Correlation between thrombus regression and recurrent venous thromboembolism. Examining venographic and clinical effects of low-molecular-weight heparins: a meta-analysis


CRD summary
This review assessed the relationship between the venographic evaluation of deep venous thrombosis and the incidence of recurrent venous thromboembolism in patients with deep vein thrombosis. The authors found an inverse correlation between venographically proven thrombus regression and recurrent venous thromboembolism. This review was generally well-conducted, but methodological weaknesses in the included studies suggest that the results should be interpreted cautiously.

Authors' objectives
To evaluate the correlation between thrombus regression assessed by venography after stopping heparin administration and the incidence of recurrent venous thromboembolism (VTE).

Searching
MEDLINE, the Cochrane CENTRAL Register, Excerpta Medica and Adis Clinical Trials Insight were searched from January 1985 to May 2003; the search terms were reported. No language restriction was applied. Abstracts from conference proceedings of the International Society on Thrombosis and Haemostasis and the bibliographies of previous reviews were checked and experts in the field contacted to identify additional articles.

Study selection

Study designs of evaluations included in the review
Randomised, controlled trials (RCTs) with at least 2 months' follow-up were eligible.

Specific interventions included in the review
Studies evaluating low molecular weight heparin (LMWH) versus adjusted-dose unfractionated heparin (UFH) were eligible. The LMWH included dalteparin (200 or 240 IU/kg per day), certoparin (various doses), nadroparin (184 IU/kg per day), enoxaparin (200 IU/kg per day), reviparin (160 IU/kg per day) and bemiparin (115 IU/kg per day). LMWH was often given subcutaneously and UFH intravenously. The duration of heparin treatment ranged from 5 to 28 days. Most of the studies also provided oral anticoagulation for at least 3 months.

Participants included in the review
Studies of patients with acute venographically diagnosed deep vein thrombosis (DVT) were included.

Outcomes assessed in the review
Eligible studies had to objectively assess the incidence of recurrent VTE. Thrombus regression was also assessed. Recurrent DVT was confirmed by Doppler ultrasound or venography, and recurrent pulmonary embolism by ventilation perfusion lung scanning or arteriography. The outcome definitions used by the primary studies were accepted. The duration of follow-up ranged from 2 to 6 months.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected the studies, but the authors did not state how any disagreements were resolved.

Assessment of study quality
The authors reported whether the study outcomes were independent and assessed in a blinded manner, but did not state how many reviewers performed the assessment.

Data extraction
Two independent reviewers extracted the data and any disagreements were resolved through discussion. Relative risks
(RRs) with 95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

How were the studies combined?
RRs were pooled using the Mantel-Haenszel and inverse variance methods. The random-effects model of DerSimonian and Laird was used to check the results. Only data obtained with the fixed-effect model are presented since the random-effects model did not modify the findings.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Mantel-Haenszel method. The influence of the type of LMWH and dose interval was explored. Linear regression with log-transformed RRs and Mantel-Haenszel weights was used to assess the statistical correlation between venographic assessment and recurrent VTE.

**Results of the review**

Thirteen RCTs (4,018 patients) were included in the review.

None of the studies used a double-blinded design, but all trials evaluated thrombus regression in a blinded manner.

In comparison with UFH, statistically significant differences in favour of LMWH were shown for both thrombus regression (RR 1.23, 95% CI: 1.15, 1.32, p<0.001) and recurrent VTE (RR 0.59, 95% CI: 0.43, 0.82, p=0.002). Effect sizes showed significant heterogeneity for venographic effects according to the type of LMWH used (p=0.013). The dose interval of LMWH did not affect the venographic findings or the incidence of recurrent VTE. There was an inverse correlation between thrombus regression and recurrent VTE (correlation, r=-0.7; p=0.008) and a very strong correlation when the results were pooled by type of LMWH (r=-0.84; p=0.037).

**Authors’ conclusions**

There is a strong correlation between the venographic assessment of the thrombus performed soon after heparin discontinuation and the risk of recurrent VTE. Both venography and clinical follow-up are valid tools to determine the efficacy of LMWH.

**CRD commentary**

This review had clearly stated inclusion criteria with respect to the study design, interventions, participants and outcomes. The authors searched several databases and efforts were made to find further information by reviewing reference lists and contacting experts in the field. The potential influence of publication bias was not evaluated. No language restrictions were applied, thereby limiting the potential for language bias. The authors attempted to minimise bias and errors during the review process by carrying out the data extraction and study selection in duplicate. However, it is unclear whether the limited assessment of study quality was conducted using similar methods. Attempts were made to investigate potential sources of statistical heterogeneity. Overall, the review was generally well-conducted. However, methodological weaknesses in the included studies suggest that the results should be interpreted with caution.

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

Practice: The authors stated that objective venographic assessment is 'a good method, in combination with the assessment of clinical assessment to evaluate the efficacy of a LMWH in the treatment of DVT'. They also stated that 'the lack of thrombus regression appears to be associated with clinical recurrence'.

Research: The authors stated that future studies should evaluate noninvasive imaging techniques to identify patients who do not respond to heparin, and assess the optimal duration of initial heparin treatment.

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