A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies
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CRD summary
This review concluded that available evidence supported prolonged warfarin therapy at a target international normalised ratio of 2.0 to 3.0 for first venous events, and >3.0 for arterial and/or recurrent events, in patients with thrombosis and definite antiphospholipid antibodies. These conclusions should be interpreted with caution given the methodological limitations of the review, especially the narrow search.

Authors' objectives
To assess the efficacy and safety of therapies for patients with antiphospholipid antibodies and thrombosis.

Searching
PubMed was searched up to October 2006; the search terms were reported. The references of eligible studies and relevant reviews were handsearched, and additional studies were located through the authors' expert knowledge. Meeting abstracts not published as full reports were excluded.

Study selection
Studies of secondary thromboprophylaxis in patients with antiphospholipid antibodies were eligible for inclusion. The participants were required to have experienced at least one thrombotic event prior to study entry. There were no specific inclusion criteria with respect to the outcomes. Randomised controlled trials (RCTs), prospective or retrospective cohort studies, or subgroup analyses of RCT or cohort data, were eligible for inclusion. Studies with less than 15 participants, case reports and case series were excluded.

The studies in the review included participants with definite or probable antiphospholipid syndrome. Most participants met Sapporo criteria for definite antiphospholipid syndrome, defined as persistent antiphospholipid antibodies (medium to high anticardiolipin antibody titres and/or lupus anticoagulant in tests repeated at least six weeks apart). Two thirds of the studies included some participants with a history of either arterial or venous thrombosis, while the others included only participants with one or other type of thrombosis, or with a specific clinical history (such as stroke). Some studies excluded participants with recent stroke or with a history of recurrent thrombosis while receiving oral anticoagulant therapy. Active interventions in the review were low-dose aspirin and warfarin. The target international normalised ratio (INR) for warfarin therapy varied widely within and between studies, with some participants on standard-intensity anticoagulation (INR <3) and others on high-intensity treatment (INR ≥3). Groups of participants receiving different therapies or intensities of therapy were compared with each other or with groups receiving no treatment. The review reported the following outcomes: number, rate and type of recurrent thromboses and bleeding episodes, and INR at the time of the event.

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 reviewers did not report a systematic assessment of study validity, but did comment on the following components of validity: design, use of intention-to-treat analysis, applicability, sample size, classification of outcomes and adherence to protocol (specifically, whether INR was within therapeutic range).

Data extraction
Binary data, including thrombosis and bleeding rates, were extracted in the form of events per study and rates per patient year and were reported in tables and in the text. A single reviewer extracted the data.

Methods of synthesis
The results were combined in a narrative since clinical and methodological heterogeneity precluded statistical pooling. The studies were grouped partly by design and partly by outcome. Heterogeneity was discussed in the text.
Results of the review

Sixteen studies were included in the review (1,740 participants): two RCTs (223 participants), two prospective (225 participants) and seven retrospective (446 participants) cohort studies, and five subgroup analyses comprising two RCTs (788 participants) and three cohort studies (one prospective, 16 participants; two retrospective, 42 participants). The duration of follow-up in the included studies ranged from five weeks to 624 patient-years.

The RCTs used intention-to-treat analysis. One failed to achieve the planned power and was terminated early. One reported assessor blinding. Many studies had questionable applicability: both RCTs excluded many high-risk patients and six of the 16 studies included participants who did not have definite antiphospholipid syndrome. Most studies classified patients by the target INR rather than the achieved INR. Only one study reported venous and arterial events separately.

There was marked heterogeneity between the studies with respect to the participants, outcomes, interventions, analysis and findings.

Recurrent thrombosis:

All patients in the 2 RCTs had definite antiphospholipid syndrome. Neither RCT found any benefit from high-intensity anticoagulation (target INR 3.0 to 4.0) compared with standard anticoagulation (target INR 2.0 to 3.0) in preventing recurrent thrombosis. However, patients randomised to receive high-intensity therapy frequently failed to achieve the target INR (43% of the time in one RCT).

In seven of the nine cohort studies all patients had definite antiphospholipid syndrome. With the exception of one prospective cohort study (67 participants), thrombosis recurrence rates were high among untreated patients (19 to 29% per year). Among treated patients there were generally fewer events among those treated with high-intensity coagulation (target INR 3.0 to 4.0) than among those treated with low-intensity coagulation (target INR 2.0 to 3.0) or aspirin. Patients with arterial events were at higher risk of recurrence than those with venous events in all therapeutic groups, in the single study that reported this outcome (61 participants).

In the 5 subgroup analyses, only one analysis was restricted to participants with definite antiphospholipid syndrome. The frequency of events in these studies was lower than in the cohort studies in both treated and untreated groups. In one RCT subgroup (720 participants), among patients presenting with stroke there was no significant difference in the risk of recurrent thrombosis between those with a single positive antiphospholipid antibodies test who were treated with aspirin and those treated with warfarin (median INR 1.9). Rates of recurrent events among both treated and untreated patients were lower than in the cohort studies.

Bleeding (eight studies):

Rates of major bleeding varied widely, ranging from 0.57 to 10% per year. Seventy-four per cent of bleeding episodes occurred in patients with an INR ≥3.0 (where recorded). The proportion of bleeds that were major was 20% in patients receiving standard therapy and 29% in those receiving high-intensity therapy. The relative proportions of major and minor bleeding were similar for patients treated with standard- or high-intensity anticoagulation.

Mortality due to thrombosis and bleeding (four studies):

Eighteen deaths were reported to be directly related to recurrent thromboses (12 arterial, five venous, one multiple) and one due to bleeding. Ten patients in one study died as a result of the presenting thrombosis.

Treatment and INR at time of thrombosis (13 studies):

Among patients receiving warfarin who experienced recurrent thrombosis (49 participants), 86% of total events (42 participants) occurred while the INR was <3.0. Fifteen per cent of events (27 participants), mostly arterial, occurred in patients taking aspirin and 57% (104 participants) occurred when patients were not taking any anticoagulant or anti-aggregant drug.

Authors' conclusions
Patients with definite antiphospholipid syndrome and arterial and/or recurrent thrombosis were at high risk of recurrent events. Most thrombotic events in patients on warfarin occur at an INR <3; recurrences were infrequent among those with an INR of 3.0 to 4.0. Patients with venous embolism or stroke and a single positive antiphospholipid antibodies that did not persist were at relatively low risk of recurrent thrombosis. The available evidence was of questionable quality and generalisability.

CRD commentary
The review addressed a clear question and was supported by suitable inclusion criteria. Only one database was searched and studies published solely as meeting abstracts were excluded, which meant that some studies might have been missed. It was not stated whether there was any restriction by language of publication. It was unclear how the studies were selected for inclusion, no systematic assessment of validity was reported, and a single reviewer extracted the data; these factors increased the possibility of bias and error.

No measures of statistical significance were reported for the study findings and there were few details about the quality of the primary studies. However, several potential sources of bias and threats to generalisability were well-addressed in the text. The decision not to meta-analyse the data appeared appropriate in view of the heterogeneity between the studies.

The data appeared to support the authors' conclusions, but they should be interpreted somewhat cautiously in view of the heterogeneity between the studies and the methodological limitations of the review, especially the rather narrow search.

Implications of the review for practice and research
Practice: The authors stated that, after a first venous thrombosis, patients with antiphospholipid syndrome should be treated with warfarin at an INR of 2.0 to 3.0; those with arterial or secondary thrombosis should be treated with warfarin at an INR >3.0. Patients with venous thrombosis or stroke and a single positive antiphospholipid antibodies test should be retested, and should be treated no differently from other patients unless the antibody persists. Among patients on oral anticoagulants with an INR of 3.0 to 4.0 and recurrent thrombosis, the effect of additional antithrombotic treatment was unknown, as is the effect of correcting cardiovascular risk factors.

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

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