Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events
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CRD summary
The authors concluded that combined clopidogrel and aspirin reduced the likelihood of major cardiovascular events associated with acute coronary syndrome or percutaneous coronary intervention compared with monotherapy, but increased the likelihood of major bleeding. Although the review had limitations, in particular the restriction to published studies in English, in most respects it was well conducted and the conclusions appeared reliable.

Authors' objectives
To evaluate the role of dual antiplatelet therapy (clopidogrel plus aspirin) for the treatment and prevention of vascular disease.

Searching
MEDLINE (from 1966), Cochrane Central Register of Controlled Trials, DARE, Cochrane Database of Systematic Reviews and the ACP Journal Club were searched to August 2006. The reference lists of potentially relevant articles were also checked. The search was limited to studies in English.

Study selection
Randomised controlled trials (RCTs) comparing combined clopidogrel and aspirin therapy with aspirin or clopidogrel monotherapy were eligible for inclusion. Required outcomes were efficacy and safety. Primary review outcomes for efficacy were major coronary events (a composite of death, stroke or myocardial infarction). The primary safety outcome was major bleeding (for example, substantially disabling bleeding that was causing a drop in haemoglobin of at least five grams per decilitre or the transfusion of over two units of blood). Secondary efficacy outcomes were fatal or non-fatal myocardial infarction, all-cause mortality and ischaemic stroke. Studies with surrogate outcomes (for example, platelet aggregation) were excluded.

Patients in the included studies had acute coronary syndrome with or without ST-segment elevation, had undergone percutaneous coronary intervention or had other disorders (for example, recent ischaemic stroke or transient ischaemic attack, established vascular disease, multiple athero-thrombotic risk factors). Patients' mean age ranged from 57.2 to 66.5 years. Most were male (mean 70 per cent). Mean/median duration of follow up ranged from 28 days to 18 months.

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed study validity using the Jadad scale (measures adequacy of randomisation, blinding, and management of withdrawals and dropouts). Disagreements were resolved by consensus.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the number of events in each group, using intention to treat analysis. Numbers needed to treat (NNT) or harm were also calculated. Studies were subgrouped by patient diagnosis (acute coronary syndrome, percutaneous coronary intervention or other) and by duration of follow up. Two reviewers independently extracted data using a standardised protocol. Disagreements were resolved by consensus.

Methods of synthesis
Where three or more studies in one subgroup reported the same outcome, a meta-analysis examining pooled ORs with 95% CIs was performed using both fixed- and random-effects models. Results from random-effects models were used in interpretation of findings. Heterogeneity was assessed by visual scan of the forest plot and with the Q statistic. Subgroup analyses were conducted by duration of follow-up.
Results of the review

Eight RCTs were included in the review (n=91,744). All were of high quality.

Combined therapy versus aspirin monotherapy in patients with acute coronary syndrome (three RCTs):
Combined therapy significantly reduced the odds of a major coronary event or fatal/non-fatal myocardial infarction (OR 0.85, 95% CI: 0.77, 0.94, p=0.002, NNT=67) or fatal/non-fatal myocardial infarction (OR 0.81, 95% CI: 0.74, 0.89). There was significant heterogeneity in the results for major bleeding (p=0.001). There was no significant difference between the groups for all-cause mortality or major bleeding.

Combined therapy versus aspirin monotherapy in patients with percutaneous coronary intervention (three RCTs):
Combined therapy significantly reduced the odds of a major coronary event (OR 0.66, 95% CI: 0.56, 0.78, p=0.002, NNT=9) or fatal/non-fatal myocardial infarction (OR 0.81, 95% CI: 0.74, 0.89). There was no significant difference between the groups for all-cause mortality or major bleeding.

Combined therapy versus monotherapy in patients with other conditions (two RCTs):
There was no statistically significant difference between the groups for efficacy outcomes, but combined therapy significantly increased the odds of major bleeding compared with either clopidogrel (OR 3.37, 95% CI: 2.09, 5.44; one RCT) or aspirin (OR 1.64, 95% CI: 1.27, 2.10; one RCT) monotherapy.

Subgroup analyses:
When studies were subgrouped by duration of follow up, the odds of major bleeding were significantly increased in longer studies (OR 1.80, 95% CI: 1.41, 2.30, p<0.00001; five RCTS, duration eight to 28 months), but not in shorter studies (two RCTS, duration 30 days or less).

Authors’ conclusions
Combined clopidogrel and aspirin reduced the likelihood of major cardiovascular events associated with acute coronary syndrome or percutaneous coronary intervention compared with monotherapy, but increased the likelihood of major bleeding.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched. However, it did not appear that specific efforts were made to retrieve unpublished studies and the search was limited by language, so the review is prone to publication and language biases. Steps were taken to minimise the risk of bias and error by having more than one reviewer involved in data extraction and validity assessment, but it was unclear whether this also applied to study selection. Although most of the characteristics of the included studies were reported in adequate detail, very little information was provided about the results of the validity assessment. The sub-grouping of studies by patient diagnosis and the statistical techniques used to pool studies and assess for heterogeneity appeared appropriate. However, where statistically significant heterogeneity was detected it was not explored further. Publication bias was not assessed. Although the review had limitations, in particular the restriction to published studies in English, in most respects it was well conducted and the authors’ conclusions appeared reliable.

Implications of the review for practice and research
Practice: The authors stated that the benefits of dual therapy outweighed the risks for patients with acute coronary syndrome or percutaneous coronary intervention, but not for other patient subgroups. However, the risk-benefit balance was uncertain beyond the immediate acute-care phase, as the bleeding risk appeared to increase over time.

Research: The authors stated that there was a need for clinical trials to clarify the role of drug-eluting stents and long-term dual-antiplatelet therapy for stable and unstable coronary disease.

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