Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants

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CRD summary

This review compared long term low molecular weight heparin (LMWH) treatment of venous thromboembolism with oral anticoagulation. The authors concluded that LMWH for 3 months is as safe and effective as oral anticoagulation in preventing the recurrence of venous thromboembolism. The authors' conclusions are likely to be reliable.

Authors' objectives

To compare the efficacy and safety of long term treatment of venous thromboembolism (VTE) using low molecular weight heparin (LMWH) with oral anticoagulation (OA).

Searching

MEDLINE and EMBASE were searched from inception to January 2001; the search terms were stated. In addition, relevant journals, meeting proceedings and the reference lists of relevant studies were handsearched. The authors' colleagues were contacted for details of further studies.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion. The authors stated that two studies were excluded (one on the basis of poor methodological quality; data in the other study were later published in full).

Specific interventions included in the review

Studies that compared long term treatment using LMWH with OA were eligible for inclusion. The initial treatment in the included studies was with adjusted unfractionated heparin (UFH), UFH or LMWH; all but one study used the same initial treatment in both treatment groups. The included studies used the following daily LMWH regimens: enoxaparin 4,000 IU, dalteparin 5,000 IU, nadroparin 85 IU/kg, and tinzaparin 175 IU/kg. These were compared with warfarin (international normalised ratio, INR 2.0 to 3.5) or acenocoumarol (INR 2.0 to 3.0). The included studies lasted from 3 to 9 months, but in some studies treatment beyond 3 months was not balanced between treatment groups.

Participants included in the review

Studies in patients with symptomatic VTE were eligible for inclusion. The studies had to use accepted diagnostic tests to confirm the diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE).

Outcomes assessed in the review

The primary review outcomes were incidence of recurrent symptomatic VTE, major bleeding complications and mortality. Recurrent symptomatic DVT had to be diagnosed using venography, compression ultrasonography, or plethysmography plus D-dimer. PE had to be diagnosed using pulmonary angiography, ventilation or perfusion scans, and autopsy. The review classified bleeding complications as major if haemorrhage was clinically overt and accompanied by a fall in haemoglobin of 2 g/dL or more, or required a transfusion of at least two of packed cells; if bleeding was intracranial, retroperitoneal or intra-articular; or if it led to death or a break in antithrombotic treatment. The review also evaluated cancer mortality.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed the relevance of studies and resolved any disagreements on inclusions through discussion with a third author.

Assessment of study quality

Validity was assessed on the basis of concealment of randomisation, blinding of treatment, blinding of the outcome assessment and the method of randomisation (further details were not provided). The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction

Two reviewer independently extracted the data using a standardised form. The odds ratio (OR) for recurrent symptomatic VTE, major bleeding and death were calculated for each study. Authors of studies were contacted where necessary for additional information.

Methods of synthesis

How were the studies combined?

The studies were combined using a meta-analysis. The pooled OR and 95% confidence intervals (CIs) were calculated using a fixed-effect model (Mantel-Haenszel). Three studies did not provide data to allow analysis on an intention-to-treat basis. Data from all patients during the period of randomisation were used for the primary analysis. The statistical power of the meta-analysis was recalculated using methods described by Altman (see Other Publications of Related Interest).

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared test. Pooled ORs were calculated separately for patients with and without malignancies. A meta-regression was used to explore the relationship between dose and efficacy or safety outcomes. The pooled ORs were re-calculated for VTE and major bleeding after excluding one study published only as an abstract. The pooled OR for VTE recurrence was also re-calculated after excluding the one study that used a different initial treatment in each group.

Results of the review

Seven RCTs (1,379 patients) were included in the review.

In five RCTs randomisation was adequately concealed, while in four of these treatment was not blinded. The outcome assessment was blinded in four RCTs.

Recurrent symptomatic VTE (7 RCTs): LMWH reduced the risk of recurrent symptomatic VTE at 3 months compared with OA, but the reduction was not statistically significant (OR 0.66, 95% CI: 0.41, 1.07). No significant heterogeneity was detected (P=0.12). The meta-analysis had 78% power of detecting a 50% reduction in recurrent symptomatic VTE.

Bleeding (7 RCTs): there was no statistically significant difference in major bleeding rates at 3 months between the treatments (OR 0.45, 95% CI: 0.18, 1.11). No significant heterogeneity was detected (P=0.77). The meta-analysis had 38% power.

Mortality (7 RCTs): there was no statistically significant difference in mortality at 3 months between the treatments (OR 1.19, 95% CI: 0.78, 1.83). No significant heterogeneity was detected (P=0.89). There was no statistically significant difference in mortality due to PE between the treatments (OR 1.64, 95% CI: 0.39, 6.91). The meta-analysis had 66% power of detecting a 50% reduction. There was no statistically significant difference between treatments in mortality due to cancer mortality (6 studies; OR 1.12, 95% CI: 0.63, 1.98). No significant heterogeneity was detected (P=0.95).

There was no statistically significant difference between treatments in mortality for patients who were known to have cancer at baseline (126 patients; OR 1.13, 95% CI: 0.54, 2.38).

There was a non-statistically significant linear trend between LMWH dose and VTE recurrence (r2=0.194, P=0.33) and a significant linear trend between dose and bleeding complications (r2=0.65, P=0.027).

The results for VTE recurrence and major bleeding were similar after excluding one study published only as an

abstract.

After excluding the one study that used a different initial treatment in the two groups, the pooled OR for VTE recurrence was 0.90 (95% CI: 0.51, 1.6). No significant heterogeneity was detected (P=0.26).

Authors' conclusions

The findings suggested that LMWH for 3 months is as safe and effective as OA in preventing VTE recurrence. The authors suggested that LMWH can be used in patients in whom OA may be contraindicated or difficult.

CRD commentary

The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources appear to have been searched, but no details were given of the specific journals searched and it was unclear whether any language restrictions had been applied. Two reviewers independently selected the studies and extracted the data, thus reducing the potential for bias and errors. One study was subsequently excluded because of poor methodological quality, but this appears to have been a post hoc decision and the influence of this study on the results was not discussed. Validity was assessed but the process was poorly described.

Some relevant information on the included studies was tabulated, but no information on the participants was provided. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. Sensitivity analyses were used to explore the influence of two studies with defined characteristics. The evidence presented appears to support the authors' conclusions.

Implications of the review for practice and research

Practice: The authors stated that LMWH could be used in patients in whom OA may be contraindicated or problematic.

Research: The authors did not state any implications for further research.

Bibliographic details

Iorio A, Guercini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. Journal of Thrombosis and Haemostasis 2003; 1(9): 1906-1913

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Other publications of related interest

Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.

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MeSH

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.