as among haemodialysis patients).

Research: Antiplatelet regimens that are more effective than aspirin alone are required, but these may require large trials (of thousands or even tens of thousands of patients). Trials are needed to test for the additional benefits of adding a second antiplatelet to aspirin.
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