Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis
Andersen L V, Vestergaard P, Deichgraeben P, Lindholt J S, Mortensen L S, Frost L

CRD summary
This review concluded that warfarin reduced the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, but increased the risk of major bleeding. There were several limitations with the included trials and the reporting in the review, such as no validity assessment and potential bias, so the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the efficacy of warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation.

Searching
MEDLINE, EMBASE, the Cochrane Library, and SveMed+ (Swedish medical bibliographic database) were searched from 1966 to November 2007 for publications in any language. Search terms were reported. References of identified papers and recent reviews were manually searched.

Study selection
Randomised controlled trials (RCTs) comparing the long-term efficacy (three months or more) and safety of warfarin (with international normalised ratio (INR) of up to 2) versus placebo, antiplatelet agents, low-dose warfarin (1.25 mg/day or target INR of up to 2), or a combination of low-dose warfarin and aspirin, were eligible for inclusion. Eligible trials were of adults aged 18 years and over with atrial fibrillation or flutter. The outcomes of interest were systemic embolism and major bleeding (as defined in the included trials). Studies of patients with postoperative atrial fibrillation or valvular disease were excluded.

Where reported, included trials were of patients with a mean age ranging between 63.3 and 81.5 years. Most patients had at least one risk factor for cerebral embolism (e.g. previous myocardial infarction, hypertension, diabetes mellitus, heart failure and/or stroke). The INR ranged from 2.0 to 4.5 in the warfarin group, and (where reported) between 1.1 and 2.1 in the low-dose warfarin groups. Comparator treatment doses varied among trials. Some of the trials were stopped early due to publication of results, or evidence of superiority of warfarin treatment.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity, but did report on methods of randomisation for individual trials.

Data extraction
Two reviewers independently extracted outcome data on an intention-to-treat basis, regardless of the INR range at the time of the event, to calculate odds ratios (ORs) with their 95% confidence intervals (CIs). Where the number of systemic embolic outcomes was not reported, investigators were contacted for further details. It was unclear how discrepancies were resolved.

Methods of synthesis
A fixed-effect model was used to combine odds ratios and their 95% confidence intervals, weighted by sample size. Statistical heterogeneity was assessed and p values were presented.

Publication bias was assessed using the Egger test and funnel plots.
Results of the review

Fifteen RCTs (n=15,111) were included in the review. Sample sizes ranged from 75 to 6,706 participants. Trials were randomised by computer, centrally, by telephone, or by a pre-determined random order (e.g. stratified by study centre). Mean follow-up durations, where reported, ranged from 1.0 to 3.1 years.

Warfarin versus placebo (four RCTs): There was no significant difference in the number of thromboembolic events between patients receiving warfarin and those receiving placebo. Trials assessing major bleeding showed a statistically significantly greater frequency in the warfarin group compared to placebo, OR 3.01 (95% CI: 1.31 to 6.92).

Warfarin versus antiplatelet agents (nine RCTs): There was a significant difference in the prevention of systemic embolism, with fewer systemic embolisms occurring in patients receiving warfarin compared to those receiving antiplatelet, OR 0.50 (95% CI: 0.33 to 0.75). There was no significant difference in risk of major bleeding between the two treatment groups.

Warfarin versus low-dose warfarin with or without aspirin (five RCTs): There were no statistically significant differences in the number of thromboembolic events in trials comparing warfarin with low-dose warfarin (four RCTs), or low-dose warfarin with aspirin (two RCTs). There was a significantly greater risk of major bleeding in patients receiving warfarin compared to low-dose warfarin (OR 2.88, 95% CI: 1.09 to 7.60; four RCTs), but no difference between warfarin and low-dose warfarin with aspirin (two RCTs).

There was no significant statistical heterogeneity among trials for any analyses. There was no evidence of publication bias among trials comparing warfarin and antiplatelet agents, but analysis for other comparisons were unclear due to the small number of trials.

Authors’ conclusions

Warfarin reduced the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Warfarin increased the risk of major bleeding compared with placebo and low-dose warfarin, but not compared with antiplatelet agents.

CRD commentary

The review question and supporting inclusion criteria were clear. An appropriate literature search was undertaken without language restrictions, reducing the potential for language bias. The review was restricted to published studies, which meant that potentially relevant papers may have been missed. Publication bias was assessed, but could not be determined for some comparisons due to the small number of trials, thus publication bias cannot be completely ruled out. The authors did not assess trials for validity. Also, they did not state how the process for study selection was undertaken, so reviewer error and bias cannot be ruled out. Appropriate methods were used to synthesise the data and investigate for statistical heterogeneity. There were several limitations with the included trials, such as the small number of trials or events in some treatment comparisons. Given the limitations with the included trials and the reporting in the review, the authors’ conclusions should be interpreted with caution and their implications for the generalisability of the results should be taken into account.

Implications of the review for practice and research

Practice: The authors stated that only patients eligible for treatment with warfarin were included in the studies and patients at high risk of bleeding were excluded. Thus decisions regarding warfarin treatment in patients with atrial fibrillation should be made on an individual basis.

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

Funding

Not stated

Bibliographic details

Andersen L V, Vestergaard P, Deichgraebler P, Lindholt J S, Mortensen L S, Frost L. Warfarin for the prevention of

**PubMedID**
18208828

**DOI**
10.1136/hrt.2007.135657

**Original Paper URL**
http://heart.bmj.com/cgi/content/abstract/94/12/1607

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Aged, 80 and over; Anticoagulants /therapeutic use; Aspirin /therapeutic use; Atrial Fibrillation /complications; Embolism /prevention & control; Female; Humans; Male; Middle Aged; Platelet Aggregation Inhibitors /therapeutic use; Warfarin /therapeutic use; Young Adult

**AccessionNumber**
12009101750

**Date bibliographic record published**
29/04/2009

**Date abstract record published**
21/10/2009

**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.