



Jacky Tiplady. *Mountain Shadows*. Photograph.

The high prevalence of venous thromboembolism in cancer patients and the factors that increase the risk for this complication deserve emphasis.

Current Perspectives on Primary Prophylaxis and Patient Risk Factors for Venous Thromboembolism in the Cancer Patient

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Introduction

Venous thromboembolism (VTE) is a serious complication in patients, representing a \$500-million burden on the health care system in the United States.¹ There is a strong association between the incidence of thrombosis and malignancy, with one fifth of all VTE occurring in cancer patients.^{2,3} Also, identification of an idiopathic VTE increases the likelihood of a diagnosis of cancer within 1 to 2 years.⁴

Once a VTE occurs, the cancer patient is at much greater risk for a recurrent event, uncontrolled bleeding, and death.⁵ Considering the ramifications associated with

VTE in the cancer setting, hematologists and oncologists are beginning to examine this complication more closely.

Because of the strong relationship between thrombosis and cancer, a number of pressing questions need to be addressed. Critical issues include deciding what role anticoagulants should play in the primary prevention of VTE in cancer patients and determining when the use of these agents is appropriate. To consider these issues, this review examines available epidemiological and clinical evidence, experience with low-molecular-weight heparins (LMWHs) and other anticoagulant options, appropriate evidence-based recommendations for anticoagulant therapy, and areas for further consideration due to the potential for increased risk that may require greater vigilance.

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Abbreviations used in this paper: VTE = venous thromboembolism, LMWH = low-molecular-weight heparin, DVT = deep vein thrombosis, PE = pulmonary embolism, UFH = unfractionated heparin.

VTE in the Cancer Setting

The epidemiological literature has observed a strong association between VTE and cancer. The Olmsted County analysis by Silverstein et al⁶ from the Mayo Clinic has provided some of the most notable observations. This 25-year retrospective epidemiological study examined the medical records of 2,218 patients living in Olmsted County, Minnesota. The investigators found an annual incidence of thrombosis of approximately 1 in 1,000 in the overall pop-

ulation. What was striking was that the risk of VTE in patients with cancer was elevated by a factor of 4.

Other population studies have identified an elevated incidence of VTE in cancer patients. The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, a case-controlled trial examining 3,220 patients, described a 7-fold (odds ratio 6.7, 95% confidence interval [CI] 5.2–8.6) greater risk for VTE in patients with malignancies compared with individuals without cancer.⁷ Sallah et al⁸ retrospectively examined 1,041 patients with solid tumors who were admitted to three major medical centers. Of the 1,041 patients, 81 (7.8%) with solid tumors were diagnosed with deep vein thrombosis (DVT) or pulmonary embolism (PE).

Further evidence has been observed in autopsy studies, which suggest that PE might be associated with 20% to 30% of cancer patient mortality.^{9,10} Ambrus et al⁹ performed a retrospective chart review of clinical and pathology reports of 506 patients in the Roswell Park Memorial Institute and Hospital. PE was a contributing factor to mortality in nearly 40% of patients. The increase in the risk of VTE varies from 20% to 40%, depending on tumor type.¹¹⁻¹³

While these studies have provided strong evidence related to the risk of thrombosis and cancer, prospective clinical trials have been less robust. The most significant data have been observed within the surgical area.¹⁴

Risk Factors

While the evidence from clinical trials and the ACCP has supported prophylaxis only in certain high-risk settings, such as surgery, a number of other risk factors associated with VTE encourage vigilance on the part of the clinician for a potential thrombotic event. The epidemiology literature has provided some insight into the risk factors associated with VTE. Heit et al¹⁵ examined the characteristics of patients with VTE in the Olmsted data set and quantified the impact of a number of risk factors (Table 1). While

Table 1. — Risk Factors Associated With Venous Thrombosis: The Olmsted County Study Population

Risk Factor	Odds Ratio	95% Confidence Interval
Surgery	21.7	4.9 – 49.9
Trauma	12.7	4.1 – 39.7
Hospital or nursing home confinement	8.0	4.5 – 14.2
Malignant neoplasm with chemotherapy	6.5	2.1 – 20.2
Malignant neoplasm without chemotherapy	4.1	1.9 – 8.5
Central venous catheter or pacemaker	5.6	1.6 – 19.6
Superficial vein thrombosis	4.3	1.8 – 10.6
Neurological disease with extremity paresis	3.0	1.3 – 7.4
Varicose veins at age 45	4.2	1.6 – 11.3
Varicose veins at age 60	1.9	1.0 – 3.6
Varicose veins at age 75	0.9	0.6 – 1.4

Adapted from Heit et al.¹⁵

most episodes of VTE have been observed in the common malignancies such as lung and colorectal cancers, the Medicare data base observed the highest rate of VTE in patients with pancreatic, brain, observed ovarian, lymphoma, and gastric cancers.¹⁶ Sallah and colleagues⁸ found that patients with advanced malignancies, renal, pancreatic, gastric, and brain tumors were significantly more likely to develop VTE. In addition, patients were also more likely to develop VTE while receiving chemotherapy. The MEGA study revealed that the level of risk depends on the specific type of tumor, the stage of the cancer, and factors involved in the therapy of the malignancy.⁷ In this study, the malignancies most strongly associated with VTE were hematologic malignancies, lung cancer, and gastrointestinal cancer, with the greatest risk in patients with metastatic disease and in those undergoing active therapy.

Systemic cancer therapy can increase the risk of thrombosis. In breast cancer patients, treatment with tamoxifen (generic, multiple manufacturers), a selective estrogen receptor inhibitor, was associated with increased risk of a thrombotic event.¹⁷⁻¹⁹ Chemotherapy can further elevate the risk of VTE in patients with breast cancer²⁰⁻²⁴ as well as those with colon cancer.²⁵⁻²⁸

Antiangiogenic therapy has been associated with increased risk of thrombosis. Combination treatment of multiple myeloma and other malignancies with thalidomide (Thalomid®, Celgene Corp, Warren, NJ) has been associated with a significant number of venous thromboembolic events.²⁹⁻³⁴ Depending on the chemotherapeutic-thalidomide combination employed and the specific malignancy being treated, the rate of VTE ranges from 8% to 42%.²⁹⁻³³ Two nonrandomized studies of LMWH prophylaxis in patients with multiple myeloma receiving thalidomide combination therapy found a lower incidence of VTE in patients receiving LMWH.^{29,30} The addition of bevacizumab (Avastin®, Genentech Inc, South San Francisco, CA) to irinotecan (Camptosar®, Pfizer Inc, New York, NY), fluorouracil (generic, multiple manufacturers) and leucovorin (generic, multiple manufacturers) combination for the treatment of advanced colon cancer resulted in an incidence of vascular events, including VTE and arterial thrombosis, of 19.4%.³⁴

Finally, there has been recent evidence of increased risk for VTE with epoetin (Procrit®, Ortho Biotech LP, Raritan, NJ; Epogen®, Amgen Inc, Thousand Oaks, CA) in cervical or vaginal cancer patients treated undergoing radiation and chemotherapy.^{32,35} In patients requiring blood transfusions at baseline in order to maintain hemoglobin levels greater than 11 g/dL, erythropoietin therapy during chemotherapy and radiation therapy increased the risk of peripheral thrombosis by a factor of 10.3.³⁵

The literature is maturing with respect to risk factors, but in the meantime, clinicians should be aware that several VTE risk factors may occur simultaneously in patients with cancers, thus compounding risk. Consider a sedentary elderly woman with breast cancer who is living in a

nursing home and undergoing chemotherapy. Should that hypothetical patient be a candidate for prophylaxis? While by definition that patient may not fit into the prophylaxis definition as recommended by ACCP guidelines, the clinician may need to watch such patients more closely for signs of a developing thrombosis in order to minimize the risk of serious consequences from VTE for this patient.

Low-Molecular-Weight Heparin Therapy in VTE Prophylaxis in Cancer Patients

Key Trials

The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey found that thromboprophylaxis was utilized routinely by 50% of responding surgeons, as opposed to only 5% by responding medical oncologists.³⁶ LMWH was the most frequently used thromboprophylactic by both groups; however, 20% of respondents reported using aspirin for prophylaxis despite the lack of clinical evidence of efficacy in this group of patients.³⁶

Some of the earliest clinical trials (Table 2) documented the efficacy and safety of thromboprophylaxis in patients undergoing both general and cancer surgery.^{37,38} A meta-analysis of 10 randomized clinical trials with 919 patients who received low-dose unfractionated heparin (UFH) indicated a reduction of objectively documented venous thromboembolic events from approximately 30% to 13%.³⁹ Low-dose heparin administered prior to surgery and every 8 to 12 hours afterward reduced VTE rates from

approximately 22% to 9% after cancer surgery.⁴⁰ Subsequent studies have evaluated the safety and efficacy of LMWHs for surgical prophylaxis.⁴¹

The first evidence regarding the efficacy of LMWH therapy as surgical prophylaxis in cancer patients emerged in trials with dalteparin sodium (Fragmin®, Pfizer Inc, New York, NY).^{38,40} In a study evaluating the importance of dose in the treatment of both cancer and noncancer patients undergoing abdominal surgery, dalteparin doses of 2,500 units and 5,000 units were compared. Patients were evaluated at approximately 9 to 10 days with a radiolabeled fibrinogen uptake leg scans.³⁸ Significantly fewer patients (8.5% vs 14.9%) developed VTE when treated with the higher dose of dalteparin.³⁸ There were no statistical differences in major or minor bleeding events.

Rasmussen⁴² examined the impact of duration of prophylaxis, beginning with 5,000 units of dalteparin as a once-a-day dose for 1 week followed by an extended placebo-controlled arm out to day 28 in patients with and without cancer. VTE was documented by bilateral venography. Ninety-one out of 198 cancer patients received the extended prophylaxis. At day 25, VTE was documented in 8.8% of patients who had received extended prophylaxis compared with 19.6% of patients who had received placebo ($P=.03$). Further, 10.4% of the patients who had received no extended prophylaxis developed proximal DVT compared with only 2.2% of patients who had received extended prophylaxis ($P=.02$).⁴²

Studies with enoxaparin (Lovenox®, Sanofi-Aventis, Bridgewater, NJ) have provided further evidence to support a longer duration of prophylaxis in the surgical setting. The study of thromboprophylaxis in cancer surgery (ENOXACAN) was designed to compare enoxaparin and UFH.³⁷ LMWH was given 2 hours before elective “curative” abdominal or pelvic surgery for cancer and then was given daily for 7 to 10 days postoperatively.³⁷ An initial 5,000-unit dose of UFH was given 2 hours prior to surgery and then 3 times daily for 7 to 10 days. VTE was documented by bilateral venography or pulmonary scintigraphy at days 7 through 10.³⁷ VTE rates were equivalent for both agents and occurred in 18.2% of patients who received UFH and in 14% of patients who received enoxaparin.³⁷ A follow-up study evaluated VTE prophylaxis that had been extended to 30 days with enoxaparin.^{43,44} Patients received standard prophylaxis for 7 to 10 days and then were randomized to either continue prophylaxis up to day 30 or discontinue further prophylaxis. Patients receiving extended prophylaxis had a 4.8% incidence of venographically documented VTE at day 30 compared with 12% of patients receiving prophylaxis for only 7 days and no extended prophylaxis.⁴⁴ There was no difference in major or minor bleeding events in patients who received the extended prophylaxis.^{43,44}

Like surgical patients, hospitalized and debilitated cancer patients have been observed as having significantly higher risk for developing VTEs than those who were ambulatory. Three studies of prophylaxis in medical

Table 2. — Surgical Oncology Studies

Surgical Studies	Source
Dalteparin before surgery has a good thromboprophylactic effect in high-risk general surgery, with a small bleeding risk. In patients with malignant disease, there is no increased risk of bleeding.	Bergqvist ³⁸
Lower rate of DVT in 28 days vs 14 days of dalteparin 5,000 U within the abdominal surgical setting: 2.2% vs 10.4% ($P=.02$). Day 25 VTE was 8.8% on those continuing LMWH vs 19.6% on placebo ($P=.03$)	Rasmussen ⁴²
Enoxaparin is as safe and effective as UFH in preventing VTE in major elective surgery for abdominal or pelvic malignancy.	ENOXACAN Study Group ³⁷
Both heparin and enoxaparin provide highly safe and effective prophylaxis in colorectal cancer surgery patients. LMWHs are preferred due to lower cost.	McLeod ⁶¹
LMWH and UFH are equally effective and safe for thromboprophylaxis in general surgery.	Mismetti ⁴⁹
Four-week prophylaxis with enoxaparin is equally safe and more effective than 1-week enoxaparin in prophylaxis in pelvic and abdominal cancer surgery.	Bergqvist ⁴³
Meta-analysis: LMWH and UFH treat initial pulmonary thromboembolism with equal efficacy and safety. LMWH and UFH equally reduce mortality and recurrence of VTE in pulmonary thromboembolism. The risk of major bleeding is similar between LMWH and UFH.	Zhai ⁴¹

patients included only small populations of cancer patients and therefore were not balanced in regard to the additional risk factors that occur in cancer patients. Each study documented a statistically significant reduction in the incidence of objectively documented VTE or a clinical DTE compared with patients not receiving prophylaxis. In the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, investigators prospectively examined the safety and efficacy of dalteparin for VTE prophylaxis in 3,706 high-risk acutely ill medical patients. They found that 5,000 IU of subcutaneous dalteparin for 14 days resulted in a 45% relative risk reduction (relative risk 0.55; 95% CI 0.38-0.80; $P=0.0015$) in the development of symptomatic VTE over 90 days of follow-up.⁴⁵ Unfortunately, too few cancer patients were enrolled in this study to provide evidence of a specific benefit of prophylaxis in this patient population. Similar observations were noted with fondaparinux (Arixtra®, GlaxoSmithKline, Research Triangle Park, NC), a synthetic Factor Xa inhibitor, as part of the Thromboembolism Prevention in a Medical Indications Study (ARTEMIS).⁴⁶ A subset analysis of cancer patients in the Medical Patients with Enoxaparin (MEDENOX) study reported that enoxaparin reduced the relative risk ratio for VTE to 0.50 (95% CI 0.14-1.72) in the cancer cohort.⁴⁷

Interestingly, in each of those studies cancer patients accounted for only a minority of the patients. Approximately 14% of the patients in the MEDENOX study and 5% of the patients in the ARTEMIS and PREVENT studies had cancer. Therefore, these results cannot fully characterize the impact of VTE prophylaxis in the cancer population.

Comparisons Among Various Anticoagulant Options

One question that emerges from these studies involves the comparability of various anticoagulant treatment options. Investigators have examined LMWH and UFH therapies in

the management and prevention of VTE in cancer patients.^{42,48} A meta-analysis of LMWH in the prevention of VTE in general surgery found no statistical evidence that LMWH therapy was superior to UFH given 3 times a day for prevention of DVT in surgical patients.⁴⁹

With respect to warfarin, an early trial evaluated the use of 1 mg of warfarin (Coumadin®, Bristol-Myers Squibb Co, New York, NY) daily for 6 weeks and looked for prevention of VTE in patients receiving chemotherapy for metastatic breast cancer.⁵⁰ The study documented a relative risk reduction of nearly 85%. In spite of the apparent efficacy of treatment with warfarin, prophylaxis has not been uniformly recommended for those patients. To date, there have been no additional prospective clinical trials addressing a role for prophylaxis in those patients.

Among LMWH products, the current literature does not indicate that any single LMWH has been shown as superior to any other in the primary prevention setting since no direct comparisons in the cancer setting have been conducted or published. Two agents have shown efficacy and safety for VTE prophylaxis in cancer patients under a certain set of clinical conditions: dalteparin and enoxaparin for abdominal or pelvic surgery for malignancy. However, beyond the unique product characteristics with each LMWH, differences in study design and subject characteristics have limited the ability to make an effective comparison between those agents for VTE prophylaxis within the cancer setting, although strong data have pointed to dalteparin for treatment and secondary prevention after a primary thrombotic event.⁵¹

American College of Chest Physicians Guidelines

In reviewing the literature, the American College of Chest Physicians (ACCP) has graded the strength of randomized

Table 3. — Grading the Strength of Management Recommendations by the American College of Chest Physicians

Grade	Requirements	Methodology	Applicability of Recommendations
1A	Clear evidence of benefit	Randomized clinical trial with no critical limitations	Strong recommendations applicable to most patients in most circumstances
1B	Clear evidence of benefit	Randomized clinical trial with inconsistent results or methodological flaws	Strong recommendations likely to apply to most patients
1C+	Clear evidence of benefit	Observational trial with overwhelming evidence in most circumstances	Strong recommendations applicable to most patients
1C	Clear evidence of benefit	Observational trial	Intermediate recommendations that may change when stronger evidence becomes available
2A	Evidence unclear	Randomized clinical trial with no critical limitations	Intermediate recommendations; best action may differ depending on circumstances or patient's societal values
2B	Evidence unclear	Randomized clinical trial with methodological flaws	Weak recommendations; alternative actions likely to be better for some patients under some circumstances
2C+	Evidence unclear	Observational trial with overwhelming evidence depending on circumstances or patients societal values	Weak recommendations; best action likely to differ
2C	Evidence unclear	Observational trial	Very weak recommendations; alternative actions may be equally reasonable

Adapted from Guyatt.⁵² Note: C+ grade indicates stronger evidence than C grade.

clinical trials and observational studies to set forth guidelines for the prevention of VTE in the cancer setting (Table 3).⁵² The guidelines have provided 1A evidence-based recommendations therapy for LMWH or UFH in only high-risk patients, with cancer patients undergoing surgery considered to be most significant. Hospitalized cancer patients have also been considered to be at high risk of DVT, and 1A recommendations include prophylaxis with LMWH (dalteparin or enoxaparin) or low-dose UFH 3 times daily. Those recommendations cited two studies demonstrating reduced VTE with thromboprophylaxis extended to 3 weeks.^{43,53} However, while the ACCP did not make any recommendation in regard to ambulatory cancer patients who receive systemic chemotherapy, patients undergoing high-risk chemotherapeutic regimens, such as thalidomide-chemotherapy combinations, should be either closely evaluated for prophylaxis or closely monitored for a potential VTE based on risk status.

Patients with central venous catheters have been observed at increased risk of developing upper-extremity thromboembolism. Early studies have suggested that medical prophylaxis with low-dose warfarin reduced VTE in patients with catheters.⁵⁴⁻⁵⁶ However, more recent studies have called into question the benefit of prophylactic heparin or warfarin.⁵⁷ The incidence of upper-segment thrombosis associated with catheters was lower with the use of contemporary catheters. Recent studies have shown only a 4% incidence of symptomatic thrombosis associated with catheterization. Using a protocol similar to that of Bern and colleagues,⁵⁴ Magagnoli et al⁵⁸ reported a study of 427 cancer patients receiving low-dose warfarin. Clinical bleeding occurred in approximately 3.5% of patients, most of whom developed excessively prolonged international normalized ratios while receiving 5-fluorouracil-based chemotherapy. The authors did not document clinical benefit for the use of low-dose warfarin. Based on present evidence, ACCP guidelines have not recommended prophylaxis in patients who have catheters.

The need for and the efficacy of prophylactic treatment of VTE in specific cancers continue to be examined. In patients with central nervous system malignancies, Knovich and Lesser⁵⁹ advocate a multimodality strategy featuring compression stockings, intermittent compression devices, and heparin in the perioperative setting. They also suggest that in brain tumor patients with newly diagnosed VTE and in the absence of strict contraindications such as previous intracranial hemorrhage or profound thrombocytopenia, LMWH is recommended followed by long-term warfarin or LMWH. Goldhaber et al⁶⁰ have successfully utilized LMWH prophylaxis in patients with brain tumors, resulting in a lower incidence of VTE after surgery with multimodal therapy including enoxaparin or UFH. Given the strong association between specific types of cancers such as those of the brain, ovary, or pancreas and VTE,⁸ a number of trials to evaluate primary prophylaxis are in progress.

Conclusions

VTE is a serious complication of active cancer, especially when patients are undergoing catheterization, chemotherapy, and, most important, surgery. Epidemiological and clinical evidence suggests that thromboprophylaxis with an LMWH offers a clear reduction in the incidence of VTE in cancer patients who undergo surgery. Further, extending the duration of prophylactic treatment from 1 week to 1 month after surgery reduces the risk of VTE even further. This high-risk patient group, most notably surgical and acutely ill hospitalized patients, represents the only cohort for which prophylactic therapy is currently recommended by the ACCP for prophylaxis. The ACCP no longer recommends prophylaxis specifically for patients with indwelling catheters.

There is a need for more data and for the development of a more sophisticated staging to evaluate and quantify risk factors (eg, specific tumor types, treatments, and other patient considerations) that can occur within the cancer setting either alone or in combination. Nonetheless, clinicians should be alert to these factors and should watch these patients closely in order to identify and manage a thrombotic event early.

LMWH prophylaxis is appropriate in patients identified by ACCP guidelines: those who are at high risk such as surgical or hospitalized patients. The literature supports the contention that extended prophylactic treatment of surgical cancer patients can reduce the occurrence of VTE. Additional high-risk patients such as those receiving thalidomide-chemotherapy combinations or patients with advanced metastatic colorectal cancer receiving multiagent therapy may also benefit from UFH or LMWH prophylaxis. Current data do not allow direct comparison among various anticoagulant options in the primary prophylaxis setting. Further research is needed to better define the role of VTE prophylaxis in these other high-risk settings.

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