



Jacky Tiplady. *Misty Trees*. Photograph.

Evidence from clinical trials helps answer salient questions regarding VTE prophylaxis and management in patients with cancer.

Venous Thrombotic Events in Cancer: The Bottom Line

John Horton, MB, ChB, FACP

Introduction

The articles in this supplement to *Cancer Control* have eloquently described the high morbidity and the excess mortality resulting from venous thrombotic events (VTEs) in patients with cancer as well as the pathophysiologic factors that predispose to the complication. The authors have discussed the evidence concerning VTE prophylaxis, reviewed the now robust data on the acute and long-term management of VTE with specific low-molecular-weight heparins (LMWHs), and described the possible beneficial influence of some LMWHs on the survival of patients with cancer. Data have been drawn from several well-executed studies of VTE that are specific to populations of patients with cancer. The results from these studies has allowed the American College of Chest Physicians (ACCP) to develop and publish evidence-based guidelines¹ that help define and direct optimal care of VTE in cancer patients.

To emphasize the relevance of these results to optimal clinical oncology practice, these relatively new but still

underutilized data will be summarized in answers to questions that oncologists and hematologists often ask concerning VTE in their patients. There are two key questions: *When should I use VTE prophylaxis in my cancer patients, and what is the optimum approach to secondary prophylaxis in my cancer patients who have suffered a VTE?*

Question #1. Why is VTE so common in patients with cancer?

Approximately 20% of all new VTE events are associated with malignancy.² Patients with cancer have a 6-fold higher risk for VTE than noncancer patients according to one study, and a 10-fold multiplication according to another.³ Laboratory findings of a hypercoagulable state, however, are uncommon in this population.⁴ Nonetheless, evidence is increasing that dysregulated cancer cells can produce excess tissue factor and a cancer procoagulant that can activate the coagulation system,⁵ plus induce dose-dependent platelet activation,⁶ thus promoting VTEs in cancer patients.

Patients with active cancer may be sedentary, paralyzed, or immobilized, or they may have impaired performance status and require hospitalization. All of these factors accentuate venous stasis and thus predispose to VTE. Many have comorbidities, such as pulmonary failure or infection, that further compound the risk. In addition, an

From the Department of Interdisciplinary Oncology, Moffitt Cancer Center, Tampa, Florida.

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Address correspondence to John Horton, MB, ChB, FACP, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, MCC-BRPROG, Tampa, FL 33612. E-mail: horton@moffitt.usf.edu

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Table 1. — Factors Associated With an Increased Risk of VTE in Patients With Cancer*

History:	tumor type (brain, ovary, lymphoma, pancreas, stomach) previous VTE older age cigarette smoking pregnancy
Physical examination:	obesity immobility/poor performance status (ECOG 3 or 4) heart or respiratory failure varicose veins acute medical illness atrial fibrillation nephrotic syndrome
Ancillary studies:	thrombophilia myeloproliferative disorders molecular hypercoagulability
Planned interventions:	surgery other cancer therapy (hormonal, chemotherapy, radiation)
* Risk factors are generally cumulative. Data from Geerts et al. ¹⁸	

expanding list of cancer treatments and supportive care agents — eg, tamoxifen (generic, multiple manufacturers), L-asparaginase (Elspar®, Merck & Co, West Point, PA), epoetin (Procrit®, Ortho Biotech LP, Raritan, NJ; Epogen®, Amgen Inc, Thousand Oaks, CA) — are associated with an increased VTE risk.⁶ The cancer patient who undergoes surgery is at particularly high risk for VTE since the surgery adds vascular endothelial injury to all the previously mentioned predisposing factors. These risk factors are summarized in Table 1.

Question #2. Does the hypercoagulable state predispose to cancer?

Miller et al⁷ described outcomes in over 3,000 healthy men (without cancer) who were assessed for hypercoagulability at baseline and followed for 15 years. Cancer-associated mortality was 3 times more common in patients who were hypercoagulable at baseline than in those who were not. Schulman and Lindmarker⁸ observed that in patients with VTE but without cancer, those who received 6 months rather than 6 weeks of treatment with warfarin (Coumadin®, Bristol-Myers Squibb Co, New York, NY), developed fewer cancers.

A satisfactory explanation for these intriguing clinical observations is lacking. However, these factors lend support to the concept that pharmacologic interference with hypercoagulability could exert a beneficial biologic effect.

Question #3. Is VTE an important issue for my patients with cancer?

Patients who present with cancer and thrombosis have a

shorter lifespan than those who have cancer but without VTE.⁹ In addition to the fact that patients with cancer have at least a 6-fold higher risk for VTE compared with noncancer patients,¹⁰ those who develop a VTE have a worse prognosis than those who do not.^{11,12} In addition to these sobering facts about mortality, VTE in patients with cancer commonly induces appreciable acute and chronic morbidities, such as chronic venous stasis, that significantly increase medical costs and diminish quality of life. Once a VTE occurs, a patient with cancer is at much greater risk for a recurrent event, uncontrolled bleeding, and death than is true for a patient without cancer.¹³ Thus, prophylaxis against VTE when indicated, combined with effective acute and long-term management of VTE, are key components in the provision of optimal oncologic care.

Question #4. Do oncologists provide optimal management of VTE in their cancer patients?

Not enough is currently known about all aspects of prevention and care of VTE in cancer patients to answer this question clearly, and initial guidelines for optimal management of VTE that has occurred in cancer patients have been available for less than a year.¹ Nevertheless, the European Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey¹⁴ reported that thromboprophylaxis was used routinely by 50% of responding surgeons compared with only 5% of medical oncologists! In addition, 20% of respondents reported using aspirin for VTE prophylaxis despite the lack of clinical efficacy of aspirin in this group of patients.

At the H. Lee Moffitt Cancer Center & Research Institute, long-term anticoagulation with warfarin after a VTE in a cancer patient is still a common practice, despite evidence from the “CLOT” trial¹⁵ that an alternative treatment using dalteparin (Fragmin®, Pfizer Inc, New York, NY) is more effective. It appears clear that we need to revise and update our practices regarding VTE prophylaxis and management for our cancer patients.

Question #5. Which of my cancer patients is at highest risk for VTE?

Although all patients with active cancer are at increased risk for VTE, a large case-control study (the Multiple Environmental and Genetic Assessment [MEGA] trial)³ suggested that the level of risk was highest in hospitalized patients with brain, ovarian, pancreatic and gastric cancers. Almost 8% of these had deep vein thrombosis (DVT)

or pulmonary embolism (PE) with the risk being greatest in those who had the highest stage and were receiving antitumor treatment. Other studies^{16,17} have linked lymphomas and leukemias with elevated VTE risk. Additional data regarding VTE risks with these and other tumor types have been well summarized in this supplement.⁶

While advanced age and hospitalization are both associated with elevation of the tumor-type-related risk, the VTE risk is markedly increased by surgery, especially with major neurosurgery, pelvic and abdominal surgery, and orthopedic procedures. These risks are so high that LMWH prophylaxis is recommended.¹ Acute illness, immobilization, extrinsic or intrinsic venous compression, and the use of chemotherapy and other drugs also appreciably increase the risk for VTE. A list of such predisposing factors is presented in Table 1. Unfortunately, with the exception of surgical intervention, it is currently not possible to define an exact risk for VTE in an individual cancer patient at any point in time. The risk factors are cumulative, however, so consideration of them should allow the oncologist to develop an estimate of the VTE risk in any individual and respond accordingly.

Question #6. When should I prescribe antithrombotic prophylaxis against VTE in my cancer patient?

The easiest part of this question to answer relates to VTE prophylaxis in cancer patients who are to undergo surgery. Such patients have twice the risk of postoperative DVT and more than 3 times the risk of fatal PE than that of noncancer patients who are undergoing similar procedures.¹ Geerts et al¹⁸ quantifies four levels of risk of VTE with surgery; a patient with cancer is categorized as being in at least the “moderate” risk category, where successful VTE prevention has been demonstrated with the use of low-dose unfractionated heparin (every 12 hours), LMWH ($\leq 3,400$ IU daily, graduated compression stockings [GCS], or intermittent pneumatic compression [IPC]).¹ Thus, when surgery is planned, essentially all patients with

Table 2. — Location of ACCP Recommendations for VTE Prophylaxis in Patients Undergoing Surgery

Procedure	Page No.
General surgery	346
Vascular surgery	348
Gynecologic surgery	349
Urologic surgery	349
Laparoscopic surgery	351
Hip fracture surgery	358
Elective spine surgery	364
Neurosurgery	364
Acute spinal cord injury	368

Source: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. *Chest*. 2004;126(3 suppl).

Table 3. — Trials That Demonstrate Effectiveness of LMWHs in Primary Prevention of Surgery-Related VTE

Generic Name	Trial
dalteparin	PREVENT ¹⁹ Rasmussen ²⁰
enoxaparin	ENOXACAN ²¹ MEDENOX ²²
fondaparinux	ARTEMIS ²³

active cancer are candidates for VTE thromboprophylaxis. Table 2 lists the location of the specific guidelines for surgical prophylaxis within the ACCP supplement, and the data concerning the effectiveness of LMWHs are in Table 3. They recommend against aspirin alone as prophylaxis against VTE for any group (grade 1A).

Fifty to 70% of symptomatic thromboembolic events²⁴ and 70% to 80% of fatal PEs occur in nonsurgical patients,²⁵ however, so thromboprophylaxis is also considered for medical conditions. The ACCP recommendations include:

“In acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, acute neurologic disease, or inflammatory bowel disease, we recommend prophylaxis with LDUH (grade 1A) or LMWH (grade 1A). In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, we recommend the use of mechanical prophylaxis with GCS or IPC (grade 1C+).”¹⁸

Thus, these guidelines indicate that many cancer patients who need hospitalization are also candidates for VTE prophylaxis (Table 4).

Current practice of oncology is dominated by the care of ambulatory outpatients. Although the risk for VTE is elevated in these patients, it is not elevated overall to a sufficient degree to warrant routine prescription of VTE prophylaxis. Care is taken to avoid thrombogenic drugs when possible. One example is prescribing an aromatase inhibitor (IA) rather than tamoxifen for postmenopausal estrogen receptor-positive breast cancer patients, by following the manufacturer guidelines for drugs such

Table 4. — Characteristics of Nonsurgical Patients for Whom the ACCP Guidelines Recommend Primary Prophylaxis With LMWHs Against VTE

Patient Characteristics	Recommendation
“Acutely ill who have been hospitalized with congestive heart failure or severe respiratory disease or who are confined to bed and have one or more risk factors including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease.”	LDUH (grade 1A) or LMWH (grade 1A)
LDUH = low-dose unfractionated heparin. Data from Geerts et al. ¹⁸	
Note: Aspirin is ineffective and not recommended.	

as thalidomide (Thalomid®, Celgene Corp, Warren NJ) or bevacizumab (Avastin®, Genentech, South San Francisco, CA), and by avoiding overcorrection when using erythropoietin preparations for chemotherapy-induced anemia.

Table 5 represents an attempt to identify the most significant risk factors for VTE in patients with cancer and to assign a score indicating their possible significance regarding VTE. The risk factors appear to be additive so summation of the scores from individual risk parameters may be appropriate. Cancer patients who are to undergo surgery are excluded from this scoring system since the vast majority of them require VTE prophylaxis.

The potential value of this draft scoring system can be illustrated by considering two examples. A 76-year-old woman who is bedridden due to progressing ovarian cancer and who has just developed an acute respiratory infection would score 8 of a possible 11 points and would be at sufficiently high risk for a VTE to consider anticoagulant prophylaxis. In contrast, a healthy, active, premenopausal woman receiving outpatient adjuvant antitumor chemotherapy for a resected stage II breast cancer would receive a score of only 2, reflecting an insufficient risk of VTE to warrant VTE prophylaxis.

It is hoped that a simple clinical system such as this can be validated so that rational guidelines can be developed to better address the indications for VTE prophylaxis in nonhospitalized patients with cancer.

Question #7. Should I prescribe anticoagulant prophylaxis for my patient who has a long-term indwelling central venous catheter?

The quick answer is no! ACCP guidelines make the following recommendations: “We suggest that clinicians not routinely use prophylaxis to try to prevent thrombosis related to long-term indwelling central venous catheters in cancer patients (grade 2B). Specifically, we suggest that clinicians not use LMWH (grade 2B), and we recommend against the use of fixed-dose warfarin (grade 1B) for this indication.”¹⁸

Several reasons support this recommendation. Contemporary evaluations of fixed low-dose warfarin do not support the evidence of effectiveness, and bleeding has occurred, especially in patients receiving fluorouracil-based therapy.²⁶ In addition, the incidence of catheter-related thrombosis has fallen to under 4%.²⁷

Question #8. What is the “gold standard” approach for diagnosing VTE in patients with cancer?

Clinicians are generally familiar with the “typical” symptoms of VTE: extremity swelling and pain from DVT, as

Table 5. — Draft Clinical Scoring System to Assess the Risk of VTE in Patients With Active Cancer but No Prior VTE*

Parameter	Suggested Score
Tumor type:	
– brain, ovary, pancreas, stomach	2
– other tumor types	1
Tumor stage:	
– extensive or stage IV	1
– stage 0-3	0
Activity/performance status:	
– immobile or ECOG PS 3 or 4	2
– ECOG PS 0-2	0
Comorbidities:	
– acute illness, CHF, respiratory failure	2
– no significant comorbidities	0
Age:	
– 75 or over	1
– under 75	0
Smoking:	
– active	1
– nonsmoker	0
Medications:	
– thalidomide, bevacizumab, tamoxifen, HRT, L-asparaginase, erythropoietin, cytotoxic chemotherapy	1
– other drugs	0

* This draft scoring system has been neither validated nor tested and is not currently intended to be used to guide clinical care. It is presented as an example to stimulate further work to more objectively assess VTE risk in outpatients with cancer.

well as chest pain, cough dyspnea, and fever for PE. VTE, however, may often be “silent,” without producing and signs or symptoms.

The measures to diagnose VTE in cancer patients are summarized in this supplement.⁶ For most patients, a venous compression duplex ultrasound is the initial screening test for DVT, and contrast venography is the “gold standard” to confirm the diagnosis in difficult cases. For PE, ventilation/perfusion lung scanning is supplanted by high-resolution computed tomography angiography. Use of the plasma fibrin D-dimer level to exclude a diagnosis of VTE is also discussed in this supplement.⁶ Since the prevalence of VTE is higher in patients with cancer than in noncancer patients, the predictive value of the D-dimer level to exclude a diagnosis of VTE is correspondingly lower.

Question #9. What is the best antithrombotic management for my cancer patient who has developed a VTE?

Recommendations by the ACCP are as follows:³⁰

Deep Vein Thrombosis

“For patients with objectively confined DVT, we recommend short-term treatment with SC LMWH or IV UFH or SC UFH (all grade 1A). For patients with a high clinical suspicion of DVT we recommend treat-

Table 6. — Optimum Antithrombotic Interventions for Secondary Prophylaxis Against VTE in Patients With Cancer

Drug	Trial	Results	Comments
Dalteparin	CLOT ¹⁵ (N=672)	52% reduction in new VTEs vs oral anticoagulation	Also longer survival in patients with nonmetastatic disease (6 months of therapy needed)
Tinzaparin	LITE ³¹ (N=737)	Reduction in new VTEs vs oral anticoagulation	Only limited data available in 2002 abstract

ment with anticoagulants while waiting the outcome of diagnostic tests (grade 1C+). In acute DVT we recommend initial treatment with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 (grade 1A).³⁰

Note that this latter recommendation would not be pertinent if LMWH is to be used as long-term prophylactic therapy.

Pulmonary Embolism

- For patients with objectively confirmed nonmassive PE, we recommend short-term treatment with SC LMWH, or IV UFH (both grade 1A).
- For patients with a high clinical suspicion of PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (grade 1C+).
- In patients with acute nonmassive PE, we recommend LMWH over UFH (grade 1A).
- In acute nonmassive PE, we recommend initial treatment with LMWH or UFH for at least 5 days (grade 1C).
- In patients with acute nonmassive PE treated with LMWH, we recommend against routine monitoring with anti-factor Xa levels (grade 1A).
- In patients with severe renal failure, we suggest IV UFH over LMWH (grade 2C).
- If IV UFH is chosen, we recommend administration by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (grade 1C+).
- In patients requiring large daily doses of UFH without achieving a therapeutic aPTT, we recommend the measurement of the anti-Xa level for dose guidance (grade 1B).
- We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 (grade 1A).

Thrombolytic therapy is not generally advised, and pulmonary embolectomy is used infrequently. Placement

of an inferior vena canal filter is indicated for patients with a contraindication for, or a complication of, anticoagulant treatment as well as for those with recurrent thromboembolism despite adequate anticoagulation.

Question #10. After an acute VTE event, what is optimum secondary prophylaxis program?

Long-term anticoagulation treatment is required to reduce a high frequency of symptomatic extension of thrombosis and/or recurrent VTE in patients with cancer. PE and DVT are manifestations of the same disease. Thus, the recommendations for the long-term treatment of PE and DVT are the same. Lee et al¹⁵ underscore the evidence demonstrating that dalteparin decreases the incidence of new VTEs by 52% compared with oral anticoagulation, and the ACCP recommendation for this indication in patients with cancer is as follows (Table 6):³⁰

“For most patients with DVT and cancer, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (grade 1A). Remark: The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin 200 IU/kg body weight daily for 1 month, followed by 150 IU/kg daily thereafter, or tinzaparin 175 mg/kg body weight subcutaneously daily.”³⁰

Decisions on the use of LMWHs for periods of longer than 6 months in patients with cancer require repeat clinical re-evaluation for VTE risk at the 6-month time point. Especially if the VTE was a PE, lifelong anticoagulation treatment is usually instituted.

Question #11. Are there differences between LMWHs?

LMWHs have replaced unfractionated heparins for most clinical indications since they have at least equivalent effectiveness and greater safety, and they also have the advantage of once-daily subcutaneous injection without laboratory monitoring.²⁸ However, unfractionated heparins may still be preferable in patients with renal failure.

LMWHs have a mean molecular weight of 4,000–5,000 d, with a range of 2,000–9,000 d. The agents available in the United States and Europe include dalteparin (Fragmin®, Pfizer Inc, New York, NY), enoxaparin

(Lovenox®, Sanofi-Aventis, Bridgewater, NJ), nadroparin (Fraxiparine®, GlaxoSmithKline, Research Triangle Park, NC), and tinzaparin (Innohep®, Pharmion Corp, Boulder, CO). These agents are prepared by different methods of depolymerization and have different molecular weights. LMWHs exhibit differences in pharmacokinetic properties and anticoagulant properties and thus are not clinically interchangeable.²⁸

Oncologists are already familiar with the issues surrounding addressing choices between apparently similar drugs. Three AIs — anastrozole (Arimidex®, AstraZeneca, Wilmington, DE), letrozole (Femara®, Novartis Pharmaceuticals Corp, East Hanover, NJ), and exemestane (Aromasin®, Pfizer Inc, New York, NY) — are currently available in the United States, all of which reduce levels of circulating estrogen in postmenopausal women and have been shown to be superior to tamoxifen in patients with breast cancer.²⁹ Is there a “class effect” of AIs so that substitution of an AI that is different from the one that has demonstrated effectiveness in a specific clinical trial situation is acceptable and effective management? Most clinicians prescribe the specific AI that has been demonstrated to be effective in a specific clinical trial situation rather than assume, perhaps incorrectly, that there is a “class effect” so that all drugs in that class may be exchanged for different indications with impunity.

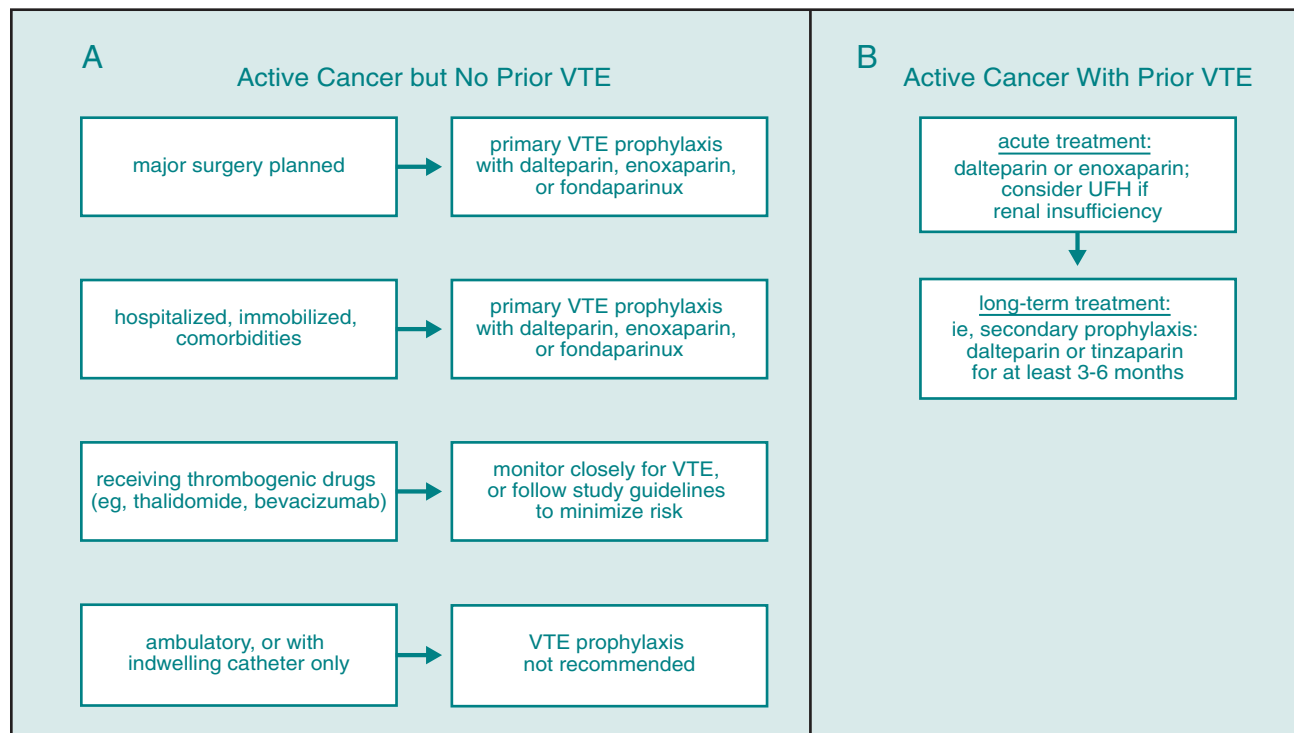
The ACCP guidelines agree with this approach of linking prescribing practice to clinical trial results. Thus, in relation to the long-term treatment (secondary prevention) of VTE in cancer patients,³⁰ they remark: “*The regimens of LMWH that have been established for long-term*

treatment in randomized trials are dalteparin 200 IU/kg body weight daily for 1 month followed by 150 IU/kg daily thereafter; and tinzaparin 175 IU/kg body weight subcutaneously daily.”

Dalteparin is the only LMWH to be published in a large-scale clinical trial in this patient population. The data relating to tinzaparin, however, are limited and only available in a 2002 abstract,³¹ and enoxaparin has not been studied for this indication. It is most appropriate, therefore, whenever possible, to prescribe the specific drug in the same dose and schedule that has been tested and shown to be effective and safe for each specific clinical indication in order to produce optimal outcomes.

Question #12. Do low-molecular-weight heparins prolong the life of a cancer patient?

This issue is fully discussed by Dr. Kakkar in this supplement.³² He summarized the tantalizing suggestions from the “FAMOUS” and “CLOT” trials, from a study in small-cell lung cancer using dalteparin, and from the “MALT” trial using nadroparin and concluded that these LMWHs may have a capacity to prolong the survival of selected patients with cancer. The effects seem to be apparent only in patients with a low cancer burden, so the generally short survival in those with extensive metastasis appears unaffected. The trial results are not sufficiently robust to recommend prescription of dalteparin or nadroparin to patients with cancer solely to extend their survival. How-



Management algorithm for prophylaxis and management of cancer with no prior VTE (A) or with VTE (B).

ever, this potential benefit is reassuring when the drugs are used for VTE. Further studies to discover the biologic mechanisms of this potential survival benefit, together with clinical trials in patients with a low tumor burden (eg, as adjuvant therapy in patients at risk for systemic recurrence), are warranted.

Conclusions

The evidence is clear that VTE is a common event and a significant issue in patients with cancer. The 2004 revision of the ACCP evidence-based guidelines¹ concerning VTE is an important contribution to medical practice, and specific recommendations have been made regarding thromboprophylaxis (especially in surgical patients) as well as the acute management of VTE and long-term secondary prophylaxis. A management algorithm that summarizes these recommendations is presented in the Figure in this paper. Of note is that thromboprophylaxis is not recommended for patients with long-term indwelling central venous catheter devices. Compliance with these guidelines will reduce the impact of VTE in the cancer population.

Nevertheless, important issues remain. One is the question of whether LMWHs can prolong survival in patients with “minimal disease” cancer. Another is the development of a reliable methodology for assessing VTE risk in individual patients with cancer who have had no prior VTE and who are not scheduled to undergo surgery. Continued research in these areas is needed.

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