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The role of low-molecular-weight heparin in cancer patients with acute venous thromboembolism and how it improves outcomes are discussed.

Treatment of Venous Thromboembolism in Cancer Patients

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Introduction

Venous thrombus embolism (VTE) is a serious complication in patients with cancer. Most often, multiple factors contribute to the development of a thrombus and its complications. While the annual incidence of thrombosis in the general population is low — approximately 1 in 1,000, with an increased risk positively associated with age — patients with a malignancy can have a 4- to 6-fold greater risk of thrombosis.¹⁻³ Furthermore, cancer

patients are at increased risk of recurrent VTE and anti-coagulant-associated bleeding compared with noncancer patients.^{4,5} These poor outcomes also may partially explain why cancer patients with thrombosis have a shorter life expectancy than cancer patients without this complication.^{6,7} The occurrence of VTE worsens the quality of life of cancer patients and adds to the management challenges faced by physicians who treat these patients because a thrombotic event may delay, interrupt, or completely halt the cancer therapy.

Current standard treatment for a VTE includes an initial therapy consisting of either a low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for at least 5 to 7 days. At the same time, long-term treatment is initiated with warfarin (Coumadin®, Bristol-Myers Squibb Co, New York, NY), a vitamin K antagonist. For most patients, the minimum duration for long-term therapy is usually 3 to 6 months. This standard treatment regimen is effective for many patients. However, managing thrombosis in patients with malignancy is more complicated for several reasons, including comorbidities, concurrent medications, and increased age of the population.^{8,9} Many of these factors can influence both the anticoagulant effect and pharmacokinetic properties of antithrombotics. Furthermore, recent literature suggests a different response to treatment in cancer patients with higher rates of recurrent thromboembolism and hemorrhagic complications compared with noncancer patients.^{4,5} Those recent observa-

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Abbreviations used in this paper: VTE = venous thrombus embolism, LMWH = low-molecular-weight heparin, UFH = unfractionated heparin, INR = international normalized ratio.

tions are prompting efforts to investigate the overall safety and efficacy of current therapy options to define the optimal treatment strategy specifically for the cancer patient population. It is against this background that this review focuses on the treatment of VTE by examining present treatment options, evidence specific to LMWH therapy, and recommendations from the recent American College of Chest Physicians (ACCP) guidelines based on published evidence.¹⁰

Initial Therapy: UFH Versus LMWHs

Treatment decisions for an episode of VTE are based on a combination of the overall safety, efficacy, and convenience of available agents. Of the two treatment options for initial treatment, LMWH therapy provides an advantage over UFH for use in cancer patients based on convenience — and likely with respect to safety and efficacy.¹¹

A comparison from a strictly biochemical or pharmacologic perspective favors LMWHs because of a number of unique properties that make them clinically easier to use. For instance, UFH binds more avidly than LMWHs to plasma proteins, platelets, and endothelial cells. Consequently, the anticoagulant effect of UFH is less predictable than LMWHs, according to dose.¹² In addition, LMWHs have a dose-independent renal clearance in contrast to UFH, which is cleared by the kidneys as well as the reticuloendothelial system by both dose-dependent and independent mechanisms.¹² LMWHs also have very good bioavailability after subcutaneous injection at various doses, whereas UFH has very poor bioavailability in small doses.¹² These properties, combined with a longer half-life, allow for LMWHs to be given as once-daily or twice-daily subcutaneous injections. The dose is based on the patient's weight, and routine laboratory monitoring is not required. LMWHs are also associated with a lower risk of heparin-induced thrombocytopenia compared with UFH.¹³ This is important in cancer patients in whom thrombocytopenia is already a frequent problem. Overall, the unique pharmacokinetic profiles of LMWHs allow for patients to be treated entirely on an outpatient basis, as opposed to the pharmacokinetics of UFH, which require in-hospital treatment and administration of an intravenous infusion.

The safety and efficacy of LMWHs in comparison to UFH have been assessed based on two outcome indicators: risk of major bleeding and risk of recurrent thrombosis. Results from a recent meta-analysis published in the Cochrane Database of Systematic Reviews¹¹ showed both a lower risk of recurrent thrombosis and a lower risk of major bleeding in patients who received LMWHs over UFH. The odds ratio for recurrent VTE was 0.68 (95% confidence interval [CI] 0.55-0.84) and for major bleeding was 0.57 (95% CI 0.39-0.83) in favor of LMWHs. Furthermore, a summary of results from four large randomized trials

Table 1. — Combined Results of 3-Month Recurrence Rates of VTE from Randomized Trials Comparing LMWH and UFH for Initial Therapy

	No. of Patients	LMWH	UFH	P Value
Cancer patients	546	9.15%	9.16%	NS
Noncancer patients	2,275	3.95%	4.23%	NS
From references 14-18.				

points to no difference in the VTE recurrence rates in both the cancer and noncancer populations with respect to whether these patients initially received LMWH therapy or UFH therapy (Table 1).¹⁴⁻¹⁸ However, the results of that analysis also show that cancer patients overall had a 2- to 3-fold risk of recurrent thrombosis despite using the optimal standard regimen. Given that no significant difference in efficacy was identified between LMWHs and UFH for initial therapy, the differences in outcomes between patients with and without cancer are likely attributable to differences in patients' responses to long-term therapy.

Long-Term Therapy: LMWH Versus Oral Anticoagulants

The standard long-term treatment consists of warfarin, a vitamin K antagonist, for a minimum duration of usually 3 to 6 months — with the exception of patients with metastatic cancer, in whom anticoagulant therapy is recommended indefinitely. Although warfarin therapy demonstrates good efficacy in noncancer patients, its performance is inadequate in patients with malignancy. Specifically, trials have shown that cancer patients — compared with noncancer patients, both groups treated with warfarin — have a 3-fold higher risk of recurrent thrombosis and a 2- to 6-fold greater risk of major bleeding.^{4,5} Furthermore, unlike noncancer patients, whose risk of bleeding plateaus over time, the risk of bleeding in patients with malignancy increases over time despite controlling for the international normalized ratio (INR).⁴

Warfarin has several limitations that may contribute to its low efficacy and safety as a long-term prophylaxis in the cancer patient population. Drug interactions, malnutrition, gastrointestinal disturbances, and liver dysfunction in cancer patients are factors that can alter anticoagulant levels.¹⁹ Warfarin dose adjustment is also complicated because it has a delayed onset of action and a prolonged period of clearance. As a result, there are often long periods of time when patients will not be adequately anticoagulated because warfarin must often be withheld for episodes of thrombocytopenia or when invasive procedures are necessary. Furthermore, cancer patients have poor venous access, making necessary routine laboratory monitoring more difficult. However, even if these logistical problems are overcome, the best-managed patients with malignancy treated with warfarin still have a higher

risk of VTE recurrence and bleeding compared to individuals without cancer.^{4,5}

As an alternative to warfarin and other oral anticoagulants, physicians now have the option of using LMWHs for long-term treatment of thrombosis. Pharmacologically, LMWHs have several distinct advantages over warfarin. For instance, LMWHs do not require routine monitoring, the dose is based on the patient's weight, and there are few if any interactions with other drugs. In addition, LMWHs can accommodate rapidly for needed invasive procedures or thrombocytopenia because of their rapid onset of action and predictable clearance. In terms of the safety and efficacy of LMWHs in comparison to vitamin K antagonists in cancer patients, however, the results from recent studies have varied among individual LMWHs.^{20,21}

Canthanox Trial

The Canthanox trial was one of the first published studies that compared a LMWH with warfarin in cancer patients.²¹ This study utilized a multicenter open-label, randomized trial design wherein cancer patients with confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or both were randomized to one of two intervention arms. The treatment options consisted of therapy with either enoxaparin (Lovenox®, Sanofi-Aventis, Bridgewater, NJ) once a day alone for 3 months or enoxaparin given once a day for a minimum of 5 to 7 days followed by warfarin (targeted INR 2-3) for a total of 3 months. Unfortunately, the study ended prematurely with a sample size of only 147 participants due to difficulty with enrollment. The limited data, however, suggested no difference in efficacy between enoxaparin and warfarin but a trend for a higher risk of bleeding among patients treated with warfarin therapy.

CLOT Trial

A second study that was successful at providing a definitive answer to whether a LMWH is more efficacious than warfarin therapy was the CLOT study (Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer).²⁰ This trial was a multicenter open-label, randomized study in which cancer patients with symptomatic, objectively confirmed DVT, PE, or both were randomized to two possible intervention arms. The initial therapy for both groups was dalteparin (Fragmin®, Pfizer Inc, New York, NY) followed by either warfarin therapy in the standard treatment group or by continued dalteparin in the experimental treatment group. The long-term treatment in this study lasted 6 months.

The patients randomized to the standard treatment received dalteparin at a therapeutic dose of 200 IU/kg

once daily for 5 to 7 days, followed by 6 months of warfarin therapy or acenocoumarol, a vitamin K antagonist used in Europe. Patients randomized to the experimental LMWH group also received dalteparin 200 IU/kg once a day for the entire first month. For the remaining 5 months of the study, the patients received 75% to 80% of the initial dose. Multidose vials were used for initial therapy, but prefilled syringes were used during the long-term treatment to enhance patient compliance and reduce dosing errors.

The unique dosing regimen of dalteparin was based on empiric observations and the rationale that the highest risk of VTE recurrence occurs within the first month after diagnosis, while the risk for major bleeding continues throughout anticoagulant treatment. Earlier studies that used a lower dose of dalteparin for 3 months or longer in patients with acute VTE found no difference in efficacy or bleeding between dalteparin and warfarin.²²

The primary outcome event for the study was objectively documented symptomatic recurrence of DVT, PE, or both. Patients who were asymptomatic or found to have an incidental extension of their DVT or PE were not included in the end point. Other major secondary outcomes for the study were major bleeding, all bleeding, and death.

A total of 27 patients out of 336 randomized to dalteparin vs 53 out of 336 randomized to warfarin developed a recurrent thrombotic event during the 6-month treatment period. DVT constituted the majority of the recurrent events, reflecting the fact that patients who have DVT tend to develop recurrent DVT and that patients who have PE initially tend to recur with PE.

A Kaplan-Meier plot (Fig 1) of the probability of recurrent thrombosis for the two groups shows a distinct separation starting within the first month of therapy —

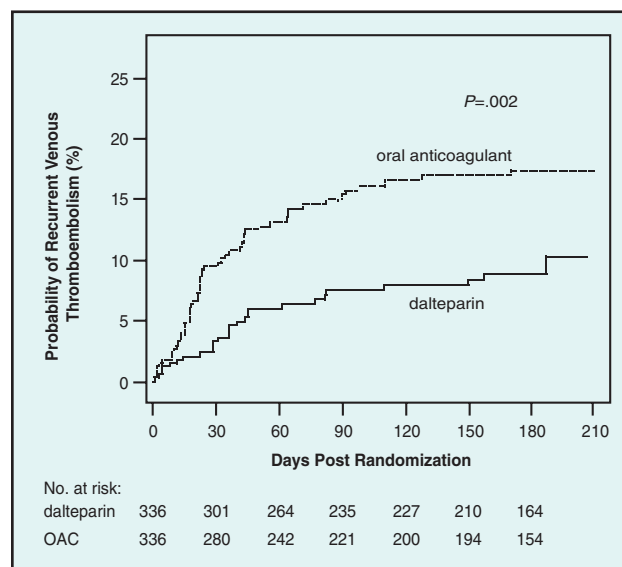


Fig 1. — Probability of recurrent VTE in patients with cancer. From Lee A, Levine M, Baker R, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146-153. Copyright© 2003 Massachusetts Medical Society.

the period of highest risk — between the two treatments that persisted throughout treatment. Over the 6-month period, a risk reduction of 52% was observed in favor of dalteparin ($P=.002$). At 6 months the probability of recurrence was 17% in the oral anticoagulant patients that was reduced to 9% in the dalteparin arm. An assessment of the INR at the time of recurrence suggested that cancer patients developed recurrent thrombosis despite adequate therapeutic treatment with warfarin. Also, there was no difference in bleeding between dalteparin and oral anticoagulant groups. A review of the INR results suggests that there was no association between INR and major risk of bleeding. This has been consistent with previous findings.^{4,5}

A subsequent post-hoc analysis performed on survival data from the CLOT trial provides interesting information on the potential impact of dalteparin on survival in cancer patients.²³ Results indicated no difference in the overall survival between the dalteparin and oral anticoagulant treatment groups, but a significant difference in survival rates between the experimental and standard treatment groups was seen in the subgroup of patients without metastatic malignancy (Fig 2). The probability of death at 12 months was 20% in the dalteparin group compared with 36% for the oral anticoagulant group in the subgroup of patients without metastatic disease (hazard ratio, 0.50; 95% CI, 0.27-0.95; $P=.03$). No difference in mortality was

found between treatments for the subgroup of patients with metastatic disease. Furthermore, the effects of dalteparin on survival were statistically significant between patients with and without metastatic disease ($P=.02$). A survival benefit in cancer patients with advanced disease has been reported for the LMWH nadroparin (Fraxiparine®, GlaxoSmithKline, Research Triangle Park, NC) in a randomized trial.²⁴ This drug has not been approved for use in the United States.

Overall, data from the CLOT trial provide compelling evidence that LMWH dalteparin is superior to warfarin with respect to efficacy and that it is equally safe in terms of bleeding for use as long-term treatment in patients with cancer and VTE. Given that the Food and Drug Administration considers LMWHs as distinct drugs that cannot be substituted for one another,²⁵ it should be recognized that the results from this landmark study are specific to dalteparin and should not be generalized to other LMWH agents. Furthermore, the CLOT study followed a specific dosing regimen that, although effective for dalteparin, cannot be assumed to be equally efficacious in other LMWHs. Finally, there is a lack of published data in support of other LMWHs as having similar outcomes as dalteparin in this clinical setting.

ACCP Guidelines and Recommendations

In the recently published seventh ACCP conference guidelines,¹⁰ the ACCP recognized the results of the CLOT study and recommended — for the prevention of recurrent thrombosis — treatment with LMWH dalteparin for 3 to 6 months for the majority of patients with DVT and cancer. Therefore, treatment with this LMWH should be considered as first-line therapy for long-term treatment in these patients after a primary thrombotic event. Of note, long-term therapy with LMWH was recently reported to be preferable to warfarin derivatives in cancer patients receiving palliative care.²⁶

Conclusions

Thrombosis in cancer patients is a significant problem that warrants attention by hematologists and oncologists. The population with cancer presents unique challenges due to various clinical factors that can affect the effectiveness and safety of antithrombotics. Recent evidence indicates that the optimal treatment strategy for this population includes LMWHs for the initial event and secondary prevention for a minimal duration of 6 months. The CLOT study provides the strongest data at present in this setting. Future research should focus on strategies to improve on the results seen within the CLOT study and to optimize treatment approaches in order to minimize complications and enhance long-term outcomes.

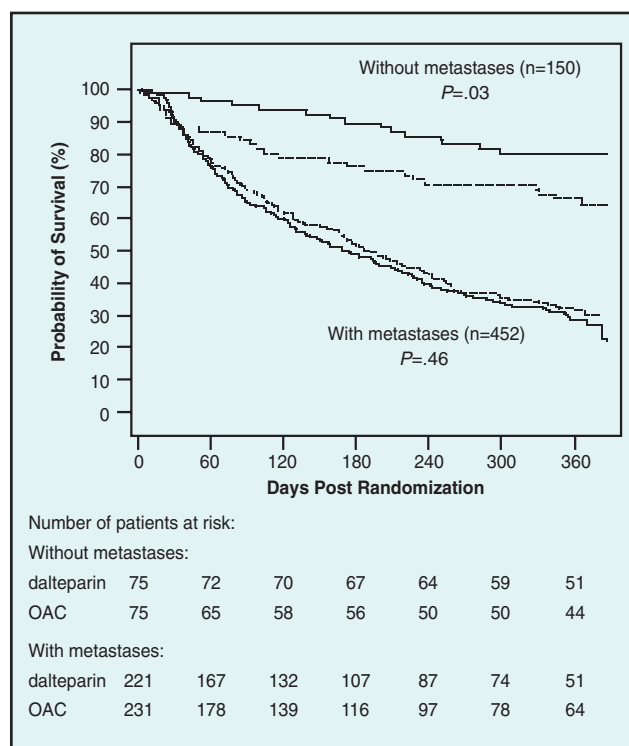


Fig 2. — Reduction in mortality in patients without metastases associated with dalteparin treatment for VTE. Solid line = dalteparin, dashed line = oral anticoagulant. From Lee AYY, Rickles FR, Julian JA, et al. Randomized comparison low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. *J Clin Oncol*. 2005;23: 2123-2129. Reprinted with permission of the American Society of Clinical Oncology.

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