Management of Venous Thromboembolism and the Potential to Impact Overall Survival in Patients with Cancer

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The risk of venous thromboembolism (VTE) in patients with cancer is 6–12-fold higher than in the general population, and VTE is the second leading cause of death in this population, after cancer itself. The etiology underlying the increased risk of VTE is multifactorial and complex, involving patient-, tumor-, and treatment-related factors. In patients with cancer, cumulative results from studies in those with VTE versus without VTE suggest that anticoagulation therapy, particularly with low-molecular-weight heparins, prevents morbidity and may reduce mortality. Despite the availability of effective and safe therapeutic options, VTE is often underrecognized and suboptimally managed. Interventions such as assessing individual patient risk of VTE, providing VTE prophylaxis and/or prompt treatment, and adopting VTE guidelines are essential aspects of cancer-related care. Aggressive VTE management and strategies are critical to improving survival in patients with cancer and VTE.

Key Words: cancer, venous thromboembolism, anticoagulation therapy, low-molecular-weight heparin, unfractionated heparin, survival
(Pharmacotherapy 2009;29(11):1344–1356)

OUTLINE

Compared with the general population, the annualized risk of venous thromboembolism (VTE) is estimated to be 6–12-fold higher in patients with cancer.[1] The outcomes of VTE in this population can be significant.[2] Thromboembolism is the second leading cause of death and is equivalent to the risk of death by infection in outpatients receiving chemotherapy.[2] An observational study of 4466 ambulatory patients reported that 9.2% of deaths during the 2.4-month median observation period were due to thromboembolism.[2] The death rate attributed specifically to VTE was 447/100,000 patients, which was estimated to be 47-fold higher than in the general population. Patients with both cancer and VTE also have a 3-fold lower 1-year survival rate than patients with cancer who do not have VTE; the reasons for this are multifactorial and complex.[3, 4]

It appears the frequency of VTE in patients with cancer may be increasing. One study of hospitalized patients with cancer, reporting trends between 1995 and 2003, estimated a 4.1% overall frequency of VTE,[5] a 2–7-fold increase over earlier estimates.[6, 7] Possible explanations for the increase include the effects of newer chemotherapeutic agents and improved technologies for detection.[5] Notwithstanding this increased frequency, VTE in patients with cancer may still be substantially underestimated. Previous estimates of clinically detectable deep

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vein thrombosis (DVT) in patients with cancer who have indwelling central venous catheters vary between 0.3–28.3%, yet one study reported that screening with venography detected an actual rate of DVT of 27–66%.[8] Postmortem evidence from the same study suggested that the rate of pulmonary embolism (PE) related to DVT approaches 50%, despite PE being clinically evident in only 15–25% of cases.

Fortunately, several effective strategies for preventing VTE are available. However, if the risk of VTE is not proactively assessed, the opportunity for prophylaxis against a potentially fatal outcome will be overlooked. Based on frequency estimates and the known impact of VTE on mortality, the potential exists for prolonging the survival of patients with cancer with appropriate prophylactic measures. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) collected data on more than 15,000 acutely ill medical patients at risk for VTE (12% had cancer) who were treated at 52 centers in 12 countries.[9] The IMPROVE study revealed that only half of the patients who met the American College of Chest Physicians guidelines for prophylactic anticoagulation received prophylaxis.[9] Proactive risk assessment for VTE in patients with cancer would help to ensure that appropriate therapy is promptly instituted.

Despite well-controlled evidence supporting the superior safety and efficacy of low-molecular-weight heparins (LMWH) over unfractionated heparin (UFH),[10] the adoption of LMWH for VTE prophylaxis could be vastly improved.[9] Due to their knowledge of drug therapy, monitoring capabilities, and experience with guideline implementation, pharmacists are particularly well suited to improve VTE management and, ultimately, to exert a positive impact on survival in patients with cancer.

Venous Thromboembolism in Patients with Cancer

Etiology

The mechanisms of thrombosis in patients with cancer are multifactorial (Figure 1).[4] Patient characteristics such as age, previous medical history, tumor type, immobility, host-tissue interactions, activation of the coagulation system, and other thrombogenic mechanisms in cancer lead to a heightened hypercoagulable state. Factors influencing those with cancer such

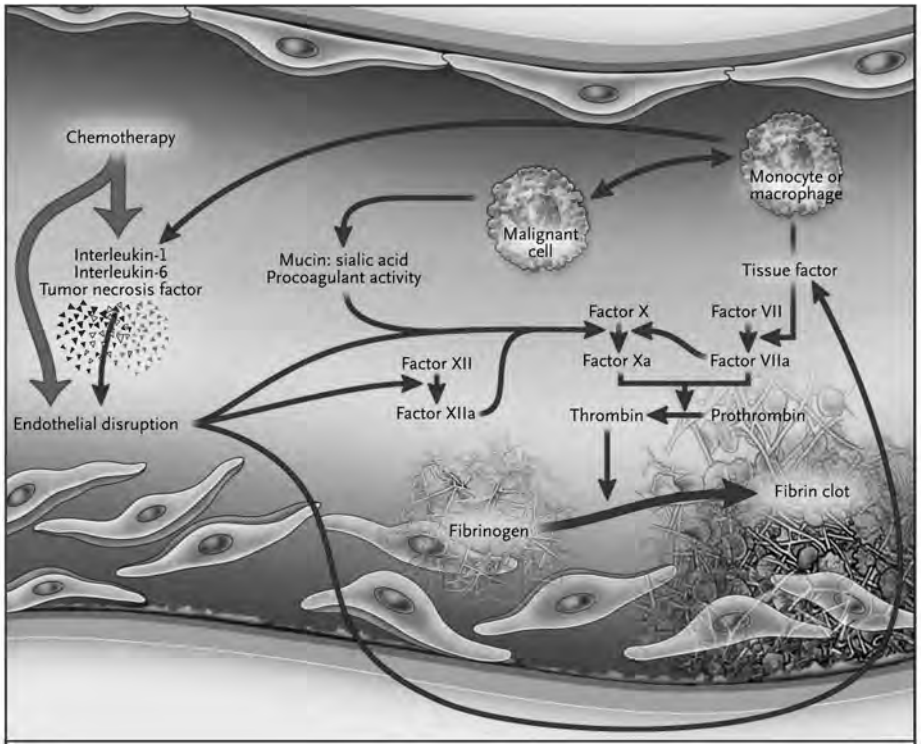


Figure 1. Mechanisms of thrombosis in patients with cancer. (Reprinted with permission from reference 4.)

as surgery, infection, chemotherapy, and the use of central venous catheters further increase the risk of VTE.[5] Patients with cancer who experience one VTE episode have a higher risk of recurrent VTE and an increased risk of death compared with those who do not experience a VTE.[6] Risk factors can be cumulative, and the risk of DVT or PE is increased if multiple factors are present.[2]

The type of tumor is an underappreciated influence on the risk of VTE. A summary of studies that investigated the incidence and relative risk of VTE by cancer type reveals that lymphoma, leukemia, and pancreatic, brain, liver, some gastrointestinal, and cervical cancers are associated with the highest risk in a population-based analysis (Table 1).[6, 11–14] Fortunately, the most common cancers, such as breast, colorectal, and prostate, present a relatively lower risk, but still substantially higher than in the general population. The data on VTE risk in patients with lung cancer are inconsistent, with at least one study considering lung cancer to be in the high-risk category,[13] and others placing it in a lower risk category.[14] The inconsistency in reporting of the data regarding relative risk for all tumor types is likely due to study design and outcome measures. One group of authors reported the relative risk of VTE for patients with cancer in Olmsted County, Minnesota, compared with the expected frequency based on the Surveillance Epidemiology and End Results (SEER) database.[14] Other researchers reported an odds ratio based on an observational study with the goal of documenting chemotherapy-related complications, including VTE.[13]

In addition to the tumor type, the stage of disease also dramatically affects VTE risk. For example, the frequency of VTE increased to 15–17% in patients with stages III–IV breast cancer, compared with 3–10% in those with stage II breast cancer who were receiving tamoxifen plus chemotherapy.[15]

Patients with cancer undergoing surgery have twice the risk of DVT and 3 times the risk of a fatal PE compared with patients without cancer.[16] Although bed rest and immobility are considered to be relatively low-level risk factors (risk score of 1 compared with a score of 3 for cancer or previous VTE and 2 for recent major surgery),[17] bed rest is a risk factor that can be additive. Other causes of immobility, including spinal cord compression and debilitation, can increase the risk for VTE in patients with cancer.[5]

Hormone or hormone-related therapies that increase VTE risk in patients with cancer include medroxyprogesterone, dexamethasone, leuprolide, and tamoxifen, used either alone or in combination with other therapies.[18–20] Healthy women at risk of developing breast cancer randomized to receive tamoxifen in the large National Surgical Adjuvant Breast Project (P-1 study) were found to have a slightly, although not significantly, higher rate of DVT than the placebo group (0.13% vs 0.084%/yr). The rate of PE, however, was significantly higher compared with placebo (0.69% vs 0.23%/yr). The risk of these events increased with age.[20]

Chemotherapy is another important risk factor for the development of VTE. The annual incidence of VTE has been estimated at 11% in patients with cancer receiving chemotherapy.[21] Asparaginase, cisplatin, etoposide, and cladribine are among those agents that have been implicated in causing VTE, as well as many combination therapies (Table 2).[22–47]

Newer antiangiogenic agents such as thalidomide and lenalidomide pose considerably high risks of VTE.[48] Alone or in combination with dexamethasone or doxorubicin, the risk associated with these therapies can range from

Table 1. Relative Risk of Venous Thromboembolism by Cancer Type[14]

Cancer Type	Relative Risk
Administrative data set, hospitalized patients (Medicare)[11]	
Uterus	3.40
Brain	2.37
Leukemia	2.18
Ovary	2.16
Pancreas	2.05
Lymphoma	1.80
Stomach	1.49
Renal	1.41
Colon	1.36
Lung	1.13
Rectum	1.11
Prostate	0.98
Liver	0.92
Cervix	0.90
Esophagus	0.76
Breast	0.44
Bladder	0.42
Head and neck	0.29
Population based[12]	
Pancreatic, lymphoma, brain	> 25
Liver, leukemia, gastrointestinal,[a] gynecologic (cervical)	> 17
Breast, colorectal, lung, prostate	9 < RR < 12

RR = relative risk.
[a]Includes cancer of the esophagus, gallbladder, and small intestine, and other biliary cancers.

Table 2. Chemotherapeutic Agents and Combinations Implicated in Causing Venous Thromboembolism

Category	Agent
High risk (≥ 10%)	Thalidomide[22] (up to 22.5% when used with dexamethasone[23]) Bevacizumab[24] (risk of arterial and venous thrombotic events is up to 21% with bolus IFL[25]) Lenalidomide[26] (up to 22%[27]) L-asparaginase[28] (~10%) Tamoxifen[29] Estramustine[30, 31]
Low risk (< 10%)	Capecitabine[32] (8% vs fluorouracil 6% in pooled phase III colorectal analysis) Pemetrexed[33] (6% with cisplatin-pemetrexed vs 3% with cisplatin-placebo[34]) Erlotinib[35] (3.9% with erlotinib-gemcitabine vs 1.3% with gemcitabine alone[36]) Sunitinib[37] (3% vs 0% with placebo in the GIST study[38]) Vinorelbine[39] (with vinorelbine-cisplatin vs cisplatin alone; grade 3thrombosis, phlebitis, embolism 3% vs < 1% when used for lung cancer[40]) Trastuzumab[41] (2–3% when combined with chemotherapy) Paclitaxel-albumin-bound[42] (3%) Fludarabine[43] (1–3%) Cladribine[44] (2%) Paclitaxel[45] (1%) Letrozole[46] (< 2%) Bortezomib[47]

IFL = irinotecan, fluorouracil, leucovorin; GIST = Gastrointestinal Stromal Tumor.
Whereas several of the pivotal publications cited above did not include thrombosis data, the information regarding thrombosis from these trials is available in the individual prescribing information for each product as well as on the U.S. Food and Drug Administration Web site (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/).

12–28%.[49] Similarly, potentially life-threatening arterial thrombotic events have occurred in association with some of the newer targeted therapies. The vascular endothelial growth factor (VEGF) inhibitor bevacizumab is associated with an increased risk of bleeding and VTE,[49, 50] with a recent meta-analysis revealing a greater than 30% increased risk of VTE in patients with cancer receiving bevacizumab.[51]

Three proposed mechanisms of thrombogenesis are associated with chemotherapy: procoagulants and cytokines are released from tumor cells damaged by cell-targeted treatment, the vascular endothelium is damaged by chemotherapy, and a decrease in naturally occurring anticoagulants (protein C, protein S, antithrombin III) occurs.[21] For the antiangiogenic agents, proposed mechanisms include that thalidomide increases factor VIII and von Willebrand factor levels, thus favoring thrombotic complications, and that bevacizumab-induced thrombosis may result from the inhibition of VEGF and the subsequent endothelial cell perturbations.[49, 50]

The use of erythropoiesis-stimulating agents (ESAs)[52] and white blood cell growth factors in high-risk sites of cancer[13] have been associated with VTE. Conversely, a hemoglobin level below 10 g/dl is also a risk factor for VTE[13]; thus, the balance of benefits and risks must be considered when administering ESAs. Recent evidence suggests that thromboembolic events are more frequent in patients with cancer receiving ESAs. Because shortened survival has been observed when ESAs are dosed to target hemoglobin levels of greater than 13.5 g/dl,[53] the manufacturers of these agents have revised package labeling to reflect this increased risk. The United States Food and Drug Administration has recently ordered labeling changes to state that ESAs should not be used in patients receiving myelosuppressive chemotherapy when the intended outcome is cure unless the use of red blood cell transfusion is not an option. Therapy with ESAs is no longer recommended for patients whose hemoglobin levels are 10 g/dl or higher; moreover, ESAs are to be withheld when hemoglobin levels exceed those needed to avoid transfusion.[54] Administering ESAs to achieve hemoglobin levels of 10–12 g/dl was previously regarded as safe, but mortality data suggest that a more conservative approach will result in better outcomes.[55]

Since platelets play a role in the maintenance of hemostasis, an increased risk of VTE in patients with cancer who have elevated platelet counts is not unexpected. A platelet count of 350 x 10^3/mm^3 or greater before chemotherapy was associated with a 4% rate of VTE compared with 1.3% in patients with cancer whose platelet counts before chemotherapy were below 200 x 10^3/mm^3 (p=0.0003).[13] The increased risk with higher platelet counts persisted during chemotherapy, was independent of other risk factors as determined by a multivariate analysis, and agreed with a similar study assessing thromboembolic risk in medical inpatients.[56] The strength of the association between platelets and thrombosis was stronger than previously known, and the contribution of platelets to thrombotic risk deserves further study.

Finally, central catheter–related thromboembolic complications in patients with cancer are well documented.[8] A high rate of such complications, ranging from 12–64%, has been reported in

Table 3. Summary of Randomized Controlled Trials of Low-Molecular-Weight Heparin versus Warfarin for Secondary Prevention of Venous Thromboembolism in Patients with Cancer[10]

Treatment Duration and Follow-up	Exclusion Criteria	Metastatic Disease	Mortality
3 mo, followed by anticoagulation according to physician preference, with further follow-up for 3 mo[60]	< 3 mo prognosis	Warfarin group: 39/75 (52%) LMWH group: 38/71 (54%)	Warfarin group: 17/75 (23%) LMWH group: 8/71 (11%)
6 mo[62]	ECOG > 2, weight < 40 kg	Warfarin group: 232/338 (69%) LMWH group: 223/338 (66%)	Warfarin group: 136/336 (41%) LMWH group: 130/336 (39%)
3 mo, followed by oral anticoagulation according to physician preference; no further treatment for 9 mo[63]	< 3 mo prognosis	Warfarin group: 36/100 (36%) LMWH group: 47/100 (47%)	Warfarin group: 19/100 (19%) at 3 mo 47/100 (47%) at 1 yr LMWH group: 20/100 (20%) at 3 mo 47/100 (47%) at 1 yr
6 mo[61]	ECOG > 2, severe liver disease, or nonirradiated brain metastases	Warfarin group: 18/34 (53%) Enoxaparin 1-mg/kg group: 17/31 (55%) Enoxaparin 1.5-mg/kg group: 24/36 (67%)	Warfarin group: 11/34 (32%) Enoxaparin 1-mg/kg group: 7/31 (23%) Enoxaparin 1.5-mg/kg group: 15/36 (42%)

Data are no. (%) of patients.
LMWH = low-molecular-weight heparin; ECOG = Eastern Cooperative Oncology Group.

retrospective studies, as reviewed recently.[57] Although not well documented as being a distinct entity from catheter-related thrombosis, infection may be another risk factor for VTE in patients with cancer receiving chemotherapy.[58]

Impact on Survival

The rate of mortality after an acute VTE is estimated to be 4–8-fold higher in patients with cancer compared with individuals without cancer.[59] The 1-year survival rate in patients with cancer after an episode of VTE is 12% compared with 36% in those with cancer without a history of VTE.[3] As noted earlier, a 47-fold higher death rate from VTE has been estimated in ambulatory patients with cancer receiving chemotherapy compared the general population.[2]

Presentation of VTE at the time of diagnosis of cancer is often associated with advanced disease and a poor prognosis. Cancer is the most frequent cause of death in the year after a thrombotic event, suggesting that coagulation pathways may somehow intersect with tumor growth pathways.[3] Therefore, appropriate prophylaxis and management of VTE in patients with cancer are essential to improved outcomes, including both morbidity and mortality, and could have a significant impact on health care resources.[49]

Treatment Strategies

Vitamin K antagonists (VKAs), such as warfarin, have long been used for VTE treatment and prophylaxis, but they also are well known to have a narrow therapeutic index.[60–63] A well-recognized challenge with the use of long-term warfarin therapy is its associated drug interactions. Examples of agents interacting with VKAs that are especially relevant to cancer therapy include fluorouracil, capecitabine, paclitaxel, gemcitabine, tamoxifen, homeopathic remedies, antiretrovirals, nonsteroidal antiinflammatory drugs, and a variety of antibacterial agents.[64–68] To avoid excessive bleeding with VKAs, intensive monitoring and frequent dosage adjustment may be required. Treatment alternatives that minimize bleeding risks and improve the efficacy of VKAs in patients with cancer have replaced VKAs as the agents of choice for prevention of thrombosis.

Unfractionated heparin is still routinely used for thromboprophylaxis, especially in the inpatient setting. A safety and efficacy meta-analysis concluded that UFH was equivalent to LMWH in patients with cancer.[69] A traditional approach to the management of VTE in patients with cancer was to initiate treatment with UFH or LMWH, followed by long-term VKA treatment

Table 3. (continued)

Recurrent Venous Thromboembolism	Major Bleeding	Any Bleeding
Warfarin group: 3/75 (4%) LMWH group: 2/71 (3%)	Warfarin group: 12/75 (16%) LMWH group: 5/71 (7%)	
Warfarin group: 53/336 (16%) LMWH group: 27/336 (8%)	Warfarin group: 12/335 (4%) LMWH group: 19/338 (6%)	Warfarin group: 65/335 (19%) LMWH group: 47/338 (14%)
Warfarin group: 10/100 (10%) at 3 mo 16/100 (16%) at 1 yr LMWH group: 6/100 (6%) at 3 mo 7/100 (7%) at 1 yr	Warfarin group: 7/100 (7%) LMWH group: 7/100 (7%)	Warfarin group: 24/100 (24%) LMWH group: 27/100 (27%)
Warfarin group: 3/30 (10%) Enoxaparin 1-mg/kg group: 2/29 (7%) Enoxaparin 1.5-mg/kg group: 2/32 (6%)	Warfarin group: 1/34 (3%) Enoxaparin 1-mg/kg group: 2/31 (7%) Enoxaparin 1.5-mg/kg group: 4/36 (11%)	

to prevent recurrence; however, as discussed below, studies have since established that LMWHs offer advantages over both UFH and VKAs, both initially as well as in the long-term treatment of VTE.

The LMWHs provide effective anticoagulation in patients with a variety of indications such as orthopedic surgery, acute coronary syndromes, VTE of pregnancy, and cancer-related VTE, with minimal risk for bleeding.[62, 70–73] In addition to having the potential for fewer drug interactions than warfarin, advantages of LMWHs over UFH include weight-based dosing without the need for frequent monitoring of activated partial thromboplastin time; predictable anticoagulant response, longer plasma half-life allowing once-daily dosing rather than the traditional 3 times/day with UFH, and reduced frequencies of thrombocytopenia and osteopenia.[74] Four randomized trials in patients with cancer have demonstrated that LMWHs are superior to VKAs in their ability to prevent VTE recurrence (Table 3).[60–63] These trials have been reviewed in detail elsewhere.[75] Of these four studies, the largest secondary prophylaxis trial, known as the CLOT (Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) trial,[62] reported that the probability of recurrence of VTE was significantly lower in the LMWH (dalteparin) group versus the VKA (warfarin or acenocoumarol) group (9% vs 17%; p=0.002). No significant difference was observed in the rate of major bleeding between the LMWH and VKA groups (6% and 4%, respectively). Finally, LMWHs may also be effective in patients with hematologic malignancies, a population of patients at special risk of bleeding, in the treatment and secondary prevention of VTEs.[76]

A meta-analysis and systematic review of data from 19 publications including randomized, prospective, and retrospective studies concluded that LMWHs are superior to warfarin for secondary prophylaxis of VTE in patients with cancer regardless of stage, performance status, or prognosis. The authors recommended that full-dose LMWH be administered for 7 days followed by a course of indefinite length with a lower dose.[10] Duration of therapy is still an unsettled issue, but for some patients with cancer whose thrombosis risk is high, continuation of therapy indefinitely may be the most appropriate course of action.

Newer agents with either enhanced antifactor Xa activity or an oral route of administration are being studied for the treatment and prevention of VTE in patients with cancer. Fondaparinux is a parenteral synthetic pentasaccharide that has been approved for use in the treatment of DVT and PE as well as for prophylaxis in patients undergoing orthopedic or major abdominal surgeries. Ongoing studies are evaluating the use

of fondaparinux in the prevention of VTE in patients with cancer (NCT00381888 and NCT00476216). A semisynthetic ultra–low-molecular-weight heparin with enriched antifactor Xa activity (AVE5026) is being studied for the prevention of VTE in patients undergoing chemotherapy (NCT00694382). The oral antifactor Xa inhibitor, apixaban, is also being studied for the prevention of VTE in patients with advanced cancer (NCT00320255).[77]

Impact of Prophylaxis on Overall Survival

Prospective studies of anticoagulation therapies (including VKAs, UFH, and LMWHs) in patients with cancer, both with and without VTE, have assessed survival as a secondary outcome rather than a primary end point. Available information on overall survival in patients with cancer receiving anticoagulation therapy is therefore primarily derived from retrospective data or from meta-analyses of data on survival as a secondary outcome variable.

A recent retrospective analysis compared mortality and thromboprophylaxis rates using a large United States inpatient database of approximately 2.5 million medically ill patients. Cancer (15.6%), acute myocardial infarction (6.0%), ischemic stroke (6.5%), heart failure (34.5%), or severe lung disease (67.0%) were the diagnoses examined. Among patients who had an indication for thromboprophylaxis, only 30% overall and 11.5% of patients with cancer received such therapy. Except for patients with ischemic stroke, significantly lower risk-adjusted mortality rates were observed in patients who received thromboprophylactic therapy compared with those who did not (p<0.001).[78]

Several systematic reviews and meta-analyses have evaluated the effects of UFH and LMWH on overall survival. One analysis reviewed five studies with heparin therapy (four with LMWH and one with UFH) and observed a statistically and clinically significant survival benefit with heparin compared with placebo in patients with cancer (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.65–0.91; p=0.003).[79] A subgroup analysis revealed a significant survival benefit (HR 0.56, 95% CI 0.38–0.83; p=0.004) in patients with limited stage small cell lung cancer. Patients with extensive small cell lung cancer or advanced cancer of various types (e.g., breast, ovarian, prostate, colorectal, pancreatic) had a trend toward benefit that favored heparin treatment.

A meta-analysis of 11 studies comparing initial therapy with LMWH versus UFH indicated a statistically significant reduction in mortality at 3 months favoring LMWH over UFH (relative risk [RR] 0.71, 95% CI 0.52–0.98; p=0.04).[80] Long-term treatment of VTE with LMWH compared with VKAs reduced VTE recurrence (HR 0.47, 95% CI 0.32–0.71; p=0.0003) but had no significant effect on mortality (HR 0.96, 95% CI 0.81–1.14).[81] A post hoc analysis of 12-month survival data from the CLOT study (Figure 2) compared LMWH with VKA in patients with and without metastatic disease.[82] The analysis revealed that patients with VTE and nonmetastatic disease were significantly less likely to be alive at 1 year if randomized to VKA rather than dalteparin (20% vs 36%; HR 0.5, 95% CI 0.27–0.95; p=0.03). By contrast, the population with VTE and metastatic disease at baseline had no significant treatment-related survival differences, suggesting that the mechanisms of action of dalteparin may be in some way related to the stage of cancer. The authors hypothesized that the reason dalteparin was associated with improved survival in patients with nonmetastatic cancer was because in less advanced disease, an

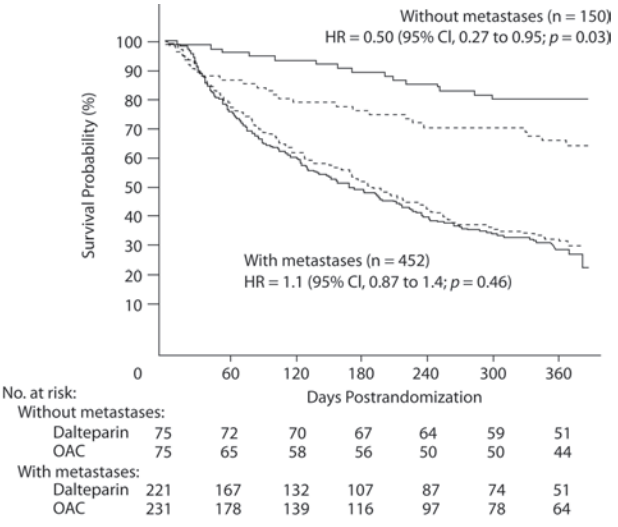


Figure 2. Results from a post hoc analysis of data from the Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial showed that patients with venous thromboembolism (VTE) and nonmetastatic cancer were significantly less likely to be alive at 1 year if randomized to vitamin K antagonists (oral anticoagulants [OAC], dashed lines) compared with dalteparin (solid lines). Patients with VTE and metastatic cancer at baseline, however, had no significant treatment-related survival differences. (Reprinted with permission from reference 82.)

antiangiogenic agent such as dalteparin could impair the development of tumor-related vasculature, thereby exerting an inhibitory effect on tumor growth. Conversely, in metastatic disease, the tumor-related vasculature is already well established and thus less susceptible to an antiangiogenic agent. Clearly, further studies in the metastatic versus nonmetastatic setting are needed to elucidate any antitumor effects of LMWHs.

Antineoplastic Effects of Heparin and Low-Molecular-Weight Heparins

Beyond thrombosis prevention, long-term anticoagulation therapy may also modulate the risk of developing cancer through the antineoplastic effects of heparin anticoagulants with subsequent effects on survival.[83] This is in contrast to VKAs which, according to a meta-analysis of five randomized clinical trials, had no significant effect on 1-year mortality rates of patients with cancer without VTE.[84] In vitro, LMWHs (specifically enoxaparin and dalteparin) exert antiangiogenic effects on microvascular endothelial cells that are significantly more pronounced than the effects with UFH.[85] Inhibition of endothelial cell growth in tumors by LMWHs is potentially an important pathway whereby LMWHs may exert a survival advantage in patients with cancer. Enoxaparin and dalteparin, but not UFH, have been shown to neutralize the angiogenic effects of cytokines including VEGF and fibroblast growth factor-2 on human capillary endothelial cells in vitro, as well as inhibit capillary tube formation induced by tumor-conditioned media.[85]

Based on the pharmacologic rationale derived from experiments of this kind, the antineoplastic and subsequent survival effects of UFH and LMWH in patients with cancer who did not have VTEs are of considerable interest and have been investigated.[86] Clinical studies in patients without VTE receiving UFH have produced mixed results. In one systematic review, two studies with UFH appeared to show a survival benefit; however, two studies in patients receiving UFH for 7 days through the portal vein reported a detrimental effect on survival. Because these studies were of short duration, no definitive conclusions were reached.[87]

Evidence is beginning to emerge that LMWHs, when used in conjunction with chemotherapy in patients with cancer who did not have VTE, may help to improve response rates and potentially increase survival duration compared with regimens without LMWHs.[88] Results of one meta-analysis suggested that the 1-year mortality rate of patients with cancer but without VTE who were receiving LMWH was significantly decreased compared with those not receiving LMWH (RR 0.877, 95% CI 0.789–0.975; p=0.015), and mortality was lower, but not significantly, than mortality associated with the use of warfarin (RR 0.942, 95% CI 0.854–1.040).[88] The absolute difference in mortality was a decrease of 8.0% and 3.0% with LMWH and warfarin, respectively. The frequency of bleeding was significantly increased with the use of LMWHs and warfarin, but the absolute risk difference was significantly lower for LMWH than for warfarin (2.4% vs 22.5%, p<0.0001). The authors were cautious to note that the data had limitations and would need to be confirmed with randomized clinical trials.

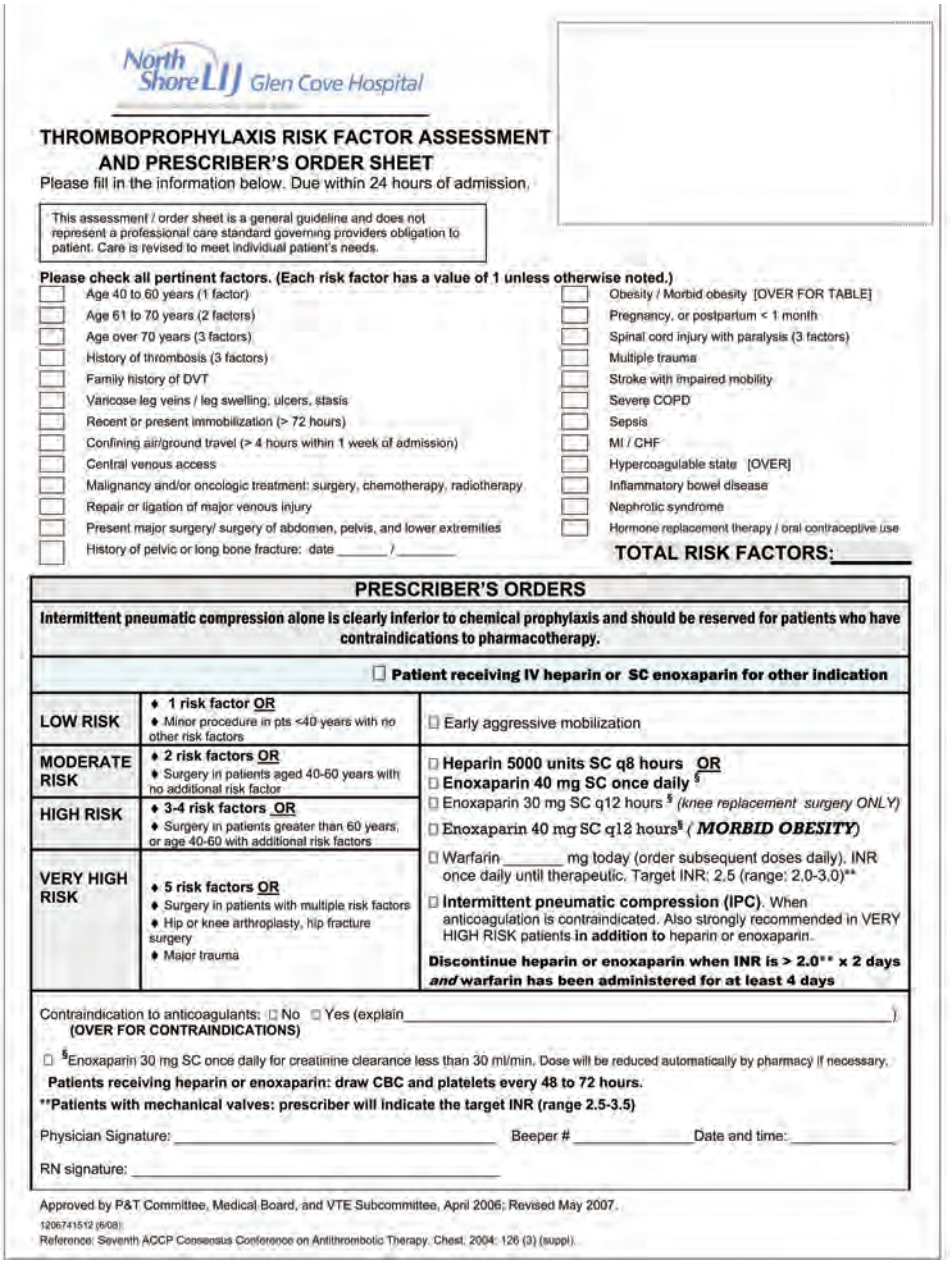
A preliminary description of a meta-analysis of 10 randomized clinical trials comparing LMWH with other supportive care (six trials of LMWH vs placebo or no treatment, and four trials of LMWH vs VKAs) in patients with cancer, both with or without VTE, reported a significant improvement of overall survival with LMWH (HR 0.87, 95% CI 0.78–0.97; p=0.02).[89] When these data were analyzed by comparing studies of patients with no VTE and VTE, the results lacked sufficient power to conclude that the survival benefit was significant in either subgroup (p=0.16 for no VTE and p=0.40 for VTE). One other nonrandomized study in patients with advanced pancreatic cancer showed that addition of LMWH (nadroparin) to gemcitabine-cisplatin significantly improved response and survival rates.[90]

In summary, many studies, although not all, have demonstrated a potential antineoplastic effect of LMWHs based on statistically significant benefits of anticoagulation therapy in terms of overall survival. Current clinical evidence suggests the use of LMWHs is likely to improve survival in patients with cancer. These agents also carry a relatively low risk of therapy-related morbidity. Currently, there is no evidence to recommend one LMWH over another. Results of prospective randomized clinical trials whose primary end points are to determine an effect of LMWH on overall survival are anxiously awaited.

Role of the Pharmacist

Given the evidence regarding the survival

prognosis of patients with VTE and cancer, reducing the occurrence of VTE is likely to improve survival and prevent complications in this population. Further underscoring the importance of proactive VTE management, the Surgeon General recently issued a call to action to prevent DVT and PE,[91] highlighting the need for increased awareness among health care professionals about the risk factors, triggers, and symptoms of DVT and PE, as well as the need for the development of evidence-based practices for preventing, diagnosing, and treating DVT and PE. Pharmacists are ideally suited to play a major role in this undertaking. As a group, pharmacists understand the antineoplastic drug–related and indwelling catheter–related risks of VTE; stay abreast of current official treatment guidelines and published literature; participate in multidisciplinary teams to develop and implement best practices for dosing and



North Shore LIJ Glen Cove Hospital

THROMBOPROPHYLAXIS RISK FACTOR ASSESSMENT AND PRESCRIBER'S ORDER SHEET

Please fill in the information below. Due within 24 hours of admission.

This assessment / order sheet is a general guideline and does not represent a professional care standard governing providers obligation to patient. Care is revised to meet individual patient's needs.

Please check all pertinent factors. (Each risk factor has a value of 1 unless otherwise noted.)

- ☐ Age 40 to 60 years (1 factor)
- ☐ Age 61 to 70 years (2 factors)
- ☐ Age over 70 years (3 factors)
- ☐ History of thrombosis (3 factors)
- ☐ Family history of DVT
- ☐ Varicose leg veins / leg swelling, ulcers, stasis
- ☐ Recent or present immobilization (> 72 hours)
- ☐ Confining air/ground travel (> 4 hours within 1 week of admission)
- ☐ Central venous access
- ☐ Malignancy and/or oncologic treatment: surgery, chemotherapy, radiotherapy
- ☐ Repair or ligation of major venous injury
- ☐ Present major surgery/ surgery of abdomen, pelvis, and lower extremities
- ☐ History of pelvic or long bone fracture: date _____ /_____
- ☐ Obesity / Morbid obesity [OVER FOR TABLE]
- ☐ Pregnancy, or postpartum < 1 month
- ☐ Spinal cord injury with paralysis (3 factors)
- ☐ Multiple trauma
- ☐ Stroke with impaired mobility
- ☐ Severe COPD
- ☐ Sepsis
- ☐ MI / CHF
- ☐ Hypercoagulable state [OVER]
- ☐ Inflammatory bowel disease
- ☐ Nephrotic syndrome
- ☐ Hormone replacement therapy / oral contraceptive use

TOTAL RISK FACTORS:_____

PRESCRIBER'S ORDERS

Intermittent pneumatic compression alone is clearly inferior to chemical prophylaxis and should be reserved for patients who have contraindications to pharmacotherapy.

☐ **Patient receiving IV heparin or SC enoxaparin for other indication**

LOW RISK	♦ **1 risk factor OR** ♦ Minor procedure in pts <40 years with no other risk factors	☐ Early aggressive mobilization
MODERATE RISK	♦ **2 risk factors OR** ♦ Surgery in patients aged 40-60 years with no additional risk factor	☐ **Heparin 5000 units SC q8 hours OR** ☐ **Enoxaparin 40 mg SC once daily** § ☐ Enoxaparin 30 mg SC q12 hours § *(knee replacement surgery ONLY)* ☐ Enoxaparin 40 mg SC q12 hours§ (***MORBID OBESITY***) ☐ Warfarin _____ mg today (order subsequent doses daily). INR once daily until therapeutic. Target INR: 2.5 (range: 2.0-3.0)** ☐ **Intermittent pneumatic compression (IPC)**. When anticoagulation is contraindicated. Also strongly recommended in VERY HIGH RISK patients **in addition to** heparin or enoxaparin. **Discontinue heparin or enoxaparin when INR is > 2.0** x 2 days *and* warfarin has been administered for at least 4 days**
HIGH RISK	♦ **3-4 risk factors OR** ♦ Surgery in patients greater than 60 years, or age 40-60 with additional risk factors	
VERY HIGH RISK	♦ **5 risk factors OR** ♦ Surgery in patients with multiple risk factors ♦ Hip or knee arthroplasty, hip fracture surgery ♦ Major trauma	

Contraindication to anticoagulants: ☐ No ☐ Yes (explain_____)
(OVER FOR CONTRAINDICATIONS)

☐ §Enoxaparin 30 mg SC once daily for creatinine clearance less than 30 ml/min. Dose will be reduced automatically by pharmacy if necessary.

Patients receiving heparin or enoxaparin: draw CBC and platelets every 48 to 72 hours.

****Patients with mechanical valves: prescriber will indicate the target INR (range 2.5-3.5)**

Physician Signature: _____ Beeper # _____ Date and time: _____

RN signature: _____

Approved by P&T Committee, Medical Board, and VTE Subcommittee, April 2006; Revised May 2007.

1206741512 (6/08)

Reference: Seventh ACCP Consensus Conference on Antithrombotic Therapy. Chest. 2004; 126 (3) (suppl).

Figure 3. Example of one hospital's thromboprophylaxis risk assessment form, designed and implemented in accordance with the American College of Chest Physicians' venous thromboembolism guidelines. (Reprinted with permission.)

duration of VTE prophylaxis; assist the medical team in performing and documenting protocol-driven risk assessments of individual patients; review and document patients' drug histories during the drug reconciliation process, which may be relevant to the selection of appropriate anticoagulant therapy; and monitor therapeutic effects and recommend or make adjustments to anticoagulant therapy.

Guideline Implementation

Guidelines for VTE management have been issued by various organizations, including the National Comprehensive Cancer Network,[92] American College of Chest Physicians,[16] American Society of Clinical Oncology,[49] and the European Society of Medical Oncology,[93] and the American Society of Health-System Pharmacists issued a position statement on outpatient VTE management.[74] These expert groups unanimously recommend LMWHs for treatment and prevention of VTEs in patients with cancer, based on efficacy, safety, ease of use, and benefit:risk ratio.

Adoption of guidelines at the institutional level requires assembly of a multidisciplinary team charged with review, discussion, and agreement on how best to adapt the guideline to specific institutional needs. Such teams are often successful in working through issues not well addressed in published guidelines such as duration of therapy. Guideline adoption and implementation require considerable effort but represents a step forward at promoting consistency of care throughout an institution or health system. Guideline committees are usually well represented by pharmacists, who often lead pharmacotherapy initiatives and implementation efforts.

Risk Assessment

Risk assessment for VTE of individual patients is a key step toward starting primary and secondary prophylaxis in individuals who will benefit most. Pharmacists are especially well suited to perform risk assessments that proactively evaluate appropriate candidates for pharmacotherapy. The screening tool can be an automated electronic alert that analyzes patient data from electronic medical records and identifies patients who may qualify for prophylaxis.[94] One example arising from a pharmacy practice is a risk assessment tool designed and implemented at Glen Cove Hospital, Glen Cove, New York (Figure 3). Use of the assessment tool has resulted in a 31% reduction in DVT and PE occurrence in the oncology setting since implementation.[95] In another example, a simple risk model predicts chemotherapy-associated thrombosis by identifying five predictive variables (Table 4).[96] This model allows health care providers to classify patients into three risk categories based on the total score derived from this model: low (score = 0), intermediate (score = 1–2), and high (score ≥ 3).

Table 4. Predictive Model for Chemotherapy-Associated Venous Thromboembolism[96]

Patient Characteristic	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, bladder, gynecologic, testicular)	1
Prechemotherapy platelet count ≥ 350 x 10^3/mm^3	1
Hemoglobin level < 10 g/dl or use of red blood cell growth factors	1
Prechemotherapy leukocyte count > 11 x 10^3/mm^3	1
Body mass index ≥ 35 kg/m^2	1

Risk category scores: 0 = low; 1–2 = intermediate; and ≥ 3 = high.

Best Practices

Oncology pharmacists have begun to establish and implement best practices for VTE management at their own institutions. In 2007, the Hematology-Oncology Pharmacy Association hosted a best-practices round-table discussion about VTEs in patients with cancer.[95] Participants outlined five different programs from their institutions in which pharmacists were actively engaged and described solutions to practice challenges involving protocol implementation, special populations, risk assessment tools, and data collection related to VTE management. Documentation and reporting of pre- and postintervention results were noted to be a particularly important best practice to ensure that health care systems recognize the impact of pharmacist-related interventions on survival outcomes.

Conclusion

Despite VTEs being the second leading cause of death in patients with cancer, they remain a large and suboptimally managed clinical challenge. Early recognition of risk factors and prompt therapeutic intervention are critical to

improving survival in these patients. Pharmacists are leading multidisciplinary teams to address these issues. Guidelines are available to assist with initiation of LMWH therapy, selection of patients who are candidates for therapy, and optimization of dosing and monitoring. Efforts expended by pharmacists in improving VTE management are likely to have a positive impact on the overall survival of patients with cancer.

Acknowledgment

The authors would like to thank Rebecca Miles, Ph.D., for writing and editorial assistance, which was supported by funding from Eisai Inc. The authors received no financial incentives for their contributions.

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