Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients

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CRD summary
The review investigated the effect of aspirin combined with warfarin in patients recovering from acute coronary syndromes. The review concluded that at an international normalised ratio of 2-3 the combination of aspirin and warfarin is superior to aspirin alone in reducing the risk of major adverse events, although it significantly increases the risk of major bleeding. The conclusion appears reliable.

Authors' objectives
To determine the effect of aspirin plus warfarin (A+W) compared with aspirin alone for the secondary prevention of major adverse events (MAEs) in patients recovering from acute coronary syndromes (ACS).

Searching
MEDLINE and the Cochrane CENTRAL Register were searched until March 2005 with no language restrictions; the search terms were reported. In addition, relevant reviews and papers were searched by hand.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with no significant imbalances in major baseline characteristics among study groups, using intention-to-treat analysis and with a follow-up of greater than 80%, were eligible for inclusion. The follow-up period ranged from 3 months to 5 years.

Specific interventions included in the review
Studies of A+W compared with aspirin alone, administered for the prevention of MAEs, were eligible for inclusion. The dose of aspirin ranged from 75 to 325 mg/day. The dose of warfarin was not reported.

Participants included in the review
Patients recovering from ACS were eligible for inclusion. The participants were patients admitted to hospital for unstable angina, unspecified acute myocardial infarction (MI), or ST-elevation or non-ST-elevation MI. The age of the patients was not reported. The average international normalised ratio (INR) in the warfarin arm ranged from less than 1.5 to 3.

Outcomes assessed in the review
The outcomes of interest were the combined rate of MAE (defined as all-cause death, nonfatal MI or nonfatal thromboembolic stroke) and the rate of major bleeding (MB) (defined as intracranial haemorrhages, bleeds requiring transfusion, or a drop in haemoglobin of at least 2 g/dL).

How were decisions on the relevance of primary studies made?
Three reviewers searched for relevant studies.

Assessment of study quality
The authors stated that the validity of the trials was assessed according to the grading outlined in the Cochrane Handbook, with A, B and C indicating a low, moderate or high probability of bias, respectively.

The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
**Data extraction**
Three independent reviewers extracted the data and any disagreements were resolved by consensus. Odds ratios (ORs) for single and composite MAEs and MB were calculated.

**Methods of synthesis**

**How were the studies combined?**
Both fixed-effect and random-effects models were used to calculate the summary ORs with 95% confidence intervals (CIs) for binary outcomes. The number-needed-to-treat (NNT) to prevent one MAE and the number-needed-to-harm (NNH) by causing one MB were also calculated. Publication bias was assessed using a funnel plot and Egger's test.

**How were differences between studies investigated?**
Heterogeneity amongst the studies was assessed using the Cochran Q statistic and the I-squared measure. A sensitivity analysis was used to assess the contribution of each study to the pooled estimates by excluding trials one at a time, starting from those with the lowest quality score. The statistical analyses were performed for all studies and also for studies with target or measured INRs of between 2 and 3.

**Results of the review**

Fourteen RCTs (n=25,307) were included.

The authors stated that, because there was no significant difference between the results of the random-effects and fixed-effect models, they only reported the results of the fixed-effect model.

All studies included in the analysis, irrespective of the INR.

The combination of A+W had no significant effect on the risk of an MAE (OR 0.96, 95% CI: 0.90, 1.03, P=0.30), but increased the risk of MB (OR 1.77, 95% CI: 1.47, 2.13, P<0.0001; NNH 100). It was also associated with an increased risk of extracranial bleeding (OR 2.2, 95% CI: 1.64, 2.96, P<0.0001) but had no significant effect on intracranial bleeding (OR 1.37, 95% CI: 0.79, 2.37, P=0.27).

Combination therapy had no significant effect on all-cause death or nonfatal MI, although it significantly reduced the risk of nonfatal thromboembolic stroke (OR 0.81, 95% CI: 0.67, 0.97, P=0.02; NNT 100).

Analyses restricted to studies with INRs of between 2 and 3.

The combination of A+W significantly reduced the risk of an MAE (OR 0.73, 95% CI: 0.63, 0.84, P<0.0001; NNT 33), but increased the risk of MB (OR 2.32, 95% CI: 1.63, 3.29, P<0.0001; NNH 100). It was also associated with an increased risk of extracranial bleeding (OR 2.37, 95% CI: 1.37, 4.10, P=0.002) but had no statistically significant effect on intracranial bleeding (OR 3.02, 95% CI: 0.61, 15.02, P=0.18).

Combination therapy had no significant effect on all-cause death, but it was associated with a 57% reduction in the risk of nonfatal thromboembolic stroke (OR 0.43, 95% CI: 0.27, 0.70, P=0.0007; NNT 100) and a 30% reduction in the risk of nonfatal MI (OR 0.70, 95% CI: 0.52, 0.95, P=0.0003; NNT 50).

Thirteen of the 14 studies were of a good quality and had greater than 97% follow-up. No study was excluded because of a follow-up of less than 80%. In the sensitivity analysis, the exclusion of any trial did not significantly alter the overall results. Significant heterogeneity was found when data were pooled for MAEs irrespective of INR (P=0.001), but when the analysis was restricted to the studies with an INR of 2-3 there was no significant heterogeneity.

The funnel plot suggested the possibility of publication bias. However, Egger's test showed no publication bias for studies with an INR of 2-3 (P=0.141 for all studies and P=0.646 for studies with an INR of 2-3).

**Authors' conclusions**

In patients recovering from ACS at INR of 2-3, a combination of A+W is superior to aspirin alone in preventing MAEs,
although it doubles the risk of MB. Whether this combined regimen is also superior to a double antiplatelet strategy or to newer evolving treatments warrants further investigation.

**CRD commentary**
The review question and inclusion criteria were clear and the search was reasonable, but the authors did not adequately describe how they selected the studies. Study quality was assessed, but only some components of the assessment were reported and the authors did not state how they performed the quality assessment; the potential for reviewer error or bias could not, therefore, be assessed. There was significant heterogeneity in the overall analysis of all studies, although the authors discussed the possible reasons for this heterogeneity and addressed the issue by restricting the analyses to studies with INRs of between 2 and 3. Overall, the authors’ conclusion appears to be supported by the evidence presented.

**Implications of the review for practice and research**
Practice: The authors stated that there is compelling evidence on the support of aspirin combined with intermediate-intensity oral anticoagulations for the prevention of MAEs in patients with ACS, particularly those at high risk of recurrent cardiovascular and cerebrovascular events who are willing to face the logistic hurdles and the predictable and uncommon risk of bleeding inherent to this treatment strategy.

Research: The authors stated that a head-to-head comparison of aspirin combined with properly-dosed oral anticoagulants with a double antiplatelet regimen, or a triple-armed study comparing these two strategies with aspirin alone during the first 9 to 12 months after ACS, is warranted.

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**Other publications of related interest**

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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.