Efficacy of low-molecular-weight heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials

Louzada ML, Majeed H, Wells PS

CRD summary
This review assessed the efficacy of low molecular weight heparin compared to Vitamin K antagonists for long-term treatment of cancer-associated venous thromboembolism in adults and found that low molecular weight heparin was the superior treatment. Based on the evidence, the authors’ conclusions and recommendation for further research appeared reliable.

Authors' objectives
To ascertain the efficacy and safety of long-term secondary thromboprophylaxis with low molecular weight heparin (LMWH) therapy compared to Vitamin K antagonists (VKAs) in adult cancer patients with an acute venous thromboembolic event.

Searching
MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and SIGLE were searched from inception to first quarter 2008. Handsearches of relevant journals and conference proceedings (American Society of Clinical Oncology, ASCO, and American Society of Hematology, ASH, 2001 to 2007) were carried out. Reference lists were reviewed to identify additional studies. Language was restricted to English, French, Portuguese or Spanish. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared long-term (>10 days) secondary thromboprophylaxis with LMWH with VKA in adult (≥18 years old) patients with cancer-associated thrombosis were eligible for inclusion. Patients needed to have an active or newly diagnosed malignancy, symptomatic venous thromboembolism (deep venous thrombosis (DVT), pulmonary embolism or both) and objectively proven (confirmed by imaging techniques) proximal or distal DVT or pulmonary embolism. Studies were excluded if they compared short-term (five to 10 days) LMWH with unfractionated heparin or other controls. Eligible studies needed to report on or more of the following outcome measures during anticoagulation treatment: rate of recurrent venous thromboembolism (primary outcome measure); major (as defined by International Society of Thrombosis and Haemostasis criteria) and minor bleeding and mortality.

Most included studies were multicentre. Participant mean age ranged from 50 to 66 years. Most studies included adult patients with cancer and an acute symptomatic venous thromboembolism. One study included patients with and without cancer. Participant baseline characteristics were similar across studies. Where reported, 89% of the patient population had solid tumors at venous thromboembolism presentation and 60% had metastatic disease. Reported outcomes included recurrent venous thromboembolism, major and minor bleeding and mortality. Included studies compared different doses of LMWH (enoxaparin, dalteparin, tinzaparin, nadroparin) to VKA (warfarin or acenocoumarol) for secondary prophylaxis of cancer-associated venous thromboembolism. All studies had VKA Target International Normalised Ratio (INR) of 2.0 to 3.0. Where reported, treatment duration was three or six months and total follow-up ranged from six-months to one year.

Two reviewers independently selected studies for inclusion in the review. Any disagreements were resolved through discussion and with the help of a third reviewer.

Assessment of study quality
Study quality and risk of bias were assessed according to Cochrane Collaboration Cochrane Handbook for Systematic Reviews of Interventions and focused on randomisation, blinding and completeness of follow-up.
Two reviewers independently assessed study validity. Any disagreements were resolved through discussion and with the help of a third reviewer.

**Data extraction**
Outcomes of interest were extracted independently by two reviewers in the intention-to-treat format.

**Methods of synthesis**
The pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated using fixed-effect and random-effects models. Intention-to-treat and per protocol analyses were carried out. Heterogeneity was assessed using the Cochrane Q ($\chi^2$) test.

**Results of the review**
Five open-label RCTs (n=1,158) were included in the review.

Type of randomisation (sequence generation and allocation concealment) was clear in two studies. Allocation concealment was clear in three studies. Outcome assessment was open in all trials. Three studies reported use of a blinded adjudication committee for evaluation of outcomes. All five trials reported withdrawals and drop outs; one study had a withdrawal/termination rate of 52%. Intention-to-treat analysis was reported adequately in two studies. In all, three of the five studies were considered to have a high methodological quality. Sample sizes ranged from 35 to 676 participants.

LMWH significantly reduced risk of venous thromboembolism recurrence (RR 0.53, 95% CI 0.36 to 0.76; n=1,158 participants) compared to VKA. Heterogeneity was not observed. Studies that evaluated anticoagulation for six months showed significant statistical evidence in favor of LMWH; the three-month therapy was not statistically significant. There was no statistically significant difference between LMWH and VKA in risk of a major bleeding event (five studies, n=1,158 participants) or minor bleeding events (four studies, n=1,012 participants) or all-cause mortality (three studies, n=1,022 participants). All results were similar for fixed-effect and random-effects models.

**Authors' conclusions**
Long-term use of LMWH (regardless of the preparation) appeared to be an effective and safe treatment for secondary prevention of venous thromboembolism for adult cancer patients.

**CRD commentary**
This review had clearly focused inclusion and exclusion criteria in terms of study design, participants, interventions, comparisons and outcomes. The authors searched relevant databases and efforts were made to identify additional studies by handsearching relevant journals and conference proceedings. Language was restricted to English, French, Portuguese or Spanish; therefore, language bias could not be ruled out. Appropriate measures to minimise reviewer bias and error were taken at all stages of the review process. Methodological quality of included studies was formally assessed and reported. Appropriate methods were used to pool results and assess statistical heterogeneity. The authors recognised methodological weaknesses of included studies with regard to attrition bias due to high withdrawal rates for one study and that two studies were underpowered for the primary outcome. The findings of the meta-analyses were driven by one study. Sensitivity analyses were not carried out. Given the level of evidence presented, the authors' conclusions and recommendation for further research appeared reliable.

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**Implications of the review for practice and research**
**Practice:** The authors stated that long-term use of LMWH after the acute first week of treatment was better than VKAs for secondary prevention of venous thromboembolism in adult cancer patients.

**Research:** The authors stated that there was a need for further research to ascertain the ideal length of time for
anticoagulation, the most effective therapeutic approaches for different types and stages of malignancy and to evaluate subsets of cancer patients for variation in susceptibility for venous thromboembolism.

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