Quantitative assessment of thrombus burden predicts the outcome of treatment for venous thrombosis: a systematic review

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CRD summary
This review concluded that clot-burden change can predict the long-term outcome of venous thromboembolism, and can be used to guide duration of anticoagulant therapy and as a surrogate outcome measure in clinical trials. The evidence presented supports the authors’ conclusion, although reviewer error and bias in the data extraction process cannot be ruled out.

Authors' objectives
To determine whether clot-burden change is predictive of subsequent recurrent venous thromboembolism (VTE).

Searching
PubMed was searched up to 2003 and the reference lists of relevant articles and abstracts from conference proceedings were checked. Investigators and pharmaceutical companies were also contacted. Studies published in all languages were eligible, as were abstracts detailing methods and results.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared the efficacy of regulatory approved anticoagulant therapy were eligible for inclusion. All of the included studies compared low molecular weight heparin (LMWH) with unfractionated heparin (UFH). The LMWH evaluated in the included studies were bemiparin, certoparin, dalteparin, enoxaparin, nadroparin and reviparin.

Reference standard test against which the new test was compared
Studies had to objectively evaluate thrombus regression before and after initial treatment using quantitative clot-burden assessment. Venography was used to provide a quantitative assessment of clot burden, with most studies using the scoring method of Marder et al. (see Other Publications of Related Interest).

Participants included in the review
Studies of participants with acute lower-extremity deep-vein thrombosis confirmed using an objective method, with or without concurrent pulmonary embolism, were eligible for inclusion. The mean age ranged from 58 years to older than 65 years. Where reported, the proportion of patients with previous VTE ranged from 0 to 29%, cancer from 5 to 21%, heart failure from 7.5 to 15%, immobilisation from 13 to 58%, and surgery or trauma from 0.3 to 45%.

Outcomes assessed in the review
Studies that objectively evaluated recurrent symptomatic VTE during long-term follow-up and objectively evaluated thrombus regression before and after initial treatment using quantitative clot-burden assessment were eligible for inclusion. Where reported, studies performed follow-up venograms after 5 days to 3 months, and defined a decrease in clot burden as a 10 to 30% decrease or a decrease in clot-burden score of 1 point or more. The studies provided data on recurrent VTE at 3 months or longer.

How were decisions on the relevance of primary studies made?
Two independent reviewers assessed the eligibility of the studies. Any disagreements were resolved through discussion.

Assessment of study quality
Validity was determined through assessment of the following: method of randomisation, concealment of allocation, blinding, loss to follow-up (clinical follow-up and follow-up venography), blinded independent review of venograms by expert radiologists, and timing of the venogram (before or after treatment).

Data extraction
It appears that one reviewer extracted the data from the included studies. Data on the number of patients with an improvement in clot burden following initial treatment and on the occurrence of recurrent thromboembolism at the 3- and 12-month follow-up were extracted; these data were used to calculated risk ratios (RRs). Data were also collected on potential sources of variability: gender, age, concurrent pulmonary embolism, distal deep vein thrombosis, history of VTE, cancer, heart failure, recent surgery or trauma, and recent prolonged bed rest. The authors of the included studies were contacted for further information, where required.

Methods of synthesis
How were the studies combined?
A pooled RR with 95% confidence intervals (CIs) was calculated separately for improved clot-burden score and recurrent VTE. Meta-regression was used to assess the association between the relative risk reductions for VTE and the relative risk reduction for improvement in clot-burden score. The possibility of publication bias was investigated using funnel plots.

How were differences between studies investigated?
Meta-regression was used to explore possible reasons for heterogeneity, based on the following study variables: type and frequency of LMWH, administration of UFH prior to randomisation, concurrent pulmonary embolism, oral anticoagulation initiation time, duration of follow-up, and definition of clot-burden score improvement (percentage change versus 1-point change). A sensitivity analysis was performed to identify whether individual studies were exerting an undue influence on the results, by repeating the analysis after the deletion of individual studies.

Results of the review
Eleven RCTs (n=3,206) met the inclusion criteria.

In terms of methodological quality, 10 studies reported adequate methods to generate allocation sequence and 9 reported adequate concealment of allocation. One study was double-blind and 11 studies used blinded independent assessment of the venogram. The proportion of patients lost to clinical follow-up ranged from 0 to 22.3% and the proportion of patients with two evaluable venograms ranged from 70.3 to 100%.

Compared with usual care, LMWH was associated with a statistically significantly improved clot burden (RR 0.82, 95% CI: 0.76, 0.88, p<0.001) and lower risk of recurrent VTE (RR 0.56, 95% CI: 0.42, 0.76, p<0.001). The meta-regression showed a strong relationship between clot-burden score and recurrence of VTE (correlation 0.81, p=0.005).

The significant heterogeneity found in the analysis of improved clot burden was removed after excluding 1 study from the analysis.

The meta-regression and sensitivity analysis suggest that study-level variables and elimination of individual studies did not influence the results. The authors stated that the funnel plot suggests that publication bias was unlikely.

Authors' conclusions
Clot-burden change predicts the long-term outcome of treatment for venous thrombosis, thus providing a clinically relevant patient-specific prognostic finding that can be used to guide the duration of anticoagulant therapy and provide a valid surrogate end point for clinical trials of innovative therapy.

CRD commentary
The review addressed a clear research question and was supported by well-defined inclusion criteria. A limited electronic search was used to identify studies, although attempts were made to minimise publication and language bias. Furthermore, publication bias was assessed and the authors stated that its presence was unlikely. Methods were used to minimise reviewer error and bias in the selection of studies for inclusion. However, it appears that only one reviewer performed the data extraction and validity assessment. Validity was assessed using appropriate criteria and the results were clearly reported, suggesting that the included studies were of high methodological quality.

Adequate details on each included study were presented. It would appear that the methods used to combine the studies were appropriate. Differences between the studies were investigated and potential sources were investigated. The authors’ conclusion follows from the evidence presented, although the possibility of reviewer error and bias in the data extraction process cannot be ruled out.

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

**Practice:** The authors did not state any implications for practice. Research: The authors stated that the use of quantitative clot-burden assessment in future trials of innovative anti-thrombotic therapy and innovative noninvasive imaging (duplex ultrasonography) may allow for more efficient clinical trials by allowing the Data Safety and Monitoring Board to stop the trial if a drug under evaluation is found to be less effective.

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**Other publications of related interest**


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