Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation

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CRD summary
The authors concluded that new oral anticoagulants were more efficacious than warfarin in prevention of stroke and systemic embolism in patients with atrial fibrillation, and have a more favourable safety profile. Possibility of missed unpublished studies, unclear levels of bias during review process and scarcity of trial quality information mean that the reliability of these conclusions is difficult to assess.

Authors' objectives
To compare the efficacy and safety of new oral anticoagulants versus warfarin in patients with atrial fibrillation.

Searching
Five databases (including The Cochrane Library and MEDLINE) were searched from inception to July 2011, with no language restrictions. Search terms were reported. Clinical trial databases, relevant reviews and reference lists of retrieved reports were handsearched to locate further studies.

Study selection
Randomised controlled trials (RCTs) that compared warfarin to non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation were eligible for inclusion. Trials had to have been published in peer-reviewed journals. Trials could be open-label or blinded but they had to have follow-up durations of at least one year. The primary outcomes were a composite endpoint of stroke and systemic embolism, and major bleeding. Secondary outcomes that related to efficacy and safety were reported in the paper.

Mean patient age ranged from 70 to 73 years; proportions of females patients ranged from 35 to 39.7%. New oral anticoagulants investigated included apixaban, dabigatran and rivaroxaban. Varying proportions of patients had previously experienced stroke, transient ischaemic attack, heart failure, diabetes mellitus and/or hypertension at baseline.

The authors did not report how many reviewers selected the studies for inclusion.

Assessment of study quality
The Cochrane Collaboration's tool was used to assess risk of bias as low, high or unclear for the following quality domains: Sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other bias.

The authors did not state how many reviewers performed the quality assessment of included trials.

Data extraction
Data were extracted by two independent reviewers to calculate risk ratios with 95% confidence intervals. Any disagreements between reviewers were resolved by consensus or a third party.

Methods of synthesis
Risk ratios and 95% confidence intervals were pooled per outcome, using DerSimonian and Laird random-effects models. Heterogeneity was assessed using Q and I² statistics.

Results of the review
Three RCTs were included in the review (44,563 patients). Mean length of follow-up ranged from 657 to 730 days. One trial was assessed as having low risk of bias for blinding, and limited use of intention-to-treat analyses led to the other two trials being rated as having an unclear risk of bias in the quality domain of other sources of bias. No other quality results were reported.
A statistically significant 22% reduction in risk of stroke and systemic embolism was observed for new oral anticoagulant groups, compared with warfarin groups (RR 0.78, 95% CI 0.67 to 0.92; three trials; I²=55.9%). Similar results were shown in relation to risks for ischaemic and unidentified stroke (RR 0.87, 95% CI 0.77 to 0.99; three trials; I²=0%), haemorrhagic stroke (RR 0.45, 95% CI 0.31 to 0.68; three trials; I²=52.2%), vascular mortality (RR 0.87, 95% CI 0.77 to 0.98; two trials; I²=0%), and all-cause mortality (RR 0.88, 95% CI 0.82 to 0.95; three trials; I²=0%). Differences observed in risk for ischaemic and unidentified stroke and vascular mortality were of borderline statistical significance. No statistically significant difference was found between the groups in risk for myocardial infarction.

A statistically significant 51% reduction in risk of intracranial bleeding was observed for new oral anticoagulant groups, in comparison with warfarin groups (RR 0.49, 95% CI 0.36 to 0.66; three trials; I²=54.9%). No statistically significant differences were found between the groups in risks for major bleeding and gastrointestinal bleeding events.

Authors' conclusions
The new oral anticoagulants were more efficacious than warfarin in prevention of stroke and systemic embolism in patients with atrial fibrillation, and appeared to have a more favourable safety profile.

CRD commentary
The review question was clear and supported by replicable inclusion criteria. Relevant databases were searched with no language restrictions, which reduced the risk of language bias. The limitation to studies published in peer-reviewed journals increased the likelihood for relevant, unpublished studies being missed. Effort was made to reduce error and bias during the data extraction stage but this was not reported for the stages of study selection and quality assessment.

Suitable quality assessment criteria were employed, but very little quality information was reported which made it difficult to ascertain potential levels of bias within the included trials. Study details showed some clinical diversity between the trials, mainly relating to the type and dosage of new agents investigated and baseline rates of previous health conditions. Methods of synthesis seemed appropriate.

Possibility of missed unpublished studies, unclear levels of bias during the review process, and scarcity of trial quality information mean that the reliability of the authors' conclusion is difficult to assess.

Implications of the review for practice and research
Practice: The authors stated that the safety and efficacy profiles of the new oral anticoagulants, relative to that of warfarin, may be augmented when used outside the controlled clinical trial setting.

Research: The authors did not state any implications for further research.

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