Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin

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CRD summary
This review concluded that novel oral anticoagulants seemed to be superior to warfarin, for reducing the composite of stroke or systemic embolism, lowering all-cause mortality, and halving the number of haemorrhagic strokes, in patients with atrial fibrillation. Despite some limitations to the trials and the review, the conclusions are likely to be reliable.

Authors’ objectives
To compare novel oral anticoagulants and warfarin, to determine which is superior for preventing strokes or systemic emboli.

Searching
MEDLINE, EMBASE, and The Cochrane Library were searched, without language restrictions, for articles from August 2000 to October 2012; search terms were reported. The reference lists of published meta-analyses were searched.

Study selection
Phase III randomised controlled trials (RCTs) that compared the efficacy and safety of a novel oral anticoagulant, with those of warfarin, were eligible for inclusion if they had at least 3,000 participants with atrial fibrillation. The outcomes of interest were stroke, systemic embolism, all-cause mortality, ischaemic stroke, haemorrhagic stroke, and major bleeding, alone or as composite outcomes; these had to be reported on an intention-to-treat basis.

The included RCTs compared ximelagatran, dabigatran, rivaroxaban, or apixaban, with warfarin. Across the trial arms, the mean age of participants ranged from 70 to 73 years; 60% to 70% of participants were male; and 30% to 87% of participants had at least three risk factors for stroke. Where reported, 72% to 91% of patients had hypertension, 23% to 40% had diabetes, and 32% to 63% had left ventricular dysfunction or heart failure.

The authors did not state how many reviewers selected trials for the review.

Assessment of study quality
Two independent reviewers assessed trial quality using the Jadad scale; disagreements were resolved by discussion.

Data extraction
Two independent reviewers extracted the data to calculate relative risks, and 95% confidence intervals; disagreements were resolved by discussion.

Methods of synthesis
The pooled relative risks and 95% confidence intervals were calculated using the Mantel-Haenszel method; a fixed-effect model was used if the trials were similar, and a random-effects model was used if they varied. The numbers needed to treat were calculated. Heterogeneity was assessed using X² (where p>0.10 indicated homogenous data) and I². Where two doses of a drug were evaluated in one trial, only the most effective dose was analysed.

A sensitivity analysis was conducted excluding the trials that evaluated ximelagatran. Heterogeneity-adjusted trial sequential analysis was conducted by calculating the optimal information size monitoring boundaries, and the cumulative Z statistics after the addition of each trial. The heterogeneity-adjusted and unadjusted information sizes were used for the trial sequential monitoring boundaries. Crossing of the monitoring boundaries was assessed with the fixed-effect and the random-effects model. Solid evidence of an intervention effect was indicated by the crossing of the monitoring boundaries by the cumulative Z-curve. Publication bias was assessed using the Egger test.

Results of the review
Five RCTs met the inclusion criteria, with 51,895 patients (range 3,410 to 18,201); all trials were designed to show non-inferiority. Three were double blind, and the other two were open label; Jadad scores were not reported. Follow-up ranged from a mean of 16 months to a median of 24 months.

Compared with warfarin, the novel oral anticoagulants had a significantly lower rate of stroke or systemic embolism (RR 0.82, 95% CI 0.69 to 0.98; NNT 200; I²=62%), death from any cause (RR 0.91, 95% CI 0.85 to 0.96; NNT 145; I²=0), haemorrhagic stroke (RR 0.51, 95% CI 0.41 to 0.64), and minor bleeding (RR 0.88, 95% CI 0.80 to 0.97), but not ischaemic stroke, systemic embolism, and major non-cerebral bleeding. The results for each drug class, the sensitivity analysis, and the sequential analyses were presented.

**Authors’ conclusions**

Novel oral anticoagulants seemed to be superior to warfarin, for reducing the composite of stroke or systemic embolism, lowering all-cause mortality, and halving the number of haemorrhagic strokes, in patients with atrial fibrillation.

**CRD commentary**

The review addressed a clear question supported by reproducible inclusion criteria. Relevant sources were searched, without language restrictions, but there was no specific search for unpublished trials. Data extraction and quality assessment were conducted by two people, but it was unclear if similar methods to reduce error and bias were used for study selection. Appropriate criteria were used to assess trial quality, but the results were not reported; two trials were open label and therefore at a high risk of performance and detection bias. Most of the outcomes were unlikely to be adversely affected by such bias, as they were not subjectively assessed. The trials were clinically varied, making the reliability and generalisability of the overall pooled results uncertain.

Despite some limitations to the trials and the review, the conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state implications for practice.

**Research**: The authors stated that an adequately powered head-to-head trial, comparing a direct thrombin inhibitor with a factor Xa inhibitor, was needed to better evaluate their relative risks and benefits.

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