Bleeding risk in randomized controlled trials comparing warfarin and aspirin: a systematic review and meta-analysis
Warkentin AE, Donadini MP, Spencer FA, Lim W, Crowther M

CRD summary
The authors concluded that no statistically significant difference in major bleeding risk was shown between warfarin (target international normalised ratio 2.0 to 3.5) and aspirin (50mg to 650 mg daily). It appears that the authors’ conclusions and recommendations for further practice and research are warranted and reliable.

Authors’ objectives
To assess bleeding risk comparing warfarin and aspirin (acetylsalicylic acid) at dose ranges recommended in evidence-based guidelines.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to September 2011 for studies published in English; search terms were reported. Reference lists of retrieved articles were handsearched. Experts were contacted to locate further studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared bleeding among adult patients who were prescribed warfarin at the international normalised ratio (INR) target of 2.0 to 3.5 versus aspirin at a daily dose of 50mg to 650mg or warfarin versus aspirin (using the same dose ranges). Patients could have any indication for long-term antithrombotic therapy. Follow-up had to be at least three months. Studies were excluded where other oral anticoagulants were used additionally to warfarin.

Patient conditions in the included studies were atrial fibrillation, chronic heart failure, acute coronary syndrome and heart valve replacement. Mean patient age ranged from 62 to 83 years. From 54.6% to 89% of patients were men. Warfarin INR ranges were between 2.0 and 3.5. Aspirin dose ranged from 75mg to 325mg daily. Only one study included a combination therapy arm. Major bleeding was defined in six studies and minor bleeding in five studies; definitions varied and were reported in the paper.

Two reviewers selected the studies for inclusion; disagreements were resolved by consensus and consultation with a third reviewer where necessary.

Assessment of study quality
Risk of bias was assessed according to Cochrane criteria for levels of risk for random sequence generation, allocation concealment, blinding of patients/personnel, blinding of outcome assessors, incomplete outcome data and selective reporting. Levels of risk were classified as low, high or unclear.

Two reviewers independently performed the quality assessment.

Data extraction
Data for major and minor bleeding events were extracted to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Authors were contacted for further information, where necessary.

Two reviewers independently extracted the data; discrepancies were resolved by consensus.

Methods of synthesis
Odds ratios and 95% CIs for individual studies were pooled using the inverse variance method and a random-effects model. Statistical heterogeneity was assessed using the $I^2$ statistic ($I^2\geq60\%$ indicated significant heterogeneity). Funnel plots were constructed to investigate presence of small-study effects. Prespecified subgroup analyses were performed according to age ($\pm70$ years) and clinical indication for antithrombotic therapy. A secondary analysis was performed to
compare RCTs that investigated warfarin alone versus warfarin plus aspirin.

**Results of the review**
Eight RCTs were included in the review and meta-analysis (2,948 patients). Mean follow-up ranged from three to 32 months (where reported). Patients lost to follow-up ranged from zero to 4.8% (where reported). Withdrawal/drop-out rates ranged from 2% to 28.7%. One trial was reported as having low risk of bias for all of the quality domains assessed. Five trials scored low risk of bias for four of the six domains. High risk of bias was assigned to one domain (blinding of patients/personnel) in six of the eight trials assessed.

A statistically non-significant increase in major bleeding was observed for patients who received warfarin versus those who received aspirin (OR 1.27, 95% CI 0.83 to 1.94; eight trials; $I^2=8\%$). Risk for minor bleeding was statistically significantly increased among patients who received warfarin compared with those who received aspirin (OR 1.50, 95% CI 1.13 to 2.00; five trials; $I^2=12\%$).

Findings from prespecified subgroup and secondary analyses were all statistically non-significant as were those from post hoc analyses of intracranial and non-intracranial major bleeding, and aspirin dosages. No evidence for small-study effects was found.

**Authors’ conclusions**
The evidence did not show a significant difference in major bleeding risk between warfarin (target INR 2.0 to 3.5) and aspirin (50mg to 650mg daily).

**CRD commentary**
The review question was clear and inclusion criteria were sufficient for replication. Relevant data sources were searched. Restrictions in the search meant that language and publication biases could not be ruled out. The authors suggested that publication bias or other reasons for small-study effects were absent but the small number of studies included in the funnel plots meant that this suggestion may not be reliable. Efforts were made to minimise reviewer error and bias throughout the review process. A suitable quality assessment tool was utilised and most trials appeared to demonstrate acceptable quality. Study details were presented and methods of synthesis seemed appropriate. Very little statistical heterogeneity was indicated. Definitions of bleeding varied between the individual trials.

It appears that the authors’ conclusion and recommendations for further practice and research are warranted and reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should consider this review's findings along with the relative efficacy of warfarin and aspirin treatment when considering the risks and benefits related to them.

**Research:** The authors stated that use of a standardised definition of major bleeding was required and that further study for comparisons of bleeding risk between warfarin and aspirin was warranted.

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