Oral anticoagulants and non-cardioembolic stroke prevention
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CRD summary
This review concluded that oral anticoagulation should not be used for secondary prevention of stroke in patients who suffered a prior transient ischaemic attack or stroke of non-cardioembolic origin. This conclusion appeared to follow from the evidence presented, but limitations in reporting made it difficult to establish the reliability of these conclusions.

Authors' objectives
To determine the efficacy and safety of oral anticoagulation in the secondary prevention of non-cardioembolic ischaemic transient ischaemic attack (TIA) and stroke.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from 1960 to 2005 for relevant published evidence. Search terms were reported. Reference lists of retrieved studies and review articles were searched for further relevant publications. Experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) that compared oral anticoagulation with control, placebo or antiplatelet therapy in patients with prior TIA or stroke for at least three months were eligible for inclusion.

Oral anticoagulation evaluated in selected studies included coumadin, phenindione, phenylindandione, warfarin, phenprocoumon and waran. Antiplatelet therapy comparators included aspirin alone or in combination with dipyridamole. Mean age among oral anticoagulation recipients ranged from 60.6 to 76 years. Length of follow-up ranged from 9.75 to 55.2 months (mean 22 months).

Two reviewers selected studies for inclusion in the review.

Assessment of study quality
Quality of individual RCTs was assessed according to the criteria: presence of randomisation; appropriate method of randomisation; presence of double blinding; and description of withdrawals/drop-outs.

The authors did not state how many reviewers performed the assessment.

Data extraction
Data were extracted to allow calculation of odds ratios (ORs) and related 95% confidence intervals for the composite primary outcome of death, recurrent ischaemic stroke and myocardial infarction. Secondary outcomes were incidence of recurrent ischaemic stroke, recurrent TIA, myocardial infarction, total bleeds and haemorrhagic strokes.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a random-effects model. Statistical heterogeneity was investigated using the X^2 statistic. In trials with a different length of follow-up between arms the monthly event rate was assumed to be constant and multiplied by the number of months patients were followed in the longest arm of the study.

Results of the review
Twelve RCTs (n=6,310, range 52 to 2,206) were included in the review. One included study was not truly randomised (patients were allocated based on odd or even year of birth).
Compared with control (four trials, n=530), oral anticoagulation showed a statistically nonsignificant trend toward reduction in combined death, recurrent ischaemic stroke and myocardial infarction (OR 0.73, 95% CI 0.39 to 1.36, p=0.073), ischaemic stroke (p=0.13) and TIA (p=0.14). Total bleeds (OR 12.72, 95% CI 2.18 to 74.15), major bleeds (OR 6.42, 95% CI 2.02 to 20.41) and haemorrhagic strokes (OR 4.90, 95% CI 1.33 to 18.11) were all significantly greater in the oral anticoagulation group. There was no impact on all-cause mortality.

Compared with antiplatelet therapy, moderate-intensity oral anticoagulation (international normalised ratio 2.1 to 3.6; eight trials, n=4,464), showed no statistically significant difference in combined death, recurrent ischaemic stroke and myocardial infarction (p=0.93), recurrent ischaemic stroke (p=0.71) and all-cause mortality (p=0.18). Total bleeds (OR 2.18, 95% CI 1.39 to 3.41) and major bleeds (OR 2.03, 95% CI 1.49 to 2.76) were significantly greater in the oral anticoagulation group.

One trial (n=1,316) that evaluated high-intensity oral anticoagulation (international normalised ratio 3.0 to 4.5) against antiplatelet therapy stopped early because of an excess of haemorrhagic stroke in the oral anticoagulation arm (OR 8.45, 95% CI 2.53 to 28.19). Major bleeds were significantly greater in the oral anticoagulation group (OR 10.29, 95% CI 3.12 to 33.94).

Authors' conclusions
Oral anticoagulation should not be used for secondary prevention of stroke in patients who suffered a prior TIA or stroke of non-cardioembolic origin.

CRD commentary
The review question was clearly defined in terms of the participants, interventions, comparators and outcomes of interest. It appeared that attempts were made to identify relevant evidence published in any language and to minimise the potential for error and bias in the selection of studies for inclusion; it was unclear whether similar attempts were made at other stages of the review process. The authors reported that they assessed the quality of included studies, but they did not incorporate this assessment into the synthesis. The limited data reported for the included studies made it difficult to determine the appropriateness of the approach used to correct for differential length of follow-up and how this imputation of data might have influenced the findings of the review.

The authors' conclusions appeared to follow from the evidence presented, but limitations in reporting made it difficult to establish the reliability of these conclusions.

Implications of the review for practice and research
Practice: The authors stated that the available evidence supported use of aspirin or clopidogrel or a combination of aspirin and extended-release dipyridamole in patients who suffered a prior TIA or stroke of non-cardioembolic origin.

Research: The authors stated further clinical trials were required to evaluate existing antiplatelet combinations as well as new oral anticoagulants with broader therapeutic indices.

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