Clinical evidence for rebound hypercoagulability after discontinuing oral anticoagulants for 
venous thromboembolism

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CRD summary
This review concluded that increasing the duration of oral anticoagulation treatment for venous thromboembolism did not significantly reduce overall adverse events. Rebound hypercoagulability accounted for approximately 2% of patients who experienced recurrent venous thromboembolism in the two months following treatment discontinuation. Significant flaws in the review mean that the reliability of this conclusion is unclear.

Authors' objectives
To assess the extent to which rebound hypercoagulability-related venous thromboembolism recurrences occur in the two months following discontinuation of oral anticoagulants.

Searching
MEDLINE was searched up to July 2008. Search terms were reported. A Cochrane review was used to identify studies, as were the bibliographies of this review and published randomised controlled trials (RCTs). Only published studies reported in English were eligible for inclusion.

Study selection
RCTs of oral anticoagulants for the treatment of venous thromboembolism were eligible for inclusion. Trials were required to report clinical recurrences or extensions of venous thromboembolism; studies that reported only surrogate outcomes such as positive Doppler leg scans were excluded. Studies in which no event data were reported for more than two months after discontinuation of oral anticoagulants or in which the timing of venous thromboembolism recurrences was not reported were excluded from the review. Venous thromboembolism recurrence was the primary outcome. Major bleeding was also assessed.

Included studies used the oral anticoagulants warfarin, fluindione, acenocoumarol, dicumarol and ximelagatran. Eligibility criteria for the studies varied slightly; some enrolled only patients with a first deep-vein thrombosis or a second deep-vein thrombosis. No further information on study participants was reported.

The author stated neither how the papers were selected for the review nor how many authors performed the selection.

Assessment of study quality
The author did not state that he assessed validity.

Data extraction
Data on recurrences of venous thromboembolism while on oral anticoagulants, in the two months after their discontinuation and subsequently were extracted. The number of patient months at risk of venous thromboembolism were calculated using the number of patients who completed each trial phase and its duration. The author did not state how many reviewers performed the extraction.

Methods of synthesis
Overall incidences of venous thromboembolism recurrence were calculated for the two time periods (two months following withdrawal of anticoagulation versus subsequently). Odds ratios (OR) with 95% confidence intervals (CI) for the incidence of venous thromboembolism recurrence in the two time periods were calculated using a $\chi^2$ function with a fixed-effect approach. The number of venous thromboembolism recurrences possibly attributable to rebound hypercoagulability resulting from withdrawal of oral anticoagulation was calculated by subtraction of the number of recurrences after the two month rebound period from the number of recurrences during this period. Subgroup analysis was used to assess the effect of longer (more than six months) versus shorter (less than three months) duration of therapy. Statistical heterogeneity was assessed using the $I^2$ statistic. Funnel plots were used to assess publication bias.
Results of the review
Thirty-seven trial arms (n=5,822) from 20 RCTs were included in the review.

The rate of venous thromboembolism recurrence while taking oral anticoagulants was 0.49% per month; 0.38% of patients had major haemorrhages. Venous thromboembolism recurrences were 2.62 times as frequent in the two months following discontinuation of oral anticoagulation (1.57% per month) as subsequently (0.56% per month, OR 2.62, 95% CI 2.19 to 3.14), which meant 2.02% of patients had rebound hypercoagulability-related venous thromboembolism recurrence.

Analysis of the trials that assessed longer and shorter duration of anticoagulation therapy found lower rates of venous thromboembolism recurrence with longer duration of therapy; removal of a large trial labelled as an outlier from the analysis meant this difference was no longer apparent and there were no differences in total adverse events between the groups (11 RCTs).

Authors' conclusions
Increasing the duration of oral anticoagulation treatment for venous thromboembolism did not significantly reduce the overall adverse events. Rebound hypercoagulability accounted for approximately 2% of patients who experienced recurrent venous thromboembolism in the two months following treatment discontinuation.

CRD commentary
The review question and the inclusion criteria were clear. The author searched only one database and limited the review to published studies reported in English. This led to the exclusion of a relevant study and may have resulted in publication and language biases and omission of other relevant studies. The author did not report using methods designed to reduce reviewer bias and error at any stage of the review process, nor did he report assessing the validity of included studies. The lack of a validity assessment made it difficult to determine the reliability of the evidence included in the review. Limited information on study characteristics was reported. The decision to assess individual arms of RCTs as standalone patient groups is rarely appropriate, since it discards the methodological benefits of randomisation. The analysis of shorter versus longer duration of therapy was subject to a questionable sensitivity analysis. Numerous problems with the review methodology and reporting made the reliability of the author's conclusions unclear.

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

Research: The author stated that RCTs that evaluate oral anticoagulation for venous thromboembolism should include data for at least two months following treatment end. Trials of antithrombotic drugs for other indications should include data for appropriate time intervals after discontinuation of therapy.

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