Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose: a meta-analysis
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CRD summary
This review looked at the effects of low- or mini-dose warfarin, compared with a regimen where the warfarin dose was adjusted to a target International Normalised Ratio (INR), in people with non-rheumatic atrial fibrillation. The risk of thromboembolic events was higher with low- or mini-dose warfarin. The review appears to have been well conducted and the conclusions are supported by the data presented.

Authors’ objectives
To assess the effects of reduced-dose (low-dose or mini-dose) anti-vitamin K therapy, compared with an adjusted dose, in people with atrial fibrillation.

Searching
MEDLINE was searched from 1983 to August 2002; the search terms were reported. The bibliographies of relevant identified papers were checked, and authors and experts were contacted for any unpublished studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that investigated the effects of low-dose warfarin were eligible for inclusion. In the included studies, the reported fixed low dose ranged from 0.5 to 3 mg/day. The comparator groups received adjusted-dose warfarin. The target International Normalised Ratio (INR) was 1.1 to 1.6 for the low dose and 2 to 3.5 for the adjusted dose. Concomitant aspirin was given in some studies.

Participants included in the review
Studies of people with non-rheumatic atrial fibrillation were eligible for inclusion. The participants in the included studies had non-valvular chronic, recurrent or intermittent atrial fibrillation. In one study the participants had additional risk factors (prior stroke, transient ischaemic attack or systemic embolism, systolic blood-pressure over 160 mmHg, or impaired left ventricular function). In other studies people with these higher risk factors were excluded, as were people with mitral stenosis or prosthetic cardiac valves, myocardial infarction, pacemaker, cardiomyopathy, chronic heart failure, mitral incompetence and, in one study, people over 78 years. The mean age of the participants ranged from 72 to 75 years.

Outcomes assessed in the review
Studies that reported thromboembolic events were eligible for inclusion. The outcomes reported include ischaemic stroke, systemic embolism, transient ischaemic attack, a combined outcome of thromboses (ischaemic stroke, systemic embolism or myocardial infarction), vascular death, major haemorrhage and haemorrhagic death. The definitions for these outcomes were those used in the included studies. In all studies stroke was diagnosed by a computerised tomographic scan.

How were decisions on the relevance of primary studies made?
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 studies were assessed for quality using the Chalmers score, where points were allocated up to a maximum of 91. Two reviewers evaluated the quality of the studies in a blinded fashion. Any disagreements were discussed.

Data extraction
Two reviewers independently extracted the data. The number of events in each study was given. The relative risk (RR) and 95% confidence intervals (CIs) were calculated for each outcome in each study.

Methods of synthesis
How were the studies combined?
The data were pooled using a random-effects model. Pooled RRs and 95% CIs were presented. For the main analysis, studies that added aspirin to low-dose warfarin were included in the low-dose warfarin groupings.

How were differences between studies investigated?
The chi-squared test was used to assess heterogeneity. The subgroup analyses excluded study arms where aspirin was used with low-dose warfarin.

Results of the review
Four RCTs (2,753 participants) were included.

In terms of study quality, scores ranged from 58 to 63 (out of a possible 91). The inter-rater agreement was high (intra-class correlations were between 0.92 and 0.98).

Adjusted-dose warfarin reduced the risk of all thrombotic events compared with low-dose warfarin; the pooled RR was 0.50 (95% CI: 0.25, 0.97, P=0.041). There was no statistically significant heterogeneity (P=0.56).

Adjusted-dose warfarin tended to decrease ischaemic stroke compared with low-dose warfarin. However, this result was not statistically significant (RR 0.46, 95% CI: 0.2, 1.07, P=0.071). No heterogeneity was found (P=0.41).

Although there was some trend for adjusted-dose warfarin to increase systemic embolism, this was not statistically significant (RR 1.18, 95% CI: 0.33, 4.31).

There was no difference between the two treatment groups in terms of vascular death; the RR was 1.1 (95% CI: 0.72, 1.67).

There was no difference in haemorrhagic death between the two treatments; the RR was 0.97 (95% CI: 0.27, 3.54). Although mini-dose warfarin tended to reduce the risk of major haemorrhage, this was not statistically significant (RR 1.23, 95% CI: 0.67, 2.27, P=0.51).

When only groups that did not include aspirin as part of the mini-dose regimen were compared with the adjusted dose, there was no difference in the risk of any thrombotic events; the RR was 0.63 (95% CI: 0.38, 1.04).

Authors' conclusions
Compared with low-dose or mini-dose warfarin, adjusted-dose warfarin was more effective at preventing ischaemic thromboembolic events in people with atrial fibrillation.

CRD commentary
The aims of this review were stated clearly. Although only one database was searched, the authors attempted to find unpublished studies. The methods of the review were appropriate and the quality of the studies was assessed. Details of the included participants and treatments were tabulated. The authors stated that two of the included studies were stopped early because of the significance of the results of a third study. Overall, the authors' conclusions are supported.
by the data presented.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies should assess the effects on older people (age 75+). A further trial should compare adjusted-dose warfarin with target INR 2 to 3 and target INR 1.6 to 2 for primary prevention, particularly in patients aged over 75 years.

Bibliographic details
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