Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation

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Authors' objectives
To examine the benefits and risks of long-term anticoagulation (warfarin) compared with antiplatelet treatment (aspirin, indobufen) in patients with non-rheumatic atrial fibrillation.

Searching
The CENTRAL Register on the Cochrane Library, EMBASE, MEDLINE, CINAHL and SIGLE were searched from 1966 to 1999 using the terms 'atherosclerosis', 'atrial fibrillation', 'myocardial infarction' or 'coronary disease' and 'anticoagulation' and a RCT filter (see Other Publications of Related Interest no.1). In addition, the authors checked references in relevant papers and approached key authors for information on missed, unpublished or ongoing trials. No information is provided concerning language restrictions.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Direct comparison of long-term oral anticoagulant (warfarin) with the antiplatelet drugs aspirin (75,150,300 or 325 mg) or indobufen (400 mg). Trials evaluating the combined use of anticoagulation with antiplatelet drugs were excluded.

Participants included in the review
Patients with non-rheumatic atrial fibrillation. Patients with atrial fibrillation due to thyrotoxicosis and mitral valve disease, and those with heart valve replacements were excluded. The mean ages of patients ranged from 64 to 80 years, and in at least one trial the age range was 38 to 91 years. Patients who had previously suffered strokes, transient ischaemic attacks (TIA) or myocardial infarction (MI) were included, as were patients with heart failure. There was no information given regarding the gender of patients.

Outcomes assessed in the review
Fatal and nonfatal cardiovascular events, i.e. stroke, MI, thromboembolism and major bleeds which required hospitalisation. Lack of information on (1) bleeding, precluded categorisation based on severity scores of bleeds, and (2) nonfatal coronary heart disease, meant it could not always be considered as an outcome.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The studies were assessed for validity from the level of concealment of random allocation, degree of blinding used, and losses to follow-up. Authors state that they considered the relationship between each criterion of quality and outcomes separately. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The data were extracted independently by two reviewers. Data were extracted for the following categories: study identification, patient characteristics (diagnosis, previous history of stroke, MI or TIA, and age), drug dose, duration of
follow-up, international normalised ratio (INR), method of random allocation, blinding used, withdrawals, number in each arm of the study, incidence of fatal outcomes (stroke, vascular, all-cause) and nonfatal outcomes (stroke, TIA, thromboembolism, MI) and other outcomes (combined fatal and non-fatal, trial-defined primary outcome and major bleeds).

**Methods of synthesis**

How were the studies combined?
A meta-analysis was performed using the fixed-effect model to pool the results across studies. Analysis was confined to intention to treat principles, in which all patients randomised were included. Where heterogeneity was found significant with the fixed-effect model, the random-effects model was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate treatment effects. STATA was used to assess funnel plot asymmetry, on order to investigate publication bias.

How were differences between studies investigated?
The authors state that pooled effect estimates and heterogeneity between studies were tested using a statistical package (REVMAN 3.1).

**Results of the review**

Five RCTs (n=3,298) were included.

Five trials were identified. One trial used age-stratified randomisation but since the duration of follow-up was longer for patients in the younger group, this was considered to be two trials for the purposes of the review.

In total, there were 82 fatal vascular events in the anticoagulation group and 95 in the antiplatelet group. Two trials were stopped prematurely, the first because of the significant treatment effect favouring warfarin, when only half of the planned numbers had been recruited, and the second because another trial indicated that low-intensity warfarin plus aspirin was significantly less effective than adjusted warfarin.

The pooled OR from the fixed-effect model showed non significant trends in favour of anticoagulation in deaths from stroke (OR 0.74, 95% CI: 0.39, 1.40), and vascular death (OR 0.86, 95% CI: 0.63, 1.17). Pooled ORs for other outcomes were: all-cause mortality, 0.94 (95% CI: 0.72, 1.21); nonfatal stroke, 0.68 (95% CI: 0.46, 0.99); nonfatal MI, 0.83 (95% CI: 0.46, 1.50); trial-defined primary outcome, 0.73 (95% CI: 0.52, 1.02). There were more major bleeding events in the anticoagulation group than the antiplatelet group (OR 1.45, 95% CI: 0.93, 2.27). Using the random-effects model, because of heterogeneity between trials, the OR for combined fatal and nonfatal events was 0.79 (95% CI: 0.61, 1.02).

A sensitivity analysis, excluding one trial that was considered methodologically weaker than the others, showed a reduction in heterogeneity between trials and attenuated non significant effects of anticoagulation, compared with antiplatelet treatment, in nonfatal stroke (OR 0.75, 95% CI: 0.50, 1.13) and combined fatal and nonfatal outcomes (OR 0.84, 95% CI: 0.67, 1.06).

In 4 of the 5 trials, the INRs were higher than the recommended range of 2 to 3 although all trials stated that anticoagulant control was adequate.

No evidence of publication bias was found. Meta-regression on quality of outcome in trials showed no significant trend.

**Cost information**
The authors state that none of the trials considered differences in the costs of treatment, although they do discuss some of the cost implications and the estimated higher relative costs of anticoagulation treatment.

**Authors' conclusions**
The authors state that the trials, individually and pooled, are underpowered. The heterogeneity between the trials and
the limited data result in considerable uncertainty about the value of long-term anticoagulation compared with antiplatelet treatment. The risks of bleeding and the higher cost of anticoagulation make it an even less convincing treatment option.

CRD commentary
This is a clear and well structured review. The search was performed over a number of databases, and included searching the grey literature and contacting key authors. The aims and inclusion criteria are clearly outlined and two of the authors extracted data independently, although they do not state how decisions were made concerning the inclusion of papers and how many trials were initially identified. The authors do say that one potentially eligible trial was excluded because of difficulties in interpreting the data. Clear tables of the characteristics of the included studies, and results, are presented. In coming to their conclusion, the authors say they have considered both heterogeneity between studies and the size of studies as part of the strength of the evidence. However, the discussion of costs, whilst including the relative costs of treatment, does not take into account other costs to the health service such as long-term costs related to events such as stroke.

The original article incorrectly stated that the name of the drug used in antiplatelet treatment was indoprofen, when it should have been indobufen.

Implications of the review for practice and research
Practice: The authors state that for patients already receiving anticoagulation, and who are stable, there is little to choose between the two treatments except cost. For new patients, some doctors may consider it unwise to risk the potential hazards of major bleeding, and associated costs to the patient and the health service, and will choose antiplatelet drugs. Patient preferences also need to be taken into consideration since evidence shows that antiplatelet treatment is the favoured option in circumstances of uncertainty of benefit. (see Other Publications of Related Interest no.2).

Research: The authors state that further large scale trials are needed to compare the costs, benefits and risk of long-term anticoagulation versus antiplatelet treatment.

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