Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials

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Authors' objectives
To assess the length of oral anticoagulation therapy (short versus long duration) after a first episode of venous thromboembolism (VTE).

Searching
MEDLINE and EMBASE were searched without language restrictions using the following keywords and textwords: 'randomised controlled trials', 'clinical trials', 'prospective studies', 'thrombophlebitis', 'deep vein thrombosis', 'pulmonary embolism', 'thromboembolism', 'venous thromboembolism', 'warfarin', 'antivitamin K or vitamin K antagonists', 'oral anticoagulants or anticoagulant', 'anticoagulant treatment', 'oral anticoagulant therapy', 'duration of anticoagulants' and 'duration of anticoagulant therapy'. The Cochrane Controlled Trials Register was also searched, and the principal researchers of each published trial were contacted to obtain updated data and check the published data. References of recent and general reviews, synthesis articles and editorials were also reviewed.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled trials (RCTs) were eligible. One recently published trial was excluded because the length of follow-up and the methodology (randomisation after 3 months of therapy) differed from the other included trials. Duration of follow-up ranged from 10 to 24 months.

Specific interventions included in the review
Studies that compared two durations of anticoagulation therapy were eligible.

Participants included in the review
The included studies used warfarin. The reporting of treatment intensity was inconsistent with some studies providing no details. The target International Normalised ratio (or prothrombin time) was between 2 and 3. Duration of the short arms of anticoagulant therapy ranged from 3 to 12 weeks whilst that for long arms ranged from 6 weeks to 24 weeks.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. The following outcomes were assessed at twelve months: recurrence of VTE, a proportion of which were not verified by objective methods (e.g. ultrasonography, venography, angiography or perfusion ventilation lung scan); and occurrence of iatrogenic haemorrhagic complications. Major haemorrhage was defined as: haemorrhage requiring a transfusion or hospitalisation; intracranial, intraocular or retroperitoneal; or when haemoglobin fell by 20 g/L or more.

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
Only RCTs were included, but no formal validity assessment was performed.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Tables reported in the review included the following information: author, location of study and year of publication; sample size and number per treatment arm; site of initial thrombosis; reported baseline characteristics of participants; duration of short and long therapies; duration of follow-up; and outcome.

**Methods of synthesis**
How were the studies combined?
The following methods were used to pool data: Peto, Mantel-Haenszel, Cochran, odds ratio logarithm, relative risk logarithm, random relative risk, percentage differences, and DerSimonian and Laird. A fixed-effect model was used. Results were reported for the relative risk (RR) logarithmic method with 95% confidence intervals (CIs), weighted according to sample size and the incidence of recurrences. The level of significance for the chi-squared test for association was set at 0.01.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test with 0.1 as the level of significance. Subgroup analysis was conducted to explore the influence of risk factors for thrombosis (temporary or permanent risk factors and idiopathic VTE) on VTE recurrence. Analysis of recurrence rates was repeated using only the three most recent studies.

**Results of the review**
Seven RCTs were included (2,304 patients, including 1,156 receiving short-term therapy and 1,148 receiving long-term therapy).

Thrombotic recurrence at 12 months (7 RCTs; 2,304 patients including 1,148 and 1,156 on short- and long-term therapy, respectively).

Recurrence rates were greater in those receiving short-term compared to long-term therapy (11.1 versus 6.4%).

Long-term treatment significantly reduced the incidence of recurrence compared to short duration, regardless of the statistical method used; RR 0.60 (95% CI: 0.45, 0.79, p<0.001). No significant heterogeneity was found (p=0.16).

Limiting analysis to the three most recent and adequately designed trials also showed a significant reduction in patients receiving long-term compared to short-term therapy; RR 0.45 (95% CI: 0.32, 0.63, p<0.001). No significant heterogeneity was found (p=0.73). Major bleeding (3 RCTs; 1,823 patients).

Major bleeding was more common in those receiving long-term compared to short-term therapy (weighted mean of major bleeding was 1.1 versus 0.7%).

Duration of anticoagulant therapy (short- versus long-term) had no statistically-significant effect on the incidence of major bleeding on any statistical method used; RR 1.43 (95% CI: 0.51, 4.01, p=0.5). No significant heterogeneity was found (P=0.34).

**Influence of risk factors.**
Permanent risk factors and idiopathic VTE (4 RCTs; 671 patients and 652 patients on short- and long-term therapy, respectively): recurrence rates were greater in the short compared to the long duration of therapy groups (13.8 versus 6.7%).

Long-term treatment significantly reduced the incidence of recurrence compared to short-term treatment; RR 0.48 (95% CI: 0.34, 0.68, p<0.001). No significant heterogeneity was found (p=0.39).
Temporary risk factors and idiopathic VTE (4 RCTs; 276 and 284 patients on short- and long-term therapy, respectively).

Recurrence rates were less than in patients with permanent risk factors, and were greater with short-term compared to long-term therapy (5.3 versus 1.4%).

There was no significant difference between long- and short-term treatment at the p>0.01 level; RR 0.34 (95% CI: 0.13, 0.93, P=0.035). No significant heterogeneity was found (p=0.91).

Data did not allow subgroup analysis using haemorrhage as the outcome, or analysis by DVT site (proximal or calf).

**Authors’ conclusions**

After a first episode of VTE, a longer treatment regimen allows a significant reduction in the incidence of recurrences without increasing the incidence of bleeding events. The optimal duration has yet to be determined.

**CRD commentary**

The aims were stated and the inclusion criteria were defined in terms of study design, intervention and participants. Several relevant databases were searched and no language restrictions were applied. No attempts were made to locate unpublished material, thus raising the possibility of publication bias. Time periods over which the sources were searched were not stated, and the methods used to select studies were not described. Included trials were restricted to RCTs but no formal validity assessment was undertaken, although some aspects of validity were mentioned (validation of outcome assessment). Some relevant data were extracted, though full details of methods used to extract data were not described, and authors were contacted to check published data. Data from studies were pooled, statistical heterogeneity was assessed, and an exploration was conducted of the influence of some factors on the results.

The evidence presented supports the authors’ conclusions.

**Implications of the review for practice and research**

Practice: The authors state that after a first episode of idiopathic VTE, or VTE with permanent risk factors, the optimal duration seems to be a long-term regimen of possibly 12 to 24 weeks. For patients with temporary risk factors, the optimal duration of anticoagulant therapy is still uncertain.

Research: The authors state that a large RCT is required to determine the optimal duration of anticoagulant therapy. Research is required to identify which subgroups of patients would benefit from a long course of anticoagulant therapy (high risk of recurrence) or a short course (high risk of haemorrhage and low risk of recurrence).

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