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Low molecular-weight heparin is better than warfarin for prevention of recurrent venous thromboembolism in cancer patients

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ABSTRACT A critical appraisal and clinical application of Lee AYY, Levin MN, Bake RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146-153. doi: [10.1056/NEJMoa025313](https://doi.org/10.1056/NEJMoa025313)

Keywords: *low-molecular-weight heparin versus warfarin, cancer, recurrent venous thromboembolism, anticoagulation*

Clinical Context

A 56-year-old female with stage IVa squamous cell cancer of the base of the tongue and supraglottic larynx s/p tracheostomy and undergoing chemotherapy and radiation treatment presented with throat pain, hemoptysis, and decreased oral intake. Patient was diagnosed with unprovoked bilateral upper extremity DVTs prior to her cancer diagnosis (1 month ago) and had been taking warfarin (Coumadin) for the past 3 months. Warfarin was held inpatient in the setting of hemoptysis; however, after hemoptysis resolved, patient was instead discharged home on enoxaparin (Lovenox), a low-molecular-weight heparin, for continued anticoagulation instead of being started back on her home dose of warfarin.

Clinical Question

Is low-molecular-weight heparin better than warfarin in preventing recurrent venous thromboembolism in patients with cancer?

Research Article

Lee AYY, Levin MN, Bake RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146-153. doi: [10.1056/NEJMoa025313](https://doi.org/10.1056/NEJMoa025313)

Literature Review

A literature review was performed using PubMed containing the keywords “low-molecular-weight heparin versus warfarin” and “cancer” yielding 23 articles. Studies that did not address the clinical question were excluded. The search was continued using Cochrane Library to identify sources of primary literature that examined the use of long-term anticoagulants for secondary prevention of recurrent venous thromboembolism in active cancer patients.

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Four randomized controlled trials (RCTs) were identified that focused on comparing recurrent venous thromboembolic events (VTEs) and complications in cancer patients assigned to either low-molecular-weight heparin or warfarin following an acute thromboembolic event. Two of the four studies showed that low-molecular-weight heparin reduced the rate of recurrent venous thromboembolic events without increasing the mortality and bleeding risk^{1,2}, while the other two did not show a statistically significant difference in outcomes^{3,4}, likely due to the small number of enrolled patients. A meta-analysis was also found⁵ that found a statistically significant decrease in recurrent VTE, without any statistical increase in adverse events. This meta-analysis did not reveal any RCTs that had been missed by the PubMed search.

Ultimately, the CLOT (Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study by Lee et al. was chosen for critical appraisal because it had the largest sample size (N=676) of the four studies. This study is the largest identified in the Noble meta-analysis⁵ and is in concordance with the overall result of that meta-analysis.

Critical Appraisal

This research article would fall into the Level 1b levels of evidence category according to the Oxford Centre for Evidence-based Medicine because it is an individual RCT with a narrow confidence interval. It was a multi-center study with participation from forty-eight clinical centers in eight countries and had the largest sample size compared to other randomized controlled studies. However, this study was not blinded, due to the need for monitoring secondary to the high risk of drug interactions and complications caused by the drug therapies studied, and introduces bias which must be recognized. Patients and physicians aware of their allocation may behave differently if they know they are on certain therapies (performance bias). Physicians and patients may also have heightened awareness of outcomes, or more diligently look for them, if they are aware of patient allocation (detection bias).

The research article clearly describes the study population – adult patients with active cancer and newly diagnosed symptomatic proximal DVT, PE, or both – and further defines these requirements along with a list of exclusion criteria. The follow-up period of 6 months was appropriate, although the article did not indicate how many patients were lost to follow-up. All clinically relevant outcomes were reported with all other study patients accounted for and patients analyzed to groups to which they were randomized. The number needed to treat for prevention of one recurrent VTE in cancer patients on low-molecular-weight heparin versus warfarin based on this study's result is 13.

The results of the primary outcome measured – the first episode of objectively documented, symptomatic, recurrent DVT, PE, or both – showed that out of the 53 of 336 patients on oral anticoagulant that had recurrent venous thromboembolism, 20 occurred when the INR was below 2.0. The target therapeutic INR goal set in the study was 2.5 and so almost half of the recurrent VTEs in the oral anticoagulant treatment arm could have been due to sub-therapeutic INRs. The INR was within therapeutic range about 46% of the time, which is typical of warfarin therapy. This represents a weakness of warfarin therapy.

Very concerning is the high possibility of publication bias as the study was funded by Pharmacia. Pharmacia not only provided the study drug but also had a representative participate as a committee member overseeing the study, interpreting the data, and preparing the manuscript. It is possible that data was collected beyond 6 months but was not published if the outcome was not favorable for the sponsor of the study drug. One way to mitigate publication bias is to undergo a pre-registration of the clinical trial, but this was not done in this case.

Lastly, though the study drug was administered at home whenever possible and could have affected the results of the study due to either non-compliance or over-adherence; it closely mirrors outpatient care and real patient compliance situations. The therapeutic maneuver is feasible in everyday practice and study patients were generalizable to patients with active cancer and new DVTs, PEs, or both concerned with future recurrences. Though dalteparin was the low-molecular-weight heparin used in this study, other studies have shown that enoxaparin also reduces the number of recurrent VTEs in cancer patients³⁻⁴, though no studies directly comparing the two in terms of efficacy or survival benefit in this patient population have been done and should be studied in the future.



Clinical Application

Patients diagnosed with cancer are in a more hypercoagulable state and are not only at an increased risk for DVTs and PEs and bleeding complications than patients without malignancy, but also have a higher risk of recurrent thrombosis despite anticoagulation treatment⁶. Many meta-analyses and systematic reviews have shown that low-molecular-weight heparin is preferred over the unfractionated heparin for initial therapy and preferred over warfarin for longer-term anticoagulation⁷, even in those with advanced cancer⁵.

For our patient who was initially started on standard treatment to prevent recurrent thrombosis and was kept on her warfarin despite being diagnosed with cancer, our team's decision to switch her to the low-molecular-weight heparin was one backed with evidence and seen often in clinical practice. In addition to its increased efficacy in preventing recurrent VTEs with similar rates of bleeding complications, the need to swallow the oral anticoagulant, warfarin, was not as desirable as an injection of the low-molecular-weight heparin in the setting of throat pain and decreased oral intake.

Three take-home points are:

- 1.) Patients with a malignancy diagnosed with a DVT, PE, or both should be managed long-term with low-molecular-weight heparin instead of warfarin.
- 2.) For our future careers, we should always keep in the mind that patients with malignancies may have different treatment guidelines and/or therapies due to their complex diagnosis, co-morbidities, and medication regimen (chemotherapeutic agents, etc.). It is important, therefore, as physicians to determine what is best for our patient on an individual basis without always automatically assuming standard of care therapies.
- 3.) Medication reconciliation is important. In this case, the patient was continued on her warfarin despite her new cancer diagnosis and ended up presenting to the emergency department with hemoptysis. Always re-evaluate the overall clinical picture when patients come in with new clinical concerns or diagnoses.

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