Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials


CRD summary
This review concluded that new oral anticoagulants offered significant reductions in stroke, intracranial haemorrhage, and mortality, compared with warfarin, with a similar risk of major bleeding and an increased risk of gastrointestinal bleeding. Despite shortcomings in the reporting, these conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of new oral anticoagulants, compared with warfarin, for stroke prevention in patients with atrial fibrillation.

Searching
MEDLINE was searched for articles from January 2009 to November 2013. ClinicalTrials.gov was searched and the keywords were reported.

Study selection
Randomised controlled trials (RCTs) of patients with atrial fibrillation, who were receiving warfarin or new oral anticoagulants, were eligible for inclusion. Trials had to report safety and efficacy outcomes.

The included trials compared warfarin with dabigatran, rivaroxaban or edoxaban, in two or three parallel groups. The mean patient age varied across the trials from 70 to 73 years, with between 31% and 43% of patients being over 75 years old. More than half the participants were male. Detailed patient characteristics were reported; most were similar between groups, with the exception of the underlying risk of stroke (CHADS2 score), which varied significantly between trials. The outcomes included stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding.

It was not clear how many researchers selected the trials.

Assessment of study quality
The authors stated that quality was assessed informally to minimise bias, but no further details were given.

Data extraction
Intention-to-treat data were extracted for the efficacy outcomes, and safety population data were extracted for the bleeding outcomes. Relative risks and 95% confidence intervals were calculated for each outcome in each trial, and they were checked against the publication for accuracy. Where necessary, the number of outcome events, based on event rates, sample size, and duration of follow-up, was calculated.

It was not clear how many researchers extracted and checked the data.

Methods of synthesis
The trials were analysed in two groups for higher and lower dosages of the new oral anticoagulants. Random-effects meta-analyses were used, and heterogeneity was assessed using Cochran's Q and I².

Sensitivity analyses looked at the effects of including only factor Xa inhibitors, and where all drug doses were combined. Relevant clinical sub-groups were analysed (gender, history of previous stroke or transient ischaemic attack, history of diabetes, renal function, CHADS2 risk score, and vitamin K antagonist status at the start). The impact of centre-based time in the therapeutic range was explored.

Results of the review
Four RCTs were included; median follow-up ranged from 1.8 to 2.8 years. A total of 42,411 patients received the new
oral anticoagulants and 29,272 received warfarin.

The new oral anticoagulants significantly reduced stroke or systemic embolic events by 19%, compared with warfarin (RR 0.81, 95% CI 0.73 to 0.91; I²=47%), mainly due to a reduction in haemorrhagic stroke (RR 0.49, 95% CI 0.38 to 0.64; I²=34%).

They significantly reduced all-cause mortality (RR 0.90, 95% CI 0.85 to 0.95; I²=0) and intracranial haemorrhage (RR 0.48, 95% CI 0.39 to 0.59; I²=32%), but increased gastrointestinal bleeding (RR 1.25, 95% CI 1.01 to 1.55; I²=74%).

There were no major differences in the analyses of stroke or systemic embolic events, for the important subgroups.

The overall reduction in stroke or systemic embolic events with low-dose regimens was similar to that with warfarin (RR 1.03, 95% CI 0.84 to 1.27; I²=70%), with a more favourable bleeding profile (RR 0.65, 95% CI 0.43 to 1.00; I²=91%), but significantly more ischaemic strokes (RR 1.28, 95% CI 1.02 to 1.60; I²=66%).

**Authors’ conclusions**
The new oral anticoagulants offered significant reductions in stroke, intracranial haemorrhage, and mortality, compared with warfarin, with a similar risk of major bleeding, but an increased risk of gastrointestinal bleeding.

**CRD commentary**
This review addressed a clear question, with detailed inclusion criteria. The searches were limited to one database and a trial register; eligible trials may have been omitted. Details of the review processes were poorly reported, and methodological quality was neither formally assessed nor described.

The analyses appear to have been appropriate and were based on the results of four major trials. While some of the overall estimates of effectiveness and safety varied statistically, the direction of the effects was consistent, and the authors’ investigations did not identify any clinically important subgroup effects.

On the basis of the presented evidence, the authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**
The authors made no recommendations for practice and research.

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