



Jacky Tiplady. *Terry's Canoe*. Photograph.

Initial observations suggest that LMWH therapy may improve survival in patients with advanced malignancy, but further study is needed to confirm its efficacy.

Low-Molecular-Weight Heparin and Survival in Patients With Malignant Disease

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Introduction

It is well recognized that patients who develop thromboembolic disease, either at presentation with the first diagnosis of cancer or during the course of their malignancy, have a poor prognosis.^{1,2} Analysis of data from the Danish Cancer Registry by Sorensen et al¹ indicates that patients who presented with cancer and thrombosis had a poorer long-term survival rate than seen in those who were diagnosed with cancer alone. Furthermore, the data strongly suggest that the activation of blood coagulation associated with malignant disease may be responsible for more frequent episodes of recurrent and potentially fatal thromboembolism or that the generation of coagulation serine proteases in the peritumor environment may be related to an alteration in the tumor phenotype itself, possibly making the tumor more aggressive in certain char-

acteristics (eg, enhanced angiogenesis or tumor growth). In other words, the development of thrombosis may be indicative of an activated coagulation system that is affecting the tumor itself. To that end, it is possible that anticoagulants may play a role in affecting the outcomes in cancer patients and that low-molecular-weight heparin (LMWH) may influence survival in patients with malignant disease.

Meta-Analyses of Treatment Studies for Deep Vein Thrombosis

Retrospective meta-analyses of deep vein thrombosis (DVT) treatment studies³⁻⁶ have sparked an interest in the potential role of antithrombotic therapy in cancer survival. In those studies, patients were randomized to receive either intravenous unfractionated heparin (UFH) or subcutaneous LMWH for the treatment of thrombosis. Analyses of patient characteristics revealed that 10% to 15% of patients in these trials had thrombosis secondary to malignant disease. The results indicated that approximately 3 months after initial treatment of DVT, no significant difference was seen in mortality with LMWH compared to UFH in the majority of patients who had thrombosis without cancer. However, unplanned subgroup analyses of those trials suggest that cancer patients who received a short course of LMWH had a survival benefit compared with cancer patients receiving UFH (Table 1). That observation was

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Abbreviations used in this paper: DVT = deep vein thrombosis, UFH = unfractionated heparin, LMWH = low-molecular-weight heparin.

Table 1. — Meta-analyses of DVT Treatment Studies

Authors	Year	Number of Studies	Cancer Mortality		Odds Ratio
			UFH	LMWH	
Green et al ³	1992	2	21/67 (31%)	7/62 (11%)	Not available
Siragusa et al ⁴	1995	13	23/81 (28%)	10/74 (14%)	Not available
Hettiarachchi et al ⁵	1999	9	71/323 (22%)	47/306 (15%)	0.61
Gould et al ⁶	1999	11	38/147 (26%)	22/132 (17%)	0.57

consistent among several studies published during the 1990s.³⁻⁶ While the derived benefit differs slightly in each trial, the results consistently favor administration of LMWH over UFH to cancer patients.

Though the observations are promising, the meta-analyses have limitations: (1) the original DVT treatment trials were not designed to assess long-term cancer mortality and (2) data regarding the distribution of prognostic variables that might predict survival in cancer patients were lacking. To that end, four clinical trials have been conducted to study the possible survival benefit of LMWH in that patient population.

Clinical Trials

The FAMOUS Trial

Launched in 1995, the Fragmin Advanced Malignancy Outcome Study (FAMOUS) trial was the first randomized,

placebo-controlled, double-blind evaluation designed primarily to study the ability of LMWH to prolong survival in patients with advanced malignant disease.⁷ The study population was composed of 385 patients with advanced solid-tumor malignancy. Patients were randomized to receive either the LMWH dalteparin (Fragmin®, Pfizer Inc, New York, NY) at a dose of 5,000 units once daily or a normal saline placebo injection for 1 year or until death, whichever occurred first. The primary end point of the trial was 1-year mortality. On the basis of findings from previous retrospective analyses, sample size calculations were based on the assumptions that the mortality rate would be 50% in the placebo group and 35% in the LMWH group.

There were no significant differences between the two randomized populations in terms of prognostic variables such as age, sex, tumor type, degree of tumor differentiation, stage of disease, and prior or concurrent chemotherapy. At the prespecified mortality end point 12 months after randomization, the investigators were

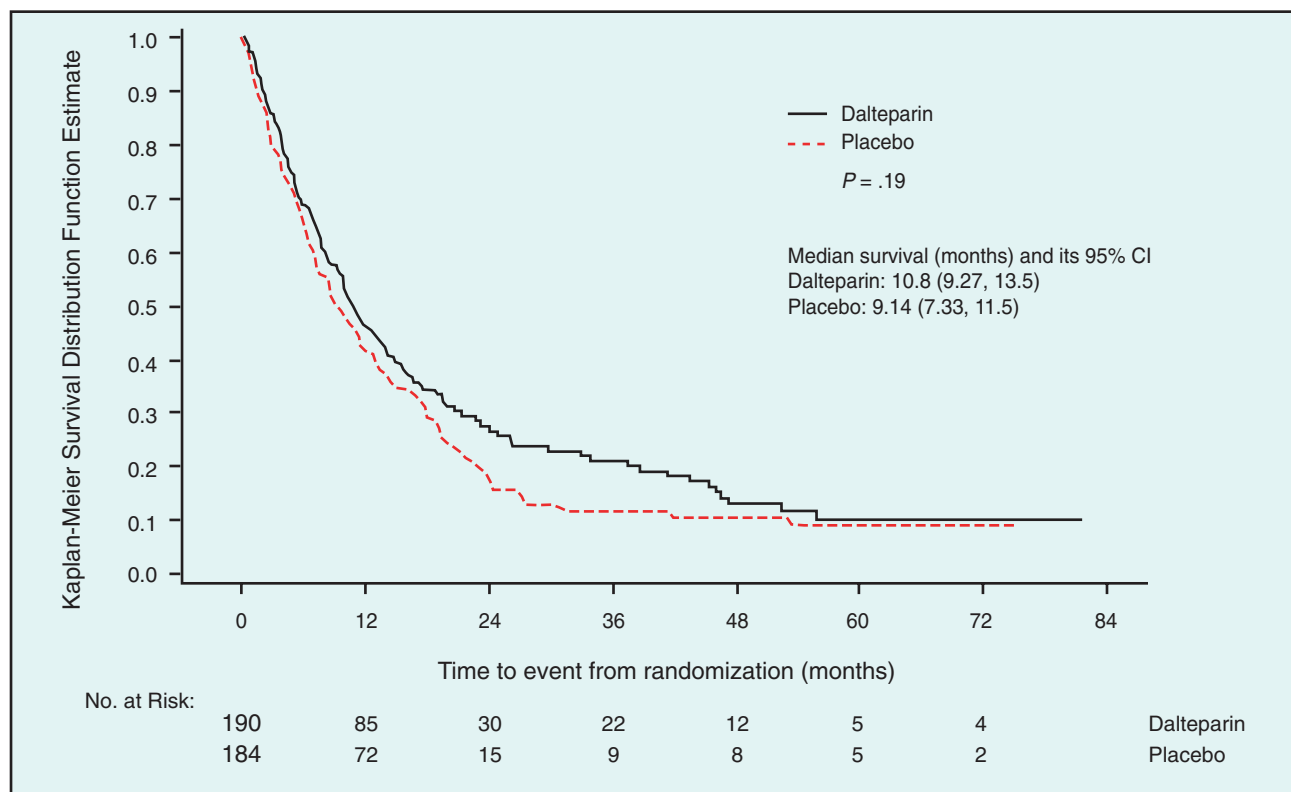


Fig 1. — The FAMOUS study: survival in the intent-to-treat population. From Kakkar AK, et al. Low molecular weight heparin therapy, with dalteparin, and survival in advanced cancer: the Fragmin Advanced Malignancy Outcome Study (FAMOUS). *J Clin Oncol.* 2004;22:1944-1948. Reprinted with permission from the American Society of Clinical Oncology.

Table 2. — The FAMOUS Study: Mortality Effect

Months After Randomization	Hazard Estimate		% Reduction
	Placebo	Dalteparin	
0 – 12	0.84	0.75	10
13 – 24	0.84	0.57	32
25 – 36	0.50	0.36	28

Data from Kakkar et al.⁷

unable to detect the 15% difference in mortality for which the study had been powered (Fig 1). Instead, the study demonstrated a 5% absolute increase in survival for patients randomized to receive LMWH compared with those receiving placebo (46% vs 41%, respectively). That observation would have been a clinically important result if the trial had been sufficiently powered to detect that difference, considering the fact that the study population consisted of patients with advanced, frequently metastatic cancer. Nevertheless, there appeared to be a persistent and increasing benefit for patients who received dalteparin compared with those given placebo, particularly in the period from 17 to 48 months after randomization. Estimated survival rates at 2 years were 27% and 18% for patients receiving dalteparin and placebo, respectively. Similarly, at 3 years after randomization, estimated survival was 21% with dalteparin compared with 12% with placebo (Table 2).

As part of the post-hoc analysis, the investigators examined survival rates for a group of patients defined as having a good prognosis — those surviving beyond 17 months (Fig 2). Median survival increased from 24 months with placebo to approximately 43 months with dalteparin. The post-hoc analysis would suggest there was a group of patients who might be sensitive to LMWH therapy in terms of prolonging survival. The survival curves would also suggest that the effects observed with chronic LMWH administration might be more biological than purely antithrombotic (ie, the prevention of potentially fatal thromboembolic events) based on the persistence of effects that appeared to increase beyond the period of active drug administration. However, definitive evidence from appropriately designed clinical trials is required.

The CLOT Trial

The CLOT trial (Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) by Lee et al⁸ was designed primarily to determine whether 6 months of LMWH therapy was more effective at preventing recurrent thromboembolic disease in cancer patients who presented with acute symptomatic venous thromboembolism compared with the standard treatment of 6 months with oral anticoagulant vitamin K antagonists. As part of the predefined analysis plan for this trial, the steering committee included a 1-year mortality analysis.

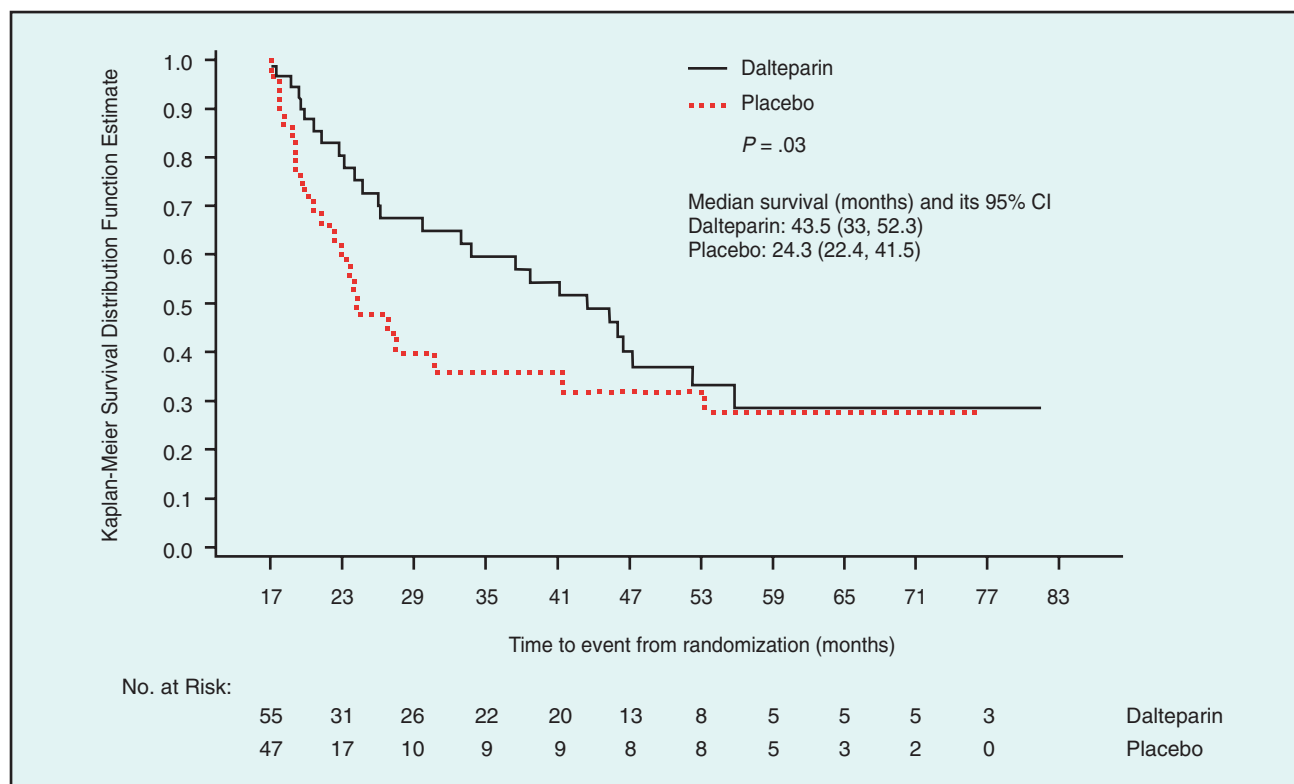


Fig 2. — The FAMOUS study: survival in patients with a good prognosis (surviving beyond 17 months after randomization). From Kakkar AK, et al. Low molecular weight heparin therapy, with dalteparin, and survival in advanced cancer: the Fragmin Advanced Malignancy Outcome Study (FAMOUS). *J Clin Oncol.* 2004;22:1944-1948. Reprinted with permission from the American Society of Clinical Oncology.

All patients in the CLOT trial received 5 to 7 days of dalteparin in full treatment doses. Thereafter, the dalteparin arm continued to receive dalteparin at full doses for 1 month followed by 75% of the full treatment dose for the remaining 5 months. The oral anticoagulant group, after its short course of dalteparin, received 6 months of vitamin K antagonist therapy with a target international normalized ratio of between 2 to 3.⁸

Survival analysis of the overall trial population failed to reveal a difference in 1-year survival rates between patients randomized to receive 6 months of dalteparin compared with those receiving oral anticoagulant therapy (Fig 3). However, in a subgroup analysis (defined a priori) there was a survival advantage at 1 year in the population of patients with a good prognosis (defined as those patients without evidence of metastasis at time of randomization) who received up to 6 months of LMWH. In this analysis, only 64% of patients receiving vitamin K antagonist therapy

survived the year, whereas 80% of patients in the dalteparin group were alive at that time point, thereby suggesting a survival benefit with LMWH therapy.

An analysis was conducted to further examine these data.⁹ There was a statistically significant difference in the Kaplan-Meier estimates of probability of death at 12 months in patients without known metastases — 20% in the group receiving dalteparin vs 36% in the group receiving oral anticoagulant therapy — with a hazard ratio of 0.50 (95% confidence interval [CI] 0.27-0.95; $P=.03$) in favor of dalteparin. When adjusted for baseline prognostic factors, the hazard ratio did not change significantly (0.41; 95% CI 0.19-0.86; $P=.02$). Due to the fact that there were fewer patients with lung cancer in the dalteparin group, the investigators excluded these patients and found that the hazard ratio still favored dalteparin (0.63; 95% CI 0.31-1.3; $P=.19$; adjusted hazard ratio 0.37; 95% CI 0.17-0.83; $P=.02$). In contrast, there was no significant difference in mortality for

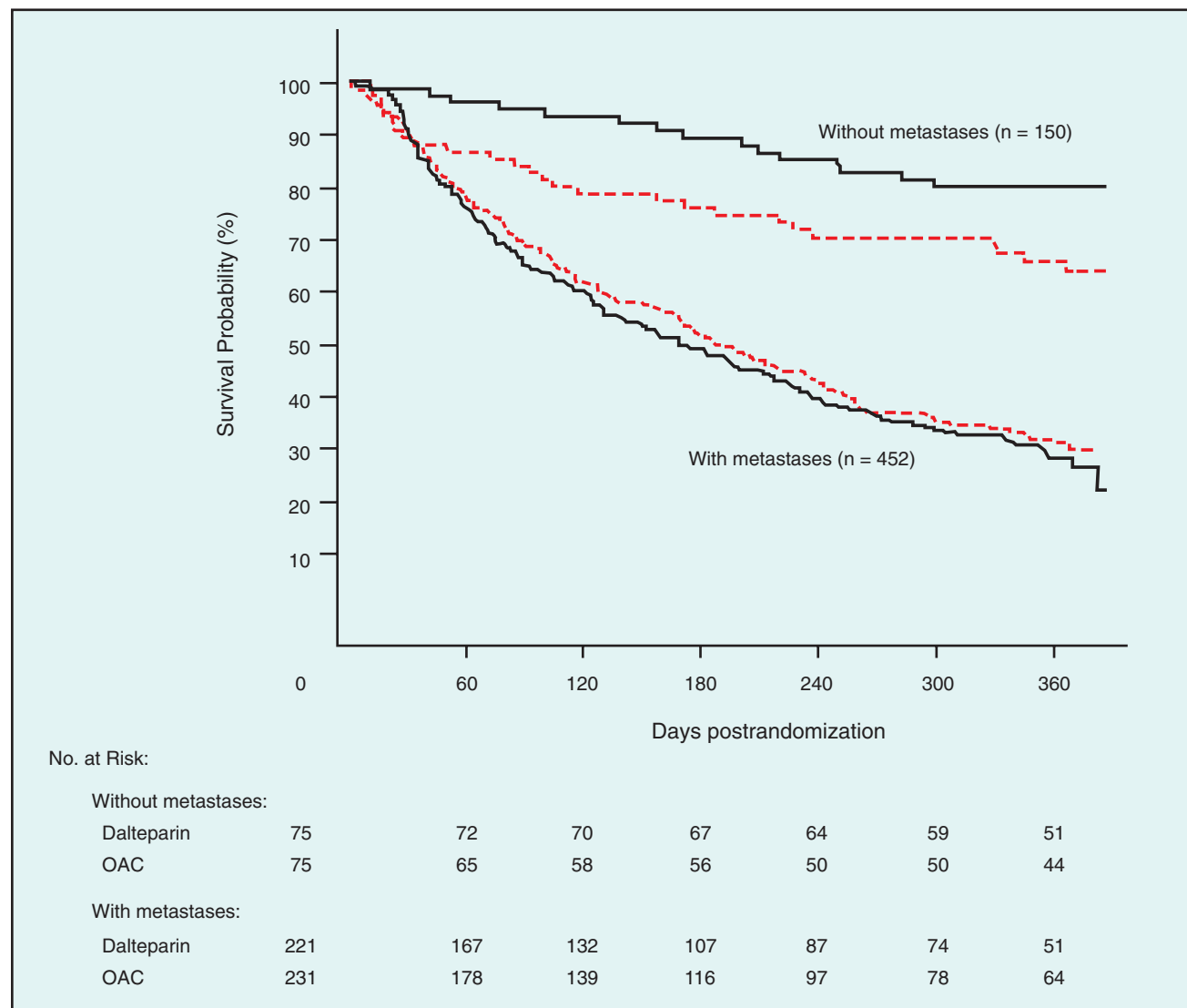


Fig 3. — The CLOT trial: survival in patients with solid tumors according to the presence or absence of metastatic disease. Dotted line: oral anticoagulant (OAC), solid line: dalteparin. From Lee AYY, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. *J Clin Oncol.* 2005;23:2123-2129. Reprinted with permission from the American Society of Clinical Oncology.

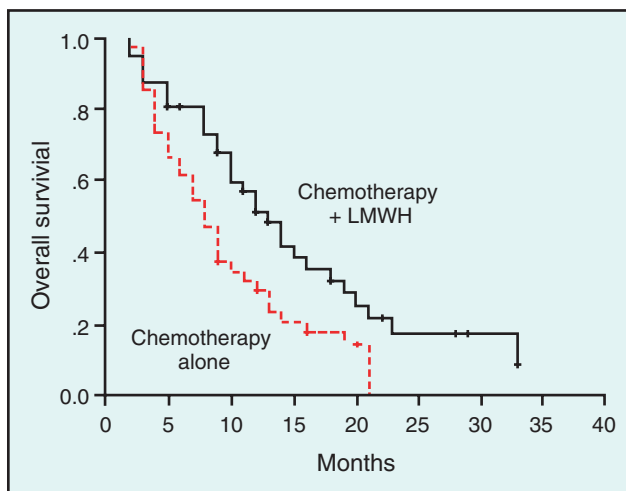


Fig 4. — The SCLC study: survival in the overall population. Adapted from Altinbas et al.¹⁰ Reprinted with permission.

patients with known metastases; the probability of mortality was 72% and 69% for the dalteparin and oral anticoagulant groups, respectively, and the hazard ratio was 1.1 (95% CI 0.87-1.4; $P=.46$). The authors found a statistically significant difference favoring dalteparin in the hazard ratios between the two subgroups in terms of presence or absence of metastatic disease ($P=.02$). As determined by regression analysis, there was a statistically significant treatment effect of 0.43 for dalteparin in patients without metastases (95% CI 0.21-0.89; $P=.02$). However, this effect was not apparent in patients with metastatic disease (treatment effect 1.1; 95% CI 0.91-1.4; $P=.24$). These data further support a positive impact of LMWH on survival in patients with cancer and support the concept also demonstrated in the FAMOUS study of patients with a better prognosis having a greater survival benefit.

Small-Cell Lung Cancer Trial

Altinbas et al¹⁰ conducted a randomized clinical trial in 84 patients with small-cell lung cancer. Patients in Turkey

Table 3. — Response to Therapy in Patients With Small-Cell Lung Cancer

Population	Response to Therapy (%)		P Value
	Chemotherapy Alone	Chemotherapy + Dalteparin	
Overall	42.5	69.2	.07
Limited disease	60.0	91.4	.02
Extensive disease	13.3	37.4	.59

Data from Altinbas et al.¹⁰

were randomized to receive a standard chemotherapy consisting of cyclophosphamide (Cytotoxan®, Neosar®, Bristol-Myers Squibb Co, New York, NY), epirubicin (Ellence®, Pfizer Inc, New York, NY), and vincristine (generic, multiple manufacturers) for 18 weeks either alone or in combination with dalteparin at a dose of 5,000 units once daily. Patients with limited disease who were responsive to chemotherapy also received thoracic radiotherapy. Outcomes included progression-free and overall survival at 1 year.

For the overall trial population, there was a modest but significant survival advantage in patients with small-cell lung cancer who received chemotherapy in combination with an LMWH (Fig 4). Again, patients with a good prognosis, defined as those with limited disease at the time of randomization, had an even greater survival advantage at 35 months with dalteparin therapy (Fig 5). The combination of chemotherapy with dalteparin was also associated with a significantly greater response to therapy for cancer patients with limited disease compared with those patients with limited disease who received chemotherapy alone (Table 3). These data further reinforced the suggestion that there may be a biological effect of LMWH administration in addition to antithrombotic activity.

The MALT Trial

The Malignancy and Low-Molecular-Weight Heparin Therapy (MALT) study conducted by Klerk et al¹¹ included 302

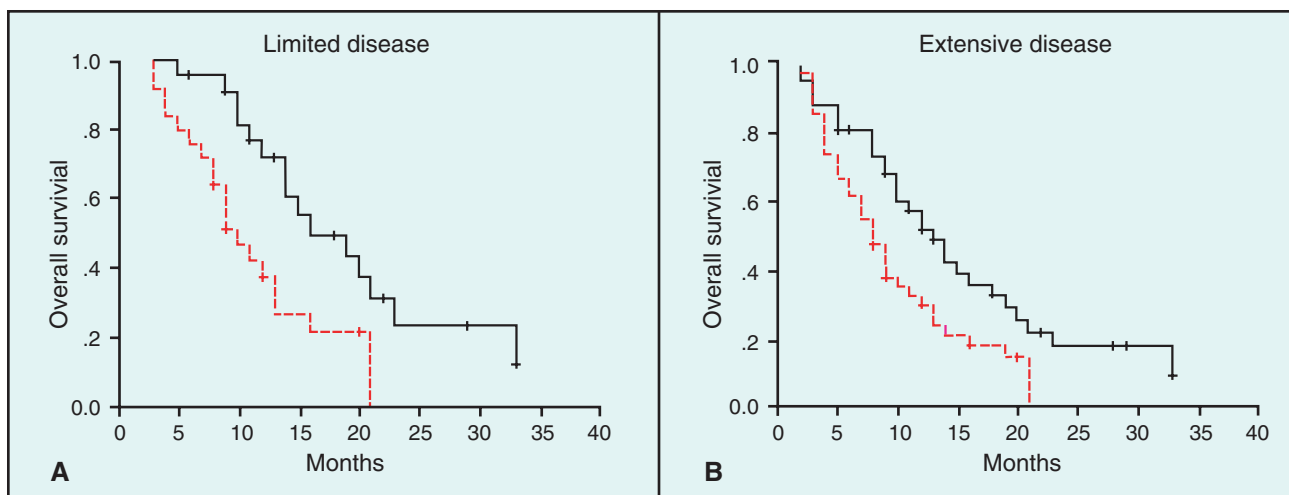


Fig 5. — The SCLC study: survival in patients with limited (A) vs extensive (B) disease. Adapted from Altinbas et al.¹⁰ Dashed line = chemotherapy alone, solid line = chemotherapy plus dalteparin. Reprinted with permission.

patients with solid tumor malignancy. The patients were randomized to receive 6 weeks of either nadroparin (Fraxiparine®, GlaxoSmithKline, Research Triangle Park, NC) or placebo. The data showed a significant difference in probability of survival with nadroparin compared with placebo (Fig 6). Again, the investigators observed an impact on mortality associated with LMWH administration, with a more pronounced effect in patients with bet-

ter prognosis at the time of randomization (defined as patients with a predicted survival greater than 6 months at the time they entered the trial).

Proposed Mechanisms

Data from these clinical trials suggest that cancer patients receiving LMWH have an improved survival rate and that this benefit is greatest for patients with a better prognosis (Table 4). What mechanistic basis underlies these observations from a biologic standpoint? There are several proposed theories.

Prevention of Fatal Thromboembolic Disease

One possible explanation could be that prolonged administration of LMWH is preventing silent but fatal thromboembolic disease, which subsequently prolongs survival in cancer patients.² Although this VTE preventive effect may indeed be a part of the mechanism, it does not fully explain the persistent influence of LMWH seen in the survival curves long after the period of active administration in these trials. The data are not reflective of effects normally expected with antithrombotic agents in terms of preventing fatal pulmonary embolism, which occur most often when the patient is actively receiving antithrombotic therapy.

Coagulation Proteases

A second potential explanation relates to activated blood coagulation seen in cancer patients.^{2,12} The coagulation proteases thrombin, activated factor X, and activated factor VII are generated in the peritumor environment and their receptors are expressed on epithelial tumor elements.^{13,14} Stimulation of the protease receptors by these coagulation proteases may change the tumor phenotype, and the effect may enhance growth, invasion, metastasis, and angiogenesis in experimental models.^{15,16}

Elegant molecular biological experiments have demonstrated that interference of the coagulation system

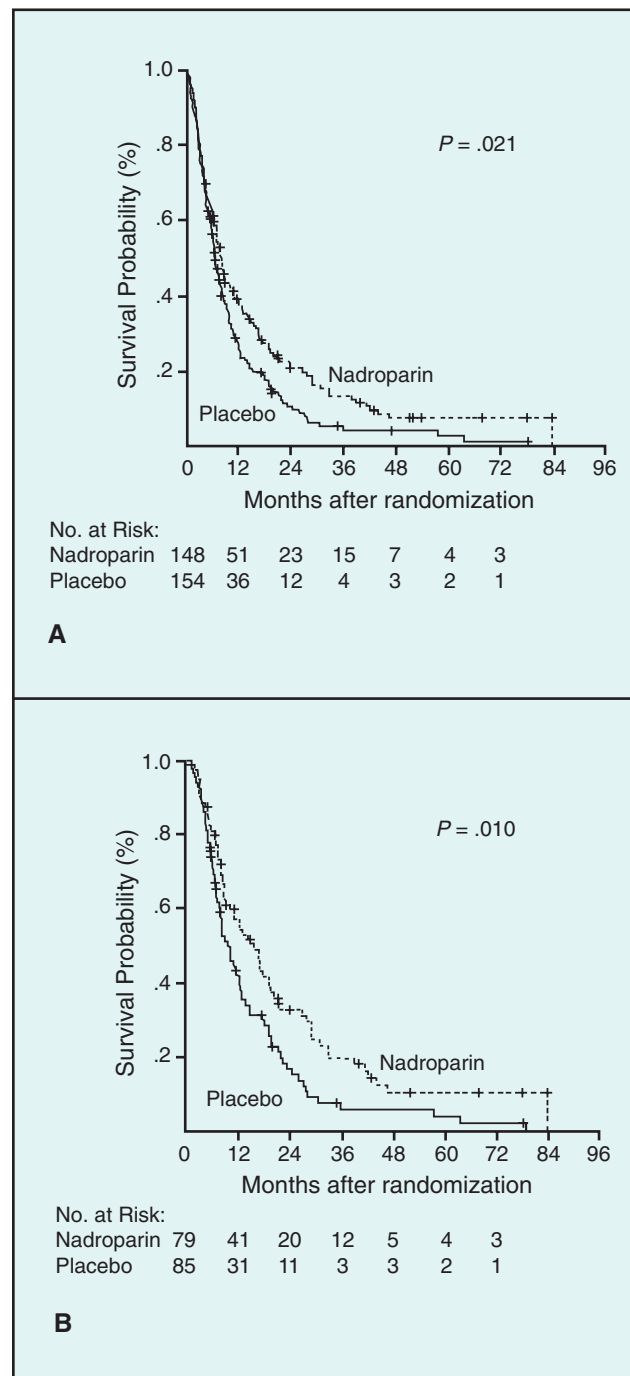


Fig 6. — The MALT study: survival in the overall population (A) vs patients with a good prognosis (B). From Klerk CPW, et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. *J Clin Oncol*. 2005;23:2130-2135. Reprinted with permission from the American Society of Clinical Oncology.

Table 4. — LMWH: Summary of Survival Studies

Study	Year	Study Medications	Median Survival	
			Overall Population	Good Prognosis
FAMOUS ⁷	2004	dalteparin	10.8 months	43.5 months
		placebo	9.14 months	24.3 months
CLOT ⁸	2005	dalteparin	62%*	80%*
		oral anticoagulant	61%	64%
		hazard ratio	1.0	0.5
SCLC ¹⁰	2004	dalteparin	13.0 months	16.0 months
		placebo	8.0 months	10.0 months
MALT ¹¹	2005	nadroparin	8.0 months	15.4 months
		placebo	6.6 months	9.4 months
		hazard ratio	0.75	0.64

* % survival at 1 year.

or, in particular, stimulation of tumor cells with activated coagulation proteases changes their phenotype or alters their ability to enhance angiogenesis.¹⁵ That area of coagulation protease biology continues to gain credence, and the inhibitory effect of LMWH at multiple stages in the coagulation cascade could provide an explanation for their ability to prolong survival of cancer patients. Their interference with the activation of coagulation proteases in the peritumor environment may subsequently prevent those proteases from altering the tumor cell phenotype.¹⁵

Direct Antitumor Effects

One of the more exciting avenues of research is that of the potential direct antitumor effects of heparins, and various mechanistic explanations have been proposed, including antiangiogenesis, induction of tumor apoptosis, and prevention of tumor cell adhesion.

Heparinase and Antiangiogenic Effects: Folkman and colleagues¹⁷ demonstrated that UFH combined with corticosteroids administered to experimental tumor-bearing animals was associated with an antiangiogenic effect. Tumors produce large quantities of an enzyme known as heparinase, which plays an important role in degradation of the extracellular matrix, and exogenous delivery of heparin neutralizes that heparinase activity.¹⁸

Tumor Apoptosis: Studies have also recently demonstrated that LMWH in certain experimental settings can induce tumor apoptosis. For example, in an experiment with a heparin knockout model — a transgenic mouse in which the enzyme *N*-deacetylase/*N*-sulfotransferase (NDST-2) had been knocked out and cells were unable to produce cellular heparin — investigators studied the growth of the murine melanoma cell line B₁₆F₁₀ and determined the effect of reintroducing heparin and LMWH into this heparin-free in vivo model in terms of tumor growth, angiogenesis, and apoptosis. The results demonstrated that UFH, administered to animals bearing these tumors, had no effect on tumor growth, angiogenesis, or apoptosis. In contrast, administration of LMWH resulted in a significant reduction in tumor growth over 21 days, a significant reduction in tumor angiogenesis by about 50% compared with control animals, and a marked, near 4-fold induction of apoptosis in these tumors compared with the control situation. Therefore, data from these elegant experimental models indicate that administration of LMWH may be associated with the induction of apoptosis, thereby potentially providing an explanation for the observations seen in clinical trials.¹⁹

Tumor Cell Adhesion and Metastasis: In terms of metastatic cascades, heparins have demonstrated the ability to inhibit adhesion events, which might offer further insight into the role of these agents in inhibiting tumor cell metastasis.²

Heparin administration can also block P-selectin-based interactions between platelets and tumor cells, thereby attenuating metastatic processes.²⁰ The progres-

Table 5. — Hypercoagulability and Mortality

Deaths/1,000 person years	Hypercoagulable		P Value
	No	Yes	
All causes (n = 184)	8.2%	16.4%	.005
Cancer (n = 100)	4.3%	12.6%	.001
Data from Miller et al. ²¹			

sion of a carcinoma is associated with changes in cell-surface glycosylation, and those carcinomas expressing highly sialylated or branched sugar chains and/or large amounts of mucins have a high rate of metastasis and therefore a poor prognosis. P-selectin is a vascular receptor that can mediate pathologic interactions between carcinoma cells and platelets, leukocytes, and endothelium. Heparin inhibits the binding of P-selectin to its natural ligands.

In summary, the ability of heparins to prevent fatal thromboembolism as well as their effects on tumor cell growth, adhesion, and metastasis, either directly or through coagulation protease or P-selectin inhibition, may offer a mechanistic explanation for their beneficial impact on survival in cancer patients.

Antithrombotic Agents in the Prevention of Cancer

In addition to improving survival in patients with cancer, there are data indicating that anticoagulant therapy may help prevent the development of cancer altogether. Recent observations from large epidemiological databases have suggested that hypercoagulability might be associated with the subsequent development of malignant disease. Miller and colleagues²¹ presented a study in which 3,052 healthy men were assessed for evidence of hypercoagulability and were then followed for mortality over a 15-year period. The results indicated that healthy men who were hypercoagulable at baseline exhibited higher mortality (approximately double) over the subsequent years of follow-up compared with those who had a normal coagulation state (Table 5). The striking finding of this study was that cancer-associated mortality was 3 times more common in patients who were hypercoagulable but completely healthy at baseline with no evidence of cancer compared with those who were not hypercoagulable.

These observations suggest possible explanations that remain to be verified. One explanation is that before patients develop cancer, tiny tumors exist and predispose the individual to a systemically hypercoagulable state. Another explanation is that individuals with an underlying predisposition to hypercoagulability are more likely to sustain development of cancers that result in death.

In the Duration of Anticoagulation Trial, Schulman and Lindmarker²² studied the effects of administration of anticoagulant drugs to populations of patients over a prolonged

period of time. Patients with DVT were randomized to either 6 weeks or 6 months of anticoagulation with warfarin (Coumadin®, Bristol-Myers Squibb Co, New York, NY), and the primary study end point was the incidence of recurrent thromboembolic disease. The study population was subsequently followed for many years, and the investigators found that the group of patients who received 6 months of anticoagulation had a lower incidence of new cancers compared with those who received 6 weeks of therapy (Fig 7). The prolonged period of anticoagulation was associated with reversal of a hypercoagulable state and therefore potentially fits the concept that a hypercoagulable state might sustain the development of cancers.

American College of Chest Physicians Guidelines

In light of the data that suggest that LMWH therapy might improve survival in patients with cancer, it is important to consider the potential impact of those findings on clinical practice. The 2004 guidelines of the American College of Chest Physicians for treatment and prevention of thromboembolic disease^{23,24} do not recommend routine administration of LMWH or anticoagulants in cancer patients for the sole purpose of prolonging survival. Such practice would not be justified at this time because the body of evidence is still being developed. Thus, further clinical trials are necessary before such a recommendation can be made. Conversely, in terms of prophylaxis for thromboembolism in cancer patients, the guidelines currently recommend primary prophylaxis with UFH or LMWH in patients undergoing surgery (and there is an argument for prolonged thromboprophylaxis in a group of patients that has yet to be fully

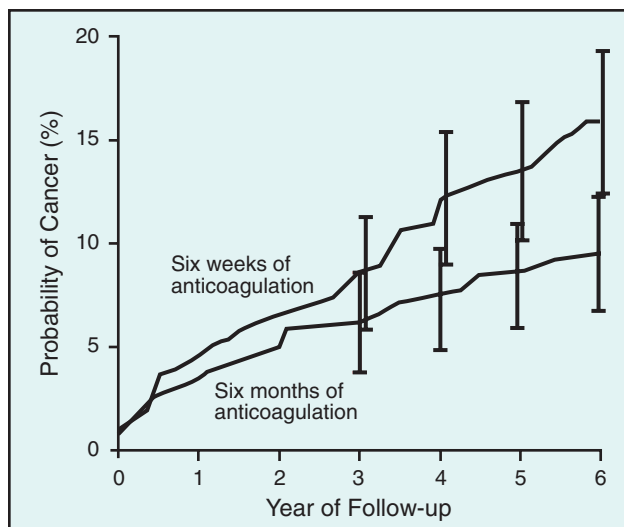


Fig 7. — The Duration of Anticoagulation trial: incidence of cancer after prophylaxis with warfarin. Bars represent 95% confidence intervals. From Schulman S, et al. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism: Duration of Anticoagulation Trial. *N Engl J Med.* 2000;342:1953-1958. Copyright© 2000 Massachusetts Medical Society. All rights reserved.

Table 6. — Summary of ACCP Guidelines for Venous Thromboembolism in Cancer Patients

Cancer Patient Population	Recommended Intervention
Acute DVT or PE	Initial therapy: IV UFH or SC LMWH Long-term therapy: SC LMWH for 3-6 months
Surgical patients	Primary prophylaxis: SC UFH or SC LMWH
Nonsurgical patients - acute illness - bedridden or immobile	Primary prophylaxis: SC UFH or SC LMWH
Patients with central venous catheters	Routine prophylaxis not recommended
Data from Geerts et al ²³ and Büller et al. ²⁴	

defined) and in acutely ill nonsurgical cancer patients who are bedridden or have limited mobility (Table 6). Routine prophylaxis is not recommended for patients with indwelling central venous catheters. For treatment of thrombosis in cancer patients, the recommendation is to use LMWH for 6 months rather than vitamin K antagonists.

Conclusions

The possibility of achieving a survival advantage with LMWH therapy in patients with cancer remains unclear. The prognosis is poor for those who develop thromboembolic complications at any point during the course of their malignancy. Results from four contemporary studies, however, offer promising observations that support a beneficial impact on survival with LMWH therapy in patients with advanced malignancy, especially those with a more favorable prognosis. In addition, anticoagulant therapy may play a role in the prevention of cancer, because studies have shown that hypercoagulable states are associated with the development of cancer. Data have been published that suggest a biological effect of LMWH administration, although the exact mechanisms remain unclear. Researchers are embarking further on a series of studies to confirm these exciting initial observations, from both basic and clinical vantages. Because the growing body of evidence is still in development, practice guidelines cannot support routine administration of LMWH for the sole purpose of promoting survival. Nonetheless, awareness of such potential influence should further support the role of LMWH therapy, when appropriate, in the treatment and prevention of thrombosis in cancer patients.

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