Long-term use of different doses of low-molecular-weight heparin versus vitamin K antagonists in the treatment of venous thromboembolism

CRD summary
The authors concluded that full-dose low molecular weight heparin treatment for three to six months was as safe as intermediate and prophylactic doses for long-term treatment of deep vein thrombosis. Evidence was based on indirect comparisons, which combined with an inadequate study quality assessment and small numbers of events for some analyses means that the conclusions may not be reliable.

Authors’ objectives
To evaluate the efficacy and safety of different doses of low molecular weight heparin (LMWH) used for long-term treatment of venous thromboembolism.

Searching
MEDLINE, EMBASE, BIOSIS Previews, PASCAL, Cochrane Central Register of Controlled Trials (CENTRAL) and American Society of Hematology and American Society of Clinical Oncology abstract databases were searched from 1990 onwards. Search terms were reported. Reference lists of reviews and abstracts from recent meetings were screened. ClinicalTrials.gov was searched. The end search date appeared to be before March 2008.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared the effects of long-term treatment with LMWH versus vitamin K antagonists in patients with objectively diagnosed symptomatic deep vein thrombosis (DVT) or pulmonary embolism. Studies had to assess recurrent venous thromboembolism or major bleeding.

Studies evaluated LMWH in varying doses that were classified in the review as full, intermediate and prophylactic doses; no details were reported of doses used to classify doses. Most LMWH arms continued long-term treatment with enoxaparin; other studies used dalteparin, nadroparin, tinzaparin or bemiparin. The reduction from full LMWH dose ranged from zero to 50% or more.

In about half of the studies, initial treatment (range five to 10 or more days) in vitamin K antagonist treatment arms was with unfractionated heparin; the other studies commenced with LMWH. Most studies used warfarin as the vitamin K antagonist drug; other studies used acenocoumarol or phenprocoumon. Studies were conducted in patients with and without cancer; where reported, the proportion of patients with cancer ranged from 3.8% to 100%. Most studies used venography to diagnose DVT and pulmonary angiography and used ventilation perfusion lung scan and helical computed tomography to diagnose pulmonary embolism.

Two reviewers independently selected studies.

Assessment of study quality
The authors did not state that they assessed validity. Presence of blinded assessment of outcome was reported in tables.

Data extraction
Numbers of patients with recurrent symptomatic venous thromboembolism were extracted and used to calculate relative risks (RR) with 95% confidence intervals (CI). Data were analysed on an intention-to-treat (ITT) basis.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Patients with and without cancer were analysed separately. Studies were also grouped by intensity of LMWH dose (full,
intermediate and prophylactic). Pooled relative risks with 95% CIs were calculated using a random-effects model. Heterogeneity was assessed using the $I^2$ statistic. Data were analysed during active treatment and during follow-up after the end of treatment.

**Results of the review**

Seventeen RCTs were included (n=4,002 patients). Where reported in tables, follow-up duration ranged from three to nine months. All of the studies were open. In 10 studies the outcome assessment was blinded. Unless otherwise stated, no significant heterogeneity was found.

**Patients without cancer:** (nine studies, n=1,957)

There was no significant difference between LMWH and vitamin K antagonists in recurrent venous thromboembolism for any dose of LMWH (nine studies), full doses of LMWH (five studies, n=1,391) and prophylactic doses of LMWH (significant heterogeneity, $I^2=73$%; four studies, n=566). There was a non-significant trend towards a lower risk of recurrent symptomatic venous thromboembolism from end of treatment to one year in LMWH compared to vitamin K antagonist treatment groups (RR 1.46, 95% CI 0.96 to 2.23; nine studies)

**Patients with cancer:**

At the end of the assessment period, compared to vitamin K antagonists, there was a significant reduction in recurrent venous thromboembolism associated with full doses of LMWH (RR 0.37, 95% CI 0.19 to 0.74; three studies, n=304) and intermediate doses of LMWH (RR 0.52, 95% CI 0.35 to 0.79; three studies, n=880). There was no significant difference in recurrent venous thromboembolism between vitamin K antagonists and prophylactic doses of LMWH (four studies, n=138).

From the end of treatment to one year, there was no significant difference in risk of recurrence of venous thromboembolism between vitamin K antagonists and full doses of LMWH (9.5% versus 1.6%; three studies, n=252) and between vitamin K antagonists and prophylactic doses of LMWH (7.4% versus 12%; two studies, n=52). The authors stated there was a trend towards a lower risk of recurrent venous thromboembolism with full compared to prophylactic LMWH treatment from the end of treatment to follow-up, but presented no details.

**Major bleeding:**

All doses of LMWH combined were associated with a significant reduction in the risk of major bleeding compared to vitamin K antagonists (RR 0.58, 95% CI 0.35 to 0.97; 13 studies, n=3,023). There was no significant difference between vitamin K antagonists and full doses of LMWH (9.5% versus 1.6%; three studies, n=252) and between vitamin K antagonists and prophylactic doses of LMWH (7.4% versus 12%; two studies, n=52). The authors stated there was a trend towards a lower risk of recurrent venous thromboembolism with full compared to prophylactic LMWH treatment from the end of treatment to follow-up, but presented no details.

For patients with cancer, there was no significant difference in rates of major bleeding between vitamin K antagonists and full doses of LMWH (four studies), between vitamin K antagonists and intermediate doses of LMWH (significant heterogeneity $I^2=64$%; three studies) or between vitamin K antagonists and prophylactic doses of LMWH (three studies). Indirect comparison found no significant difference between full and prophylactic doses of LMWH.

Results for recanalisation were reported.

**Authors' conclusions**

Full-dose LMWH treatment for three to six months was as safe as intermediate and prophylactic doses for long-term treatment of deep vein thrombosis. In patients with cancer, there appeared to be an excess of recurrence of venous thromboembolism after treatment with prophylactic doses that did not occur with full therapeutic dose.

**CRD commentary**

The review question was stated. Inclusion criteria were appropriately defined. Several relevant sources were searched and attempts were made to minimise publication bias. It was unclear whether attempts were made to minimise language bias. Study validity assessment appeared to be limited to blinding and this made it difficult to judge the reliability of the results. Methods were used to minimise reviewer errors and bias in the selection of studies; it was unclear whether
similar steps were taken during data extraction. Appropriate methods were generally used for the meta-analyses. Heterogeneity was assessed. No comment was made about significant heterogeneity even when studies showed different directions of treatment effect (as in the analysis of prophylactic LMWH doses in cancer patients). It was unclear whether the decision to analyse cancer and non-cancer patients separately was made in advance. It was unclear what percentage of the cancer group definitely had cancer. No explicit criteria for the classification of LMWH doses as full, intermediate and prophylactic were reported. Some evidence about patients with cancer was based on a small number of patients and an even smaller number of events and so may not be reliable. Findings about the relative efficacy of different doses of LMWH were based on indirect comparisons and it was unclear whether assumptions that underlay the validity of such comparisons were met. These last two potential limitations were discussed by the authors.

Evidence was based on indirect comparisons of full, intermediate and prophylactic doses of LMWH. The indirect comparison combined with an inadequate assessment of study quality and small numbers of events for some analyses mean that the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further studies were required to directly compare the efficacy and safety of different doses of LMWH for long-term treatment of DVT.

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