Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism

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CRD summary
This generally well-conducted review found that D-dimer testing after stopping anticoagulant therapy helped to predict whether venous thromboembolism would recur in patients who had stopped the treatment after a first unprovoked venous thromboembolism. The results are likely to be reliable.

Authors’ objectives
To evaluate the value of D-dimer as a predictor of recurrent venous thromboembolism in patients who have stopped anticoagulant therapy after a first unprovoked venous thromboembolism.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials were searched without language restrictions across dates spanning 1950 to March 2008. Search terms were reported. Reference lists were also searched and experts in the field contacted.

Study selection
Randomised controlled trials (RCTs) and prospective cohort studies that measured D-dimer three to eight weeks after discontinuing anticoagulant therapy in patients who had received at least three months anticoagulant therapy following their first unprovoked venous thromboembolism, were eligible for inclusion. Where reported, the studies recruited adults with either a deep vein thrombosis or pulmonary embolism. Anticoagulants most commonly used in the studies were warfarin, acenocoumarol and phenprocoumon. The minimum duration of therapy was either three or six months. Assay type and normal D-dimer cut-offs varied across studies. Where reported, the average age ranged from 62 to 67 years, and the proportion of females from 47 to 56%.

Two reviewers independently selected studies. Disagreements were resolved through consensus.

Assessment of study quality
Two reviewers independently assessed study quality in terms of study design, patient enrollment, outcome assessment, duration of treatment, loss to follow-up and funding source using the Newcastle-Ottawa score.

Data extraction
The risk of recurrent venous thromboembolism per patient-year of follow-up and 95% confidence intervals (CI) were calculated for each study. Study authors were contacted for missing data. Individual patient data were requested for patients who had experienced more than one venous thromboembolism and where D-dimer testing was conducted outside the prespecified range. Only data from control arms were utilised from studies where patients were restarted on anticoagulant therapy after a positive D-dimer test in the treatment arm.

Two reviewers independently extracted data. Disagreements were resolved through consensus or referral to a third reviewer.

Methods of synthesis
Pooled annualised rates were calculated, weighted by the reciprocal of the variance. A pooled D-dimer effect was calculated using a mixed-effect Poisson model, from which a pooled incidence rate ratio was calculated using a fixed-effect model where heterogeneity was absent and a random-effects model where present. Heterogeneity was assessed using the $I^2$ and $t^2$ tests. Potential sources investigated were differences in population, D-dimer testing and study design.
Publication bias was investigated using funnel plots.

**Results of the review**

Seven studies met the inclusion criteria (n=3,225 patients; 1888 first unprovoked venous thromboembolism), of which two were RCTs (n=1,109 patients; 550 first unprovoked venous thromboembolism) and five prospective cohort studies (n=2,116 patients; 1,338 first unprovoked venous thromboembolism); only patients with first unprovoked venous thromboembolism were included in the analysis. All studies used independent blinded outcome assessment and had at least 12 month follow-up. Four of the cohort studies reported consecutive recruitment of patients. Two studies reported loss to follow-up (less than 2%) and two reported funding source.

Of the 907 patients with a positive D-dimer test after stopping anticoagulation, 165 (18.2%) had a recurrent venous thromboembolism in 2,462 person-years follow-up, a risk of 8.9% per year (95% CI 5.8 to 11.9). Statistically significant heterogeneity was observed (p<0.001) thought to be due to variation in the location of the initial venous thromboembolism and the D-dimer cut-offs used for positive and negative results.

Of the 981 patients with a negative D-dimer test, 74 (7.5%) had a recurrent venous thromboembolism in 2,040 person years follow-up, a risk of 3.5% per year (95% CI 2.7 to 4.3). No statistically significant heterogeneity was observed (p=0.832).

The pooled incidence rate showed the risk for recurrent venous thromboembolism in patients with a positive D-dimer test was over twice that of patients with a negative test (2.2, 95% CI 1.65 to 2.94). Publication bias was thought to be present for the positive D-dimer outcome, but not the negative outcome.

A reanalysis was undertaken in 2010 using individual patient data (see Other Publications of Related Interest); the annualised risk for recurrent venous thromboembolism was 3.7 per 100 patient years (95% CI 3.2 to 4.3) with a negative D-dimer test, and 8.8 per 100 patient years (95% CI 6.2 to 11.3) with a positive D-dimer test. A univariate regression using the cut-offs for the D-dimer test reported in the source studies, gave a hazard ratio for recurrent venous thromboembolism of 2.59 (95% CI 1.90 to 3.32); the results were not significantly altered when re-analysed with cut-offs of 500 and 250 µg/L.

**Authors’ conclusions**

D-dimer testing after stopping anticoagulant therapy helped to predict whether venous thromboembolism would recur.

**CRD commentary**

The authors addressed a clear research question, and searched a number of relevant sources. All stages of the review were conducted in duplicate, reducing the risk of error and bias. Publication bias was investigated, and seemed to be present for one outcome.

Study quality was assessed, although criteria suited to observational studies were applied to RCTs rather than criteria specific for this study design. Given the presence of clinical heterogeneity between studies, namely differences in terms of study design and the definitions of D-dimer and venous thromboembolism used and the presence of statistical heterogeneity for some outcomes, pooling the results for all studies may not have been appropriate.

This was a generally well-conducted review, and the results are likely to be reliable.

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

Practice: The authors stated that clinicians must balance the risk of a recurrent venous thromboembolism if anticoagulant treatment is stopped with potential bleeding if therapy is continued. The use of D-dimer was not endorsed as a stand-alone test on which the decision should be made but as part of a clinical prediction rule that incorporates clinical and laboratory features.

Research: The authors stated that further research is required to establish the optimal interval between stopping anticoagulant treatment and performing the D-dimer test and cut-offs and to develop a clinical prediction rule for
recurrent venous thromboembolism.

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