Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review

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CRD summary
The authors concluded that new oral anticoagulants were effective for patients receiving long-term anticoagulation. The benefits compared with warfarin were small and varied depending on the control achieved with warfarin. This was generally a well-conducted review and the conclusions are likely to be reliable.

Authors' objectives
To compare the benefits and harms of new oral anticoagulants versus warfarin for patients with atrial fibrillation and venous thromboembolism.

Searching
MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews were searched for relevant studies published in English from January 2001 to July 2012. The full search strategy was reported in supplementary material. Reference lists of key primary and review articles were checked. The Food and Drug Administration's Approved Drug Products website was searched for any safety issues and ClinicalTrials.gov was searched for completed unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared new oral anticoagulants with warfarin were eligible for inclusion. Participants had to be aged 18 years or older, with a history of chronic non-valvular atrial fibrillation, deep vein thromboembolism or mechanical valve replacement. Trials had to report at least one of the following outcomes: thromboembolism events that were documented radiologically and produced clinical symptoms, mortality, health-related quality of life, or the patient's treatment experience. Trials had to last at least six months for acute and 12 months for chronic treatment. Observational studies were eligible if they reported adverse events and participants had taken the drugs for at least one week. Due to drug safety concerns, two ximelagatran trials (no longer available) were excluded from the meta-analyses.

New oral anticoagulant drugs included direct thrombin inhibitor (dabigatran, 150mg twice daily) and factor Xa inhibitor (apixaban, 5mg twice daily, or rivaroxaban, 20mg once daily). All trials were conducted in multiple countries. The mean age of participants ranged from 50 to over 70 years, and 59% were men. The mean baseline Congestive heart failure, Hypertension, Age, Diabetes, and Stroke (CHADS²) score ranged from 2.1 to 3.5 in the subgroup of patients with atrial fibrillation. The percentage of time within the target international normalised ratio (INR) ranged from 55 to 66 (median 64) in the warfarin groups. The duration of the included trials ranged from 12 months to two years.

Two reviewers were involved in study selection. Any discrepancies were resolved by discussion or by a third reviewer.

Assessment of study quality
The quality of trials was assessed by one reviewer and checked by a second, for randomisation, allocation concealment, baseline comparability, blinding, attrition, validity of outcome measures, and conflicts of interest. The quality of evidence was summarised according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. Disagreements were resolved by discussion or by a third reviewer. Observational studies were all case studies and were not assessed.

Data extraction
Data to calculate relative risks and their 95% confidence intervals were extracted by one reviewer and checked by a second. Any disagreements were resolved by discussion or by a third reviewer.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a random-effects model. The primary analysis combined data for the direct thrombin inhibitor and factor Xa inhibitors presuming an effect for the class of drugs;
secondary analyses analysed the drugs separately. Heterogeneity was assessed in graphs and using $I^2$. An $I^2$ of 25% was considered to be low, 50% was moderate, and 75% was high. If there were statistically significant differences, risk differences were calculated. Subgroup analyses were conducted by drug class.

**Results of the review**

Six RCTs, with 61,424 participants (range 2,564 to 18,201) and 10 observational studies (three subgroups from the included trials and seven case studies) were included in the review.

**Chronic atrial fibrillation**: The meta-analyses showed that all-cause mortality (RR 0.88, 95% CI 0.82 to 0.96; $I^2=0$; three RCTs; high strength of evidence) haemorrhagic stroke (RR 0.48, 95% CI 0.36 to 0.62; $I^2=52$%; three RCTs; moderate strength of evidence), and combined stroke (RR 0.77, 95% CI 0.67 to 0.88; $I^2=29$%; three trials) decreased with new oral anticoagulants, compared with adjusted-dose warfarin. No statistically significant difference was found for ischaemic stroke and peripheral embolism.

**Venous thromboembolism**: No statistically significant differences were found between new oral anticoagulants and adjusted-dose warfarin for any effectiveness outcome.

**Adverse effects**: The rate of fatal bleeding was lower with new oral anticoagulants (RR 0.60, 95% CI 0.46 to 0.77; $I^2=0$; six studies; moderate strength of evidence), compared with adjusted-dose warfarin, in all patients. There were no significant differences for any other adverse events in each population. The rate of patients discontinuing drug use because of adverse effects was higher with new oral anticoagulants (RR 1.23, 95% CI 1.05 to 1.44; $I^2=93$%; six studies; low strength of evidence).

Results from the subgroup analyses and observational studies were reported in the paper or associated report (see Other Publications of Related Interest).

**Authors’ conclusions**

New oral anticoagulants were effective for patients receiving long-term anticoagulation. The benefits compared with warfarin were small and varied depending on the control achieved with warfarin.

**CRD commentary**

This review addressed a clear question supported by reproducible inclusion criteria. Relevant databases were searched, for English-language studies, so language bias cannot be ruled out. Efforts were made to find published and unpublished studies, minimising the risk of publication bias. Attempts were made to minimise reviewer errors and bias in the review process. Appropriate criteria were used to assess the quality of evidence, but the full results were not reported. Appropriate methods were used to pool the results. Statistical heterogeneity was assessed and explored in subgroup analyses. There were some minor data differences between the published paper and the full report.

This was generally a well-conducted review and the conclusions are likely to be reliable.

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

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

**Research**: The authors stated that there were some important unanswered questions, such as which patients were most likely to benefit; which, if any, of the new drugs was most effective; and whether dose adjustment was needed for those at a high risk of adverse effects.

**Funding**

Supported by the Veterans Affairs Office of Research and Development, USA.

**Bibliographic details**


**PubMedID**
DOI
10.7326/0003-4819-157-10-201211200-00532

Original Paper URL

Additional Data URL

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anticoagulants /adverse effects /therapeutic use; Antithrombins /adverse effects /therapeutic use; Atrial Fibrillation /drug therapy /prevention & control; Comparative Effectiveness Research; Factor Xa Inhibitors; Hemorrhage /chemically induced; Humans; Randomized Controlled Trials as Topic; Risk Factors; Secondary Prevention; Treatment Outcome; Venous Thromboembolism /drug therapy /prevention & control; Warfarin /adverse effects /therapeutic use

AccessionNumber
12012045713

Date bibliographic record published
12/10/2012

Date abstract record published
02/11/2012

Record Status
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.