Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials

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CRD summary
This well-conducted review compared the effectiveness and safety of oral anticoagulant (OAC) therapy plus aspirin with OAC alone. The authors concluded that, except for patients with a mechanical heart valve, the benefits of OAC therapy plus aspirin in reducing thromboembolic events were unclear and there were increased risks of major bleeding. This conclusion is likely to be reliable.

Authors' objectives
To compare the effectiveness and safety of oral anticoagulant (OAC) therapy plus aspirin with OAC therapy alone in individuals at risk from cardiovascular disease.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register (Issue 2, 2005) were searched from inception to June 2005. The references of identified studies were checked and experts were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared combined aspirin and OAC therapy with OAC therapy alone were eligible for inclusion. Eligible studies administered OAC therapy in order to achieve the same international normalised ratio, or administered the same fixed dose, in both treatment arms. Low-dose aspirin (up to 100 mg/day) was used in 6 studies, and moderate to high doses (200 to 1,000 mg/day) in 4 studies.

Participants included in the review
Studies of adult patients requiring OAC therapy were eligible for inclusion, as were studies of patients requiring OAC therapy for any cause. The included studies contained patients with the following indications for treatment: mechanical heart valve, atrial fibrillation, coronary artery disease and high risk for cardiovascular disease. The age of the participants in the intervention groups ranged from 50.1 to 74.2 years.

Outcomes assessed in the review
Studies that reported arterial thromboembolism, all-cause mortality or major bleeding were eligible for inclusion. Arterial thromboembolism was defined as myocardial infarction, unstable angina requiring hospitalisation, stroke, transient ischaemic attack or systemic embolism. Major bleeding was defined as bleeding that required the transfusion of at least two units of packed red blood cells, or involved a critical site such as intracranial bleeding, or resulted in fatality.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection. However, multiple reviewers appear to have been involved as the authors stated that the kappa statistic was used to assess the level of agreement between reviewers.

Assessment of study quality
Two reviewers who were blinded to the study source independently assessed the validity of the studies. Agreement was
assessed using the kappa statistic. The following criteria were used in the assessment, which was based on a modified form of the Jadad scale: randomisation, double-blinding, description of withdrawals and drop-outs. Studies scoring over 2 out of a maximum of 4 criteria satisfied were considered to be high quality; those scoring 2 or less were considered to be low quality. Allocation concealment was also assessed.

**Data extraction**

Two reviewers who were blinded to the study source independently extracted the data. Any disagreements were resolved through consensus and consultation with a third reviewer. Data on patient characteristics and principal outcomes were extracted. Odds ratios (ORs), absolute risk reductions and numbers-needed-to-treat (NNT) or -harm (NNH) were calculated, along with 95% confidence intervals (CIs) for each outcome.

**Methods of synthesis**

How were the studies combined?

The studies were combined in meta-analyses for each outcome using a Mantel-Haenszel fixed-effect model, unless statistically significant heterogeneity was detected, in which case a random-effects model was used. Publication bias was assessed using a funnel plot analysis.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the I-squared and chi-squared statistics. Subgroup analyses were conducted to assess the efficacy and safety of the interventions in patient groups with the following indications for treatment: atrial fibrillation, mechanical heart valve and coronary artery disease. A sensitivity analysis, in which only high-quality studies were included, was also carried out.

**Results of the review**

Ten RCTs with a total of 4,180 patients were included in the review.

There was no indication of publication bias.

Four studies were rated as high quality and 6 studies as low quality.

Arterial thromboembolism (9 studies).

The incidence of arterial thromboembolism was significantly lower in the aspirin-OAC therapy group than in the OAC therapy alone group (OR 0.66, 95% CI: 0.52, 0.84). This represented an absolute risk reduction of 2.5% and a NNT to prevent one incident of 40. Statistically significant heterogeneity was detected (chi-squared 18.97, p=0.02; I-squared 57.8%). An analysis using a random-effects model did not alter the results. Results from the sensitivity analysis, which included only high-quality studies, supported this finding. The subgroup analyses showed that a significant difference between the groups was only present for patients with a mechanical heart valve (OR 0.27, 95% CI: 0.15, 0.49).

Fatal arterial thromboembolism (9 studies).

There was no difference between the groups in the incidence of fatal arterial thromboembolism (OR 1.08, 95% CI: 0.76, 1.53).

Mortality (10 studies).

There was no significant difference between the groups in all-cause mortality (OR 0.98, 95% CI: 0.77, 1.25). No statistically significant heterogeneity was detected. Results from the sensitivity analysis, which included only high-quality studies, supported this finding. The subgroup analyses found no difference between the treatments in any patient group.

Major bleeding (10 studies).
The incidence of major bleeding was significantly higher in patients receiving combined aspirin OAC therapy than in those receiving OAC therapy alone (OR 1.43, 95% CI: 1.00, 2.02; absolute risk increase 1%; NNH 100). The sensitivity analysis, which included only high-quality studies, found no difference between the groups. The subgroup analyses demonstrated a significantly greater incidence of major bleeding only in patients with a mechanical heart valve.

**Authors' conclusions**
The findings raised questions over the current practice of using combined aspirin-OAC therapy except in patients with a mechanical heart valve, given the questionable benefit in reducing thromboembolic events and the increased risk of major bleeding.

**CRD commentary**
The review question and the inclusion criteria were clear. The search was reasonably extensive and included attempts to identify unpublished studies, thereby reducing the possibility that relevant studies were excluded from the review. The authors used rigorous methods to minimise bias and error in the extraction of data and the analysis of study validity and, although they did not report using such methods when selecting studies for the review, it was clear that they did so. The validity assessment was appropriate and the results of this were incorporated into the analysis in an informative way. The decision to employ meta-analyses was appropriate. The authors' conclusions draw fully on the results of the review, and are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that the current practice of treating patients receiving OAC therapy with additional therapy should be considered carefully, with the benefit of reducing thromboembolic events contrasted with the increased risk of major bleeding.

Research: The authors stated that large RCTs are required to assess the risks and benefits of the two treatment approaches in patients with both atrial fibrillation and coronary artery disease, and high-risk patients with atrial fibrillation.

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**Other publications of related interest**
This additional published commentary may also be of interest. Parry MJ. Review: oral anticoagulants plus aspirin reduce arterial thromboembolism more than oral anticoagulants alone but only in patients with mechanical heart valves. Evid Based Nurs 2007;10:79.

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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.