Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review concluded that non-vitamin-K-antagonist oral anticoagulants seem to be associated with significant reductions in the rates of stroke or systemic embolism, haemorrhagic stroke, and major bleeding when compared with warfarin in patients with previous stroke or transient ischaemic attack. Given a number of limitations with the review, the conclusions should be treated with caution.

Authors' objectives
To compare the efficacy and safety of non-vitamin-K-antagonist (non-VKA) oral anticoagulants to warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack.

Searching
PubMed was searched to May 2012; search terms were reported. Reference lists of related letters, reviews and editorials were also searched for additional studies.

Study selection
Phase III randomised controlled trials (RCTs) that compared a recently developed non-VKA oral anticoagulant with a VKA such as warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack were eligible for inclusion.

The non-VKAs evaluated in the included studies were rivaroxaban, dabigatran, and apixaban; all used warfarin as the comparator. Those who received warfarin spent between 57% to 65% of time in the therapeutic international normalised ratio range. Where reported, most of the patients were hypertensive and at a high risk of stroke (CHADS2 score 3 or above); 31% to 40% of patients were receiving aspirin; 39% to 45% had not received a VKA before entry into the study; and over 60% were male.

The authors did not report the number of reviewers who selected studies for the review.

Assessment of study quality
A systematic assessment of study quality did not seem to have been undertaken.

Data extraction
Two reviewers independently extracted data on the incidence of stroke/systemic embolism, various stroke outcomes, all-cause and cardiovascular death, myocardial infarction and bleeding outcomes in order to calculate odds ratios and 95% confidence intervals; absolute risk reduction, relative risk reduction and the number-needed-to-treat were also calculated. Study authors were contacted for missing data. Disagreements between reviewers were resolved by discussion or referral to the review team.

Methods of synthesis
Pooled Peto odds ratios and 95% confidence intervals were calculated; this is a fixed-effect model. Heterogeneity was assessed using $I^2$.

Results of the review
Three RCTs were included in the review (14,527 patients; range 3,436 to 7,468). The duration of follow-up ranged from 1.8 to two years. Compared to warfarin, non-VKAs resulted in a statistically significant reduction in the incidence of stroke/systemic embolism (OR 0.85, 95% CI 0.74 to 0.99; $I^2$ 0%), haemorrhagic stroke (OR 0.44, 95% CI 0.32 to 0.62; $I^2$ 58%), major bleeding (OR 0.86, 95% CI 0.75 to 0.99; $I^2$ 52%), and intracranial bleeding (OR 0.47, 95% CI 0.36 to 0.62; 60%). No significant differences were observed between the non-VKAs and warfarin for the incidence of
stroke, ischaemic/unknown stroke, disabling/fatal stroke, cardiovascular death, all-cause death, myocardial infarction, or major gastrointestinal bleeding. Absolute risk reductions, relative risk reductions and the numbers-needed-to-treat were also reported.

Authors’ conclusions
Non-VKAs seemed to be associated with significant reductions in the rates of stroke or systemic embolism, haemorrhagic stroke and major bleeding when compared with warfarin in patients with previous stroke or transient ischaemic attack.

CRD commentary
The review addressed a clear research question with reproducible inclusion criteria. The authors conducted a limited search. Data extraction was conducted in duplicate; it was unclear whether similar measures were used to reduce error and bias during the selection of studies. Study quality was not assessed, so it was unclear how reliable the results from the included studies were. Peto odds ratios were calculated for all outcomes, but only haemorrhagic stroke had an incidence of less than 1%, which made the use of this meta-analytical method for the other outcomes questionable. The entire control group from the RE-LY trial was used as the comparator for two different doses of dabigatran, therefore, these patients were double-counted within the meta-analyses. Each of the studies evaluated a different non-VKA, so pooling these studies presumed a class effect; if these drugs varied in their effectiveness and/or safety profiles, the reliability and generalisability of the pooled results may be compromised.

Given the limitations outlined, the conclusions should be treated with caution.

Implications of the review for practice and research
The authors did not state any implications for practice or research, but they did highlight that there were ongoing trials of other non-VKAs.

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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.