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Dear Colleague:

It is a pleasure for me to share with you a topical publication entitled *Management of Thromboembolism in Cancer Patients: A Case Presentation and Discussion.*

My hope is that you find it a convenient, practical, and well-referenced monograph on the controversies associated with the management of thromboembolism in cancer.

We have incorporated a case study, which we feel is representative of the dilemmas one faces in treating many patients with cancer.

Lastly, I invite you to apply for the CME credit offered. I hope you will find this document informative and useful.

Yours sincerely,

Joseph A. Caprini, MD, MS, FACS, RVT
Louis W. Biegler Professor of Surgery

Presentation of Case Study

S.A. was a 70-year-old male who presented with a right calf deep-vein thrombosis (DVT) on December 18, 2000, involving the peroneal and posterior tibial veins without extension to the popliteal fossa or proximal venous system. He was admitted to the hospital and treated with unfractionated heparin (UFH) and warfarin. During the hospitalization a chest x-ray was done and revealed a right hilar mass. A chest CT confirmed this finding and showed mediastinal adenopathy. Mediastinoscopy revealed metastatic adenocarcinoma and subsequent workup resulted in a diagnosis of stage IIIB non–small cell lung cancer ($T_2N_3M_0$). There was no evidence of distant metastasis.

Discussion of Current Management Techniques

The case of S.A. (which will be continued throughout this monograph) illustrates the difficulties involved with the management of deep venous thromboembolism (DVT) and pulmonary embolism (PE) in patients with cancer.

Comorbid conditions, warfarin failure, difficult venous access, and a high risk of bleeding are just a few of the factors complicating anticoagulant therapy in these patients.[1]

While intravenous heparin and oral warfarin anticoagulation remain the traditional standard of care for DVT in the cancer setting, low-molecular-weight heparins (LMWHs) have been shown to be equally safe and effective in hemodynamically stable patients. They have performed favorably in acute DVT settings and are being studied as an alternative to warfarin in the chronic phase of anticoagulant therapy.[2]

Still, for long-term (chronic) treatment or secondary prophylaxis, the vitamin K antagonists remain the standard. The inconvenience of using warfarin, accompanied by its narrow therapeutic window, makes chronic or extended therapy unattractive and in fact problematic. These factors present an opportunity for the LMWHs.

The role of inferior vena cava filters in cancer patients is still poorly defined, but they appear to remain the treatment of choice in patients with contraindications for anticoagulant therapy. It must be kept in mind that in high-risk patients with proximal DVT the initial beneficial effect of cava filters for the prevention of PE has been shown to be counterbalanced by an excess of recurrent DVT, later in the therapeutic course.[3]

Patients known to have cancer, particularly those with mucin-secreting adenocarcinoma of the gastrointestinal tract or ovary, are believed to represent a very high-risk group for the development of secondary venous thromboembolism (VTE). In these patients the true risk of recurrent VTE has been reported to approach 50% in some studies.[4]

The material in this monograph will discuss the relationship between cancer and DVT and the difficult management issues that are involved in treating cancer patients with DVT.

Deep Venous Thrombosis in Cancer Patients

Epidemiology and Pathogenesis of Deep Venous Thrombosis in Cancer

A link between cancer and thromboembolic disease was initially reported in the 1800s by Trousseau.[5] This association, discovered more than a century ago, is now attributable to a variety of hemostatic abnormalities including increased platelet aggregation, activation of the coagulation cascade, changes in the fibrinolytic system, and decreased synthesis of anticoagulant proteins.[1] The risk of thromboembolic disease in cancer patients is further increased by surgery and chemotherapy.[6,7]

The prevalence of VTE in cancer patients has been estimated to range from 10% to 15%.[8] Levitan et al, using a large database of Medicare claims, found that patients with cancer had a significantly higher cumulative probability of hospitalization for DVT and/or PE than patients with nonmalignant conditions.[9] In the same study, the authors found that the incidence of DVT/PE was higher for patients with some cancers than with others. The highest incidence of DVT/PE occurred in patients with malignancies of the ovary, brain, pancreas, stomach, or kidney, and in patients with lymphoma. The lowest incidence of DVT/PE occurred in patients with malignancies of the head and neck, bladder, breast, esophagus, uterus, and cervix. There was a statistically significant difference in the incidence of DVT/PE between the group of malignancies with highest incidence and the group with the lowest incidence.

Table 1 Prevalence of VTE in Cancer

Cancer site	Prevalence (%)
All malignancies	10–15
Pancreas	28
Lung	27
Stomach	13
Colon	3
Breast (premenopausal)	1–2
Breast (postmenopausal)	3–8
Prostate	2
Unknown primary tumor	1

From Hillen[8]

Table 1 shows the estimated prevalence of VTE for the most common types of cancer.

There is also evidence that the incidence of DVT/PE recurrence is higher for cancer patients than for other patients. There are reports of the incidence of recurrent VTE in cancer patients approaching 50%.[10] In a study of patients who had an initial episode of DVT, those with cancer had 1.72 times the likelihood of having recurrent VTE as those without cancer.[11] Levitan et al in their study of Medicare patients reported that the cumulative probability of readmission with DVT/PE within 183 days was highest for patients with a previous diagnosis of DVT/PE and cancer. This group was followed, in descending order, by patients with a hospital discharge diagnosis of cancer; patients with a hospital discharge diagnosis of a nonmalignant disease such as stroke, pneumonia, diabetes, nephrotic syndrome, and congestive heart failure; and patients with only a hospital discharge diagnosis of DVT/PE. The differences between the groups in probability of readmission with DVT/PE were significant.[9] The cumulative probability of death within the same period of time was also highest for the patients with a previous diagnosis of DVT/PE and cancer.

Although nonspecific factors such as stasis can play a role in activating coagulation in cancer patients, more often coagulation is attributable to tumor-specific clot-promoting mechanisms.[12]

Figure 1. Coagulation Cascade
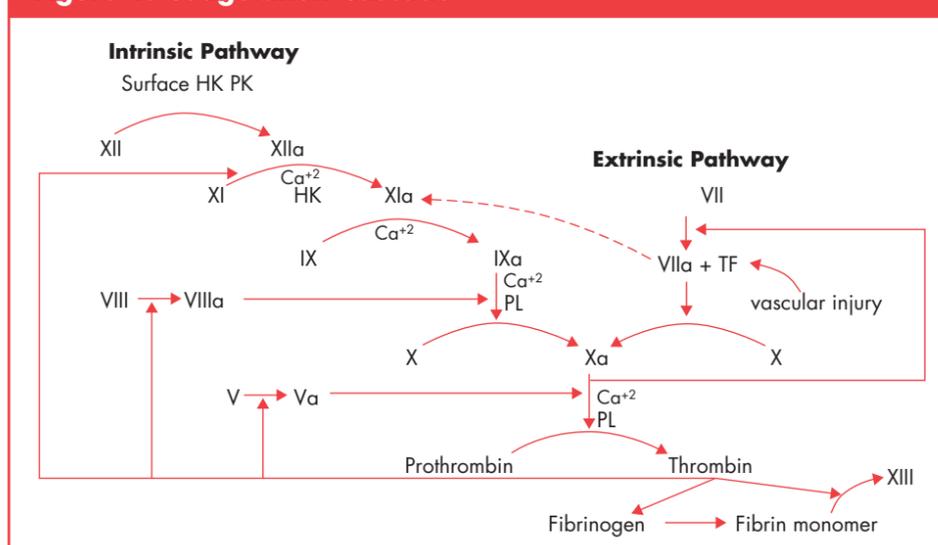
Figure 1. Diagram of the blood coagulation cascade. PL = platelet, TF = tissue factor. (Adapted from Furie B, Furie BC. N Engl J Med 1992;326:800-806.)

Figure 1 shows the currently accepted model of the blood coagulation "cascade." The cascade involves clotting factor activation reactions that follow *intrinsic* and *extrinsic* pathways. These two pathways converge at a common pathway where the final clotting factor is thrombin (factor IIa). Thrombin converts the soluble protein fibrinogen into insoluble fibrin. Covalent cross-linking catalyzed by factor XIII provides additional strength to the fibrin clot. There are a number of ways in which interactions between cancer cells and the hemostatic system can take place.

Figure 2. Regulation of Tumor Cell and Endothelial Cell Procoagulant Functions in the Pathogenesis of Thrombosis in Cancer

Rickles & Falanga. *Thromb Res* 2001;102:V215-24
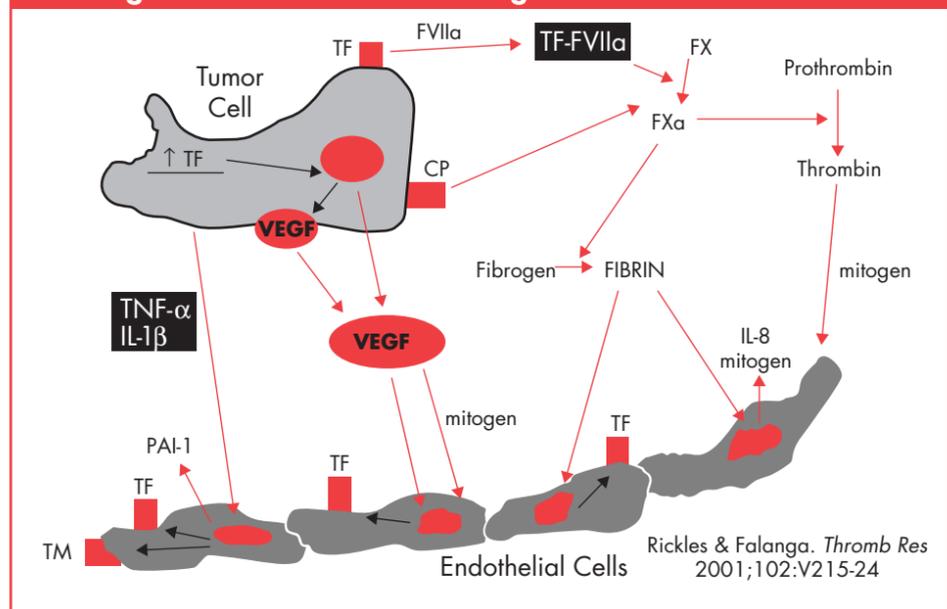
Figure 2. Principal pathways of tumor cell interactions with the hemostatic system. Tumor cells express (a) cellular procoagulants (tissue factor [TF]; cancer procoagulant [CP]; Factor V receptor) that activate the clotting cascade; (b) fibrinolysis proteins (urokinase-type plasminogen activator [u-PA]; tissue-type plasminogen activator [t-PA]; plasminogen activation inhibitor [PAI] and urokinase-type plasminogen activator receptor [uPAR]; (c) cytokines, including IL-1 and TNF, that induce endothelium thrombogenicity. They also interact (directly or through soluble mediators) with other blood cells, i.e., monocytes and platelets and also endothelial cells. F = factor, FV-R = factor V receptor, TM = thrombomodulin.

Figure 2 shows the main pathways by which interactions occur between tumor cells and the hemostatic system.[12] Rickles and Falanga have classified these interactions into two main groups:
1) synthesis of peptide and polypeptide mediators (procoagulants, fibrinolytic proteins, and cytokines) and
2) direct cellular interactions.[12]

The best-characterized procoagulants are cancer procoagulant and tissue factor (TF). Cancer procoagulant is an activator of factor X and acts at a different site on the molecule than other factor X activators.[14] TF, which in many types of cancer cells is hyperexpressed, is the main cellular activator of coagulation. The combination of tissue factor and factor VIIa results in procoagulant effects as well as nonprocoagulant effects such as angiogenesis.[1] Tissue factor pathway inhibitor (TFPI), the production of which is stimulated by LMWH and UFH,[12] inhibits both the procoagulant and nonprocoagulant effects of TF/VIIa.

Figure 3. Coagulation Balance: Inhibitors

Adapted from Bauer et al. *J South Orthop Assoc.* 2002;11:197-202
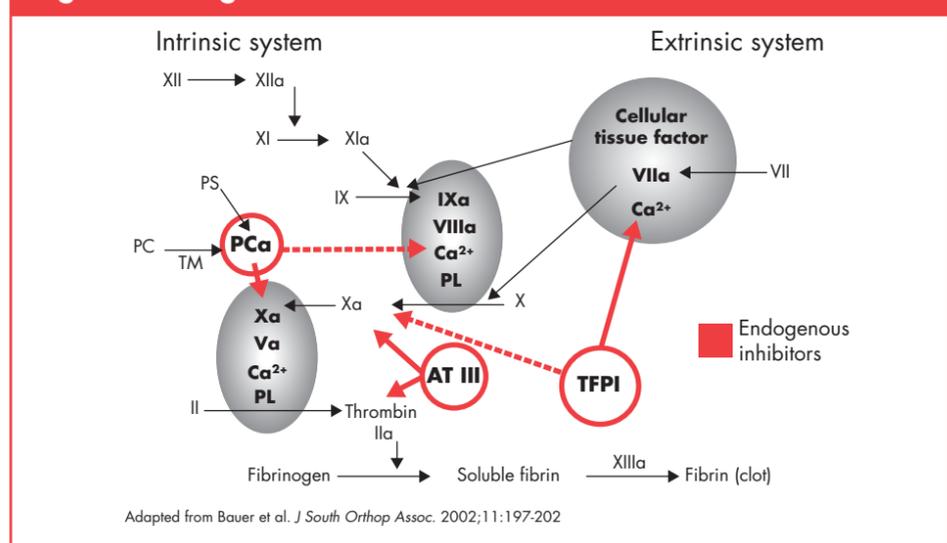
Figure 3. Diagram illustrating where tissue factor pathway inhibitor and other coagulation inhibitors act in the coagulation cascade.

Although tumor cells may express a number of fibrinolytic proteins,[15] the most widely expressed being urokinase-type plasminogen activator,[16] patients with solid tumors have been found to be impaired with regard to generation of normal fibrinolytic activity. This observation has led to the suggestion that this impairment could be a mechanism for explaining why these patients are particularly prone to developing VTE.[15]

Cytokines are also produced by malignant tumor cells.[17] These molecules can promote coagulation by acting on the vascular endothelium. In one such example it has been observed that the expression of tissue factor by vascular endothelial cells can be induced by the cytokines tumor necrosis factor-α and interleukin-1β.[18]

Direct cellular interactions of tumor cells can occur with endothelial cells, monocytes/macrophages, and platelets.[12] These interactions can promote VTE by affecting the hemostatic system through initiation of down-regulation of anticoagulant attributes and up-regulation of procoagulant effects.

Basic Science and Pharmacology of Low-Molecular-Weight Heparins

Low-molecular-weight heparins are produced by chemical or enzymatic depolymerization of unfractionated heparin, a heterogeneous mixture of sulfated polysaccharides.[19] The average molecular weight of UFH is 12,000 to 15,000 Da, whereas the average molecular weight of LMWH is 4,000 to 6,000 Da. The three LMWHs that have been approved in the United States—tinzaparin, enoxaparin, and dalteparin—have similar molecular weights; however, there is considerable variability among these LMWHs with regard to biologic activity. These differences in biologic activity result from variations in the methods of preparation.[20] Each of the LMWHs consists of mixtures of polysaccharides that are sulfated to a different degree resulting in variations of anti-factor Xa and anti-factor IIa activities. For example, the anti-Xa:anti-IIa ratios of dalteparin, enoxaparin, and tinzaparin are 2.0–4.0:1, 2.7–3.9:1, and 1.5–2.0:1, respectively.[19]

Both LMWH and UFH inhibit coagulation primarily by binding to antithrombin III. The bond depends on a pentasaccharide sequence that has a strong affinity for antithrombin III.[21] As a result of the bond, the antithrombin changes in configuration and inhibits factor IIa (thrombin) as well as factors IXa, Xa, and XIa. Unfractionated heparin simultaneously binds antithrombin III and thrombin. Because the saccharide units of LMWHs are shorter than those of heparin, LMWHs cannot simultaneously bind antithrombin III and thrombin (Figure 4). Therefore, unlike UFH, which accelerates the inhibition of thrombin to a greater extent than the inhibition of factor Xa, LMWHs mostly accelerate the inhibition of factor Xa.[19] As a consequence, LMWHs have relatively little effect on activated partial thromboplastin time (aPTT), a measure that is mainly sensitive to thrombin inactivation.

One advantage of LMWHs over UFH is greater bioavailability. The bioavailability of UFH given subcutaneously is variable, ranging from only 22% to 40%.[19] Examples of the greater subcutaneous bioavailability of LMWHs are tinzaparin, 86.7%; enoxaparin, 91.0%; and dalteparin, 87.0%.[22] Another advantage of LMWHs over UFH is longer elimination half-life. For example, the half-lives of enoxaparin, dalteparin, and tinzaparin are 2.2–6 hr, 2.0–6.0 hr, and 3.9 hr, respectively. The LMWHs also have less binding affinity for plasma proteins than does UFH. Because of the advantages of greater bioavailability, long half-life, and less binding to plasma proteins, LMWHs may be administered once a day in certain situations.

### Figure 4. Inactivation of Thrombin
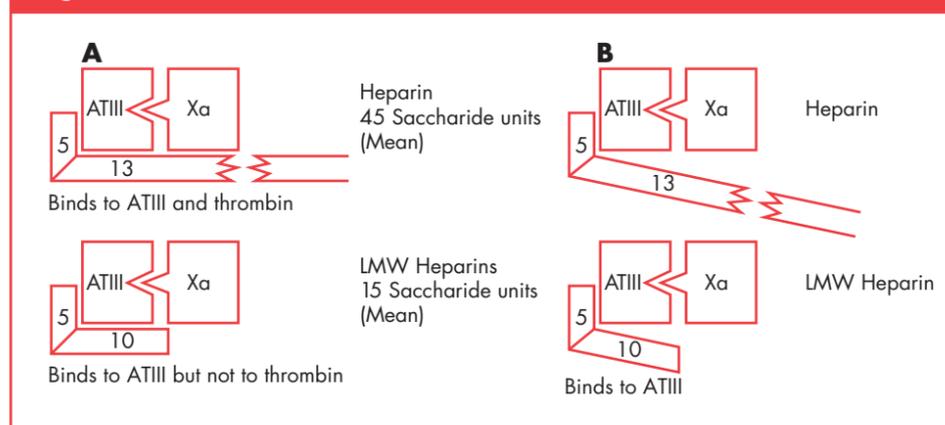
Figure 4. (A) Inactivation of thrombin. To inactivate thrombin, heparins must bind antithrombin III (ATIII) through the high-affinity pentasaccharide and to thrombin through an additional 13 saccharide units. Low-molecular-weight (LMW) heparins that contain fewer than 18 saccharide units cannot bind to thrombin and, therefore, are unable to inactivate thrombin. (B) Inactivation of factor Xa. To inactivate factor Xa, heparins must bind to ATIII through the high-affinity pentasaccharide but do not need to bind to factor Xa. Therefore, both standard heparin and LMW heparins are able to inactivate factor Xa. (from Hirsh and Levine, Blood 1992;79:1-17)

The clearance of LMWHs mainly occurs in the kidneys through a nonsaturable route.[19] This contrasts with the clearance of UFH, which occurs through a renal route that becomes saturable as the UFH dose increases.

Because LMWH given by subcutaneous injection has a high bioavailability, a nonsaturable elimination route, and a low binding affinity for plasma proteins, its anticoagulant response is more predictable than is UFH's. The predictability of the anticoagulant response has resulted in routine laboratory monitoring not being needed; the dose is based on the weight of the patient instead.[23]

S.A.'s past medical history included a smoking history of 40 pack years, previous prostatectomy in 1993 for cancer, colon resection for polyps in 1995, and bilateral inguinal herniorrhaphies twenty years earlier. The lung cancer was initially treated with induction chemotherapy, followed by concurrent chemotherapy with radiation. The chemotherapeutic agents used were Carboplatin and Gemcitabine. He tolerated this treatment program satisfactorily; however, on January 24, 2001, he presented with bilateral proximal DVT, while anticoagulation remained in the therapeutic range on oral anticoagulants with an International Normalized Ratio (INR) of 4.0 at that time. A duplex ultrasound was done because of leg swelling of about one month. The scan findings were uncertain as to acuteness, and there were no significant new symptoms aside from swelling; as a result, he was not restarted on heparin. His INR was kept above 3.0 and he was fitted with heavy compression stockings to control the leg swelling.

Risk Factors for Deep Venous Thrombosis in Cancer Patients

In hospitalized patients, having cancer and undergoing chemotherapy and having cancer without undergoing chemotherapy are associated with an increased risk of DVT (odds ratios, 6.5 and 4.1, respectively).[24] Other risk factors for DVT in hospitalized patients include surgery (odds ratio, 21.7), trauma (odds ratio, 12.7), and central venous catheter or pacemaker (odds ratio, 5.6). In outpatients, cancer is also associated with an increased risk of DVT (odds ratio, 5.6).[24] Additional risk factors for DVT in outpatients include obesity (odds ratio, 3.9), smoking (odds ratio 2.8), and oral contraceptives (odds ratio, 2.75).

There are a number of factors that influence the potential for cancer patients to develop VTE. These factors include tumor type and stage, chemotherapy, patient age, patient mobility, and surgery. Table 2 shows the percentage of cancer patients who have VTE associated with various risk factors.

Table 2 Association of VTE with Risk Factors in Cancer	
Risk Factor	**Patients with VTE (%)**
Immobilization	**14**
Cancer surgery	**20-40**
Central venous catheter	**3-21**
Chemotherapy	**8-10**
Hormonal treatment (BCP, HRT)	**2**

Modified from Hillen[9]

Table 3 Malignant Tumors Associated with VTE
Pancreatic tumors
Mucin-secreting adenocarcinoma from the gastrointestinal system
Lung carcinoma
Ovarian carcinoma
Endometrial carcinoma
Intracranial tumors
Acute promyelocytic leukemia
Myeloproliferative disorders

From Mousa[1]

Tumor Type and Tumor Stage

Table 3 lists various types of malignant tumors that have been associated with VTE.

The risk of thrombosis is higher for patients with stage IV breast cancer than for patients with stage II breast cancer. This higher risk of thrombosis has been attributed to increased tumor burden and factors such as immobility, infection, and surgery.[25]

Chemotherapy

For most types of cancer, there is little information available regarding the chemotherapy-induced incidence of thromboembolism. One exception is breast cancer, for which reliable information is available.[26] Increased rates of thromboembolism have been reported in a number of studies in which women with breast cancer were given adjuvant chemotherapy.[26-29] Postmenopausal women had a higher risk of thromboembolic events than did premenopausal women. [26]

Administering tamoxifen in addition to antineoplastics increases the risk of thromboembolism. In a study by Pritchard et al [28] postmenopausal women with stage II breast cancer who received tamoxifen plus other chemotherapy had a 9.6% rate of thromboembolism, which was significantly higher than the rate of 1.4% for such women who received tamoxifen alone. Similar results have been found in other studies of postmenopausal women with breast cancer. [30-32]

There is some information available on the risk of VTE in ovarian cancer patients who receive chemotherapy following surgery. Von Templehoff et al conducted a study of 60 patients with ovarian cancer of FIGO stage I–IV. The patients were randomly assigned to anticoagulation prophylaxis therapy with LMWH or UFH until seven days after surgery. Following surgery, the patients were treated with a regimen of cisplatin/epirubicin/cyclophosphamide. A total of 17 patients (28.3%) had VTE develop.[33]

Patient Age

There is a sharp increase in the incidence of DVT after age 40 in the general population.[34] In a longitudinal population study of men born in 1913 who were living in Sweden, the prevalence rate of confirmed VTE increased from age 50 through 80.[35]

Although the incidence of DVT increases with age, it has been suggested that, because there is an increase in comorbid medical and surgical conditions with age as well, age may not actually be an independent risk factor for DVT.[34] The effect of the kind of cancer found at surgery and patient age as a risk of DVT was analyzed in a study of 807 patients who were receiving LMWH prophylaxis.[36] The authors concluded that cancer had a greater effect than did age on DVT risk, although age also appeared to increase the risk of DVT.

Patient Mobility

A number of studies have demonstrated an association between patient immobility and the development of VTE.[34] Analysis of autopsy data from 253 patients showed that in patients who were immobilized for less than one week the incidence of VTE was 15%, whereas in patients immobilized for a longer period of time the incidence of VTE was 80%.[37] In a study of hospitalized patients, it was found that from the second to the eighth day of being bedridden, 13% of nonsurgical patients developed DVT, based on the results of daily fibrinogen I 125 leg scanning.[38]

Surgery

Cancer patients who have undergone surgery have higher rates of DVT than patients with nonmalignant conditions who have undergone general surgery. In a study of 203 general surgery patients by Kakkar et al, the authors found that the incidence of DVT was 41% for the patients with cancer and 26% for the patients who did not have cancer.[39] Walsh et al reported similar results in a study of patients with gynecological malignancy who underwent surgery.[40]

It has been reported that among patients undergoing surgery who are at very high risk for venous thromboembolism, including patients with cancer, 40% to 80% will develop calf vein thrombosis and 10% to 20% proximal vein thrombosis.[41] A study was reported that included 491 cancer patients and 1585 patients with nonmalignant conditions who underwent surgery and did not receive thromboprophylaxis; the rate of fatal PE was 1.6% for the cancer patients compared with 0.5% for the patients with benign conditions.[42]

The results of multivariate analysis suggest that although the incidence of DVT is higher for cancer patients who undergo surgery than for other patients who undergo surgery, malignancy itself may not be an independent risk factor for DVT.[43] Rather, the increased risk of DVT may be attributable to other well-known risk factors such as debility, advanced age, and a prolonged and complicated postoperative course.[2]

LMWH Prophylaxis for Deep Venous Thrombosis in Cancer

For cancer patients undergoing surgery, LMWH is increasingly becoming the agent of choice for VTE prophylaxis, although low-dose heparin (LDH) is also widely used.[44] Studies have been carried out to assess the safety and efficacy of LMWHs for VTE prophylaxis in cancer patients undergoing surgery.[45]

In one study, a prospective, randomized, double-blind, multicenter trial that included 2070 patients, 63% of whom had cancer, the patients were given the LMWH dalteparin in doses of 2500 anti-Xa units daily or 5000 anti-Xa units daily.[46] The administration of dalteparin began during the evening before surgery and was continued within 24 hours after surgery and then daily for at least five consecutive days, or until discharge from the hospital or an adverse event. Patients given 5000 anti-Xa units daily had a lower DVT rate than the patients given 2500 anti-Xa units daily (8.5% vs 14.9%, $P = 0.001$). At 30 days after surgery there was no significant difference in mortality rate between the groups. The higher dose did not increase the rate of bleeding complications for the cancer patients, even though, overall, the rate of bleeding complications in patients given the higher dose was 4.7% compared with 2.7% in patients given the lower dose.

In another study, which was also a prospective, randomized, double-blind, multicenter trial, patients with cancer who were undergoing elective surgery were randomly assigned to receive either the LMWH enoxaparin 40 mg once daily or LDH 5000 U three times a day.[47] The incidence of DVT in the enoxaparin and low-dose heparin groups was 14.7% and 18.2%, respectively. There were no differences between the groups with regard to bleeding complications, non-hemorrhagic complications, or mortality after 30 days and after 90 days.

In a prospective, double-blind study by von Tempelhoff et al, patients with previously untreated breast or pelvic cancer were randomly assigned to thrombosis prophylaxis therapy with a LMWH (n = 160) or UFH (n = 164) until seven days after surgery.[48] After 650 days the LMWH group had a 63.5% reduction in mortality rate compared with the UFH group ($P = 0.005$). Subgroup analysis demonstrated that a significant reduction in mortality associated with LMWH therapy applied only to the patients with pelvic cancer.

The treatment program worked very well and S.A. improved clinically: the lung tumor markedly decreased in volume, and his leg swelling disappeared. He did very well for about one year but then presented with bilateral leg pain, tenderness, and swelling. Duplex scan examination on March 28, 2002, revealed bilateral recurrent acute deep and superficial venous thrombosis. His INR was 8.0 and the warfarin was stopped. He was started on LMWH in a once-a-day, weight-based treatment dose. His leg symptoms quickly resolved, and a repeat CT scan of the chest showed no expansion of the lung tumor. He did well for three weeks. However, he presented to the emergency department on April 20, 2002, with blurry vision and confusion. Head CT scan revealed a large occipital tumor thought to be metastatic. At that time his platelet count had dropped below 50,000/mm³. Tests confirmed the presence of heparin-induced thrombocytopenia, and one of the consultants suggested the use of a thrombin inhibitor to block thrombosis. This plan was vetoed by the oncologist due to the cerebral lesion; a vena cava filter was placed. The patient had no respiratory symptoms at this time and a repeat chest CT scan showed little, if any, progression of the lung tumor. The patient deteriorated, became bedridden with leg swelling due to recurrent thrombosis including the inferior vena cava, and died suddenly on May 10, 2002. No autopsy was performed, but widespread thrombosis was judged to be instrumental in his death.

Approach to the Patient with Recurrent Thromboembolism and Cancer

Recurrent VTE is a common problem in cancer patients. Even when cancer patients are given adequate oral anticoagulant therapy, the rate of recurrent VTE is approximately 10%.[8] Prandoni et al have reported that patients with cancer have significantly higher rates of DVT during the first three months of oral anticoagulation therapy than do patients without cancer.[49] Confirmation of this finding was obtained in a multicenter study of more than 1000 patients with VTE.[50] As emphasized earlier, cancer patients with mucin-secreting adenocarcinomas of the gastrointestinal tract or ovary are believed to be at particularly high risk for recurrent VTE.[13]

Treatment protocols for patients with recurrent VTE during oral anticoagulation vary.[45] The main therapeutic options are LMWH or UFH, warfarin, and vena cava filters.

Low-Molecular-Weight Heparin Versus Unfractionated Heparin

For anticoagulation of cancer patients with VTE, the use of LMWH appears to have advantages over the use of UFH.[51] These advantages are in safety and efficacy as well as cost-effectiveness and ease of use.

The results of a meta-analysis of studies in which the safety and efficacy of LMWH and UFH for treating patients with VTE were evaluated led Siragusa et al to conclude that LMWH tends to be more effective overall for preventing recurrent VTE and that major bleeding episodes are less likely with LMWH.[52] The findings also indicated that LMWH is associated with reduced mortality in this population compared with UFH. The reduction in mortality was noted in the subgroup of cancer patients as well as in the overall treatment group. Reduced mortality associated with LMWH was also seen in a meta-analysis of nine studies comparing LMWH with UFH for treating cancer patients with VTE.[53] The findings of reduced mortality associated with LMWH compared with UFH led Prandoni et al to speculate that LMWH might exert an inhibitory effect on tumor growth that is not apparent with standard heparin.[45]

Hull et al compared tinzaparin with UFH in a multicenter, double-blind clinical trial of 432 patients, including 96 with cancer, who were being given initial treatment for proximal-vein thrombosis.[54] The incidence of major bleeding episodes was significantly lower in the group receiving tinzaparin compared with the group receiving UFH during initial therapy (0.5% vs 5.0%, $P = 0.006$).

Figure 5. LMWH vs UFH: Effect on Total and Cancer-Related Mortality

Hull et al. *N Engl J Med.* 1992;326:975-982.
Green et al. *Lancet.* 1992;339:1476.
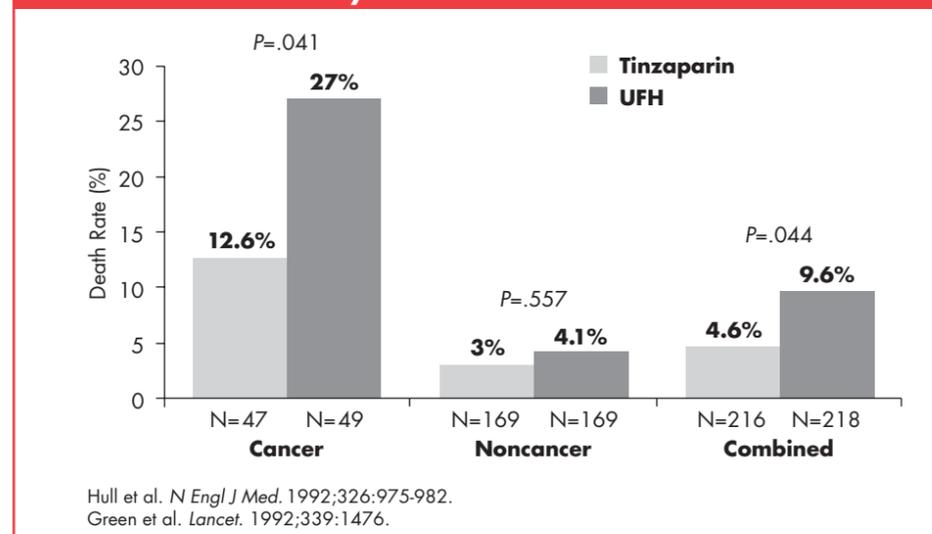
Figure 5. Comparison of the effects of tinzaparin versus UFH on total and cancer-related mortality. Based on Hull et al. N Engl J Med 1992;326:975-982 and Green et al. Lancet 1992;339:1476

As is shown in Figure 5, the mortality rate for the cancer patients given tinzaparin was lower than for the cancer patients given UFH (12.6% vs 27%). Green et al[55] examined mortality data for cancer patients from the study of Hull et al[54] and found that the mortality rate was significantly lower for the patients given LMWH ($P = 0.005$) than for those given UFH. Prandoni et al[56] also made a comparison of LMWH and UFH. In another study of 125 cancer patients initially being treated for venous thrombosis, the patients received either LMWH bid, LMWH qd, or UFH. A phlebographic response was observed in a significantly higher proportion of patients in both LMWH groups compared with the UFH group (both $P = 0.03$).[57] In a study of 185 advanced cancer patients without VTE the patients were given either dalteparin or placebo for one year.[58] Although there was no significant difference in survival between the two groups after three years, in a subgroup of 100 patients with a "good prognosis," survival was significantly better after three years for the patients given dalteparin than for those given placebo (59% vs 37%, $P = 0.04$).

Zacharski and Ornstein have listed a number of characteristics that might explain the observed differences in treatment outcome between LMWH and UFH that favor LMWH.[51] These characteristics include the following:
1) Neoplastic angiogenesis might be inhibited to a greater extent by LMWH than UFH;[59]
2) LMWH stimulates megakaryopoiesis, which could lead to attenuation of chemotherapy-induced thrombocytopenia;[60] and
3) the activating effect on osteoclasts is less for LMWH compared with UFH and therefore osteoporosis may be less of a concern.[61]

Heparin may play a role in the regulation of many biological processes and molecules in patients with cancer. However, most of the evidence indicates that the beneficial effects of heparin on malignant tumors are probably attributable to its effects on cell growth and proliferation, angiogenesis, or enzyme systems.[52] At least five specific mechanisms have been proposed to explain how heparin may affect malignant growth.[63] These mechanisms are based on inhibition of the following:
1) heparin-binding growth factors that promote malignant cell growth;
2) tumor angiogenesis;
3) tumor cell heparinase that mediates tumor cell invasion and metastasis;
4) cell surface selectin-mediated tumor cell metastasis; and
5) activation of blood coagulation, which may provide an environment conducive to tumor growth.

The effect of tinzaparin on angiogenesis has been studied in the chick chorioallantoic membrane (CAM) model.[1] Tinzaparin was applied to the CAM 24 hours after angiogenesis had been stimulated. Tinzaparin significantly inhibited angiogenesis and tumor growth induced by colon or lung carcinoma.

In these studies TFPI produced similar effects suppressing tumor vascularity leading to the speculation that the effects of angiogenesis mediated by LMWH are related to its ability to release TFPI.[1]

The use of UFH for treating patients with DVT raises safety concerns with regard to major bleeding, thrombocytopenia, and osteoporosis. According to Martineau and Tawil, although animal studies suggested that LMWHs may possess lower potential for hemorrhagic complications than UFH, the difference was significant in only two human clinical trials.[19] There are two types of heparin-induced thrombocytopenia: one type is nonimmune and resolves even with continuation of heparin therapy, and the other type involves an immune response. Clinical evidence is convincing that the incidence of the immune type of thrombocytopenia is lower with LMWHs than with UFH.[63] However, in vitro studies have demonstrated cross-reactivity between UFH and LMWHs; therefore, LMWHs should not be given to patients with a history of heparin-induced thrombocytopenia.[19] Long-term heparin therapy is associated with a 2.2% incidence of osteoporotic vertebral fractures.[64] Based on a study in rats, bone calcium loss might be significantly less with LMWHs than with UFH.[65]

As mentioned above, one of the advantages of LMWH versus UFH is cost-effectiveness. A number of studies have demonstrated this advantage. For example, in one such study, in which inpatients with DVT were given tinzaparin or UFH once daily, the savings by giving tinzaparin for 100 patients was approximately $40,000.[66] In another study in which patients received either tinzaparin or UFH for treatment of DVT, the total savings per patient was $621 when the patients were treated using tinzaparin as inpatients; the saving with tinzaparin ranged between $3000 and $5000 per patient when patients were discharged early or treated as outpatients.[67] A study of patients with DVT that was conducted in Switzerland showed that treatment with a LMWH reduced the cost of inpatient treatment over five days by about $150 per patient compared with treatment with UFH.[68]

The Role of Warfarin

The oral anticoagulant warfarin inhibits the formation of vitamin K–dependent clotting factors II, VII, IX, and X.[21] In standard therapy for prevention of recurrent VTE, "full-dose" warfarin is given for 3 to 12 months and the patient is monitored to maintain the INR between 2.0 and 3.0.[69] The extended use of full-dose warfarin reduces the rate of recurrent VTE; however, it is associated with a considerable risk of major bleeding.[70] Recently published findings from the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial indicate that low-intensity warfarin therapy, which attempts to maintain the INR between 1.5 and 2.0, is also effective for reducing the incidence of recurrent VTE but is not associated with a significant increase in the risk of major hemorrhage.[69] Patients randomized to low-intensity warfarin therapy had a 64% reduction in risk of recurrent VTE compared with patients randomized to placebo ($P<0.001$). Five patients in the warfarin group had major bleeding compared with two in the placebo group, a nonsignificant difference. This strategy can only be used after the regular 6–12 months course of full warfarin therapy has been completed.

In another recent study, LMWH has been compared with warfarin for prevention of recurrent VTE in cancer patients.[71] The patients (n = 146), who had various types of malignancies, were randomly assigned to three months of treatment with enoxaparin or with warfarin adjusted to an INR between 2.0 and 3.0. In the warfarin group, 15 patients had either major hemorrhage or recurrent VTE compared with seven patients in the enoxaparin group. The authors concluded that the long-term use of enoxaparin may be an effective and safe treatment for secondary prevention of venous thromboembolism in patients with cancer and venous thromboembolism. In an open-label randomized study of cancer patients with DVT and/or PE, the patients were treated with either the LMWH dalteparin for five to seven days (n = 336) and then warfarin for six months or dalteparin for six months (n = 336).[72, 73] The hazard rate for VTE recurrence was 0.48% in the dalteparin alone group compared with the warfarin group ($P = 0.0017$). The cumulative rate of recurrent VTE over six months was 8.8% in the group given dalteparin alone compared with 17.4% in the group that received warfarin. The incidence of bleeding episodes was similar for both groups. The authors concluded that long-term treatment with dalteparin is more effective than warfarin for preventing VTE recurrence in cancer patients without causing an increase in the risk of bleeding.

Hull et al, in a multicenter, randomized clinical trial of patients with proximal DVT, compared long-term treatment (84 days) with tinzaparin with five days of UFH treatment followed by long-term treatment (84 days) with warfarin.[74] During the 84-day study period a significantly smaller proportion of patients in the tinzaparin group had bleeding complications than in the warfarin group (13.0% vs 19.8%, $P = 0.01$). According to the authors, this finding demonstrated that initial long-term LMWH therapy is safer than initial therapy with UFH followed by warfarin. In another study by the same group, patients with proximal DVT were given tinzaparin for 84 days (n = 237) or LMWH for six days with warfarin, which was continued, for 84 days (n = 234).[75] Major bleeding occurred in one patient given only tinzaparin and in two patients given LMWH and warfarin.

Vena Cava Filters—Indications and Contraindications

The use of inferior vena cava filters to prevent PE from venous thrombi has been common since the 1960s. However, the effectiveness of these filters had not been assessed in a randomized trial until a recent trial was carried out by Decousus et al.[3] In this trial, 400 patients with confirmed proximal DVT who did or did not have concomitant PE and who were considered to be at high risk for PE were randomly assigned to receive a vena cava filter or not to receive a filter. The patients were also randomly assigned to receive LMWH (enoxaparin) or UFH. Beginning with day 4, the patients were started on oral anticoagulant therapy; the dose was adjusted to maintain the INR between 2 and 3. The main study endpoint was symptomatic or asymptomatic PE by day 12 after randomization. By day 12, a significantly smaller proportion of patients in the filter group had sustained PE than in the no-filter group (1.1% vs 4.8%, $P = 0.03$). Five patients in each group died during the first 30 days; thus in this study accurately placed prophylactic filters did not affect acute mortality. The results remained significant after adjustment for heparin therapy and PE at randomization. After two years of follow-up, recurrent DVT had occurred in a significantly higher proportion of patients in the filter group than in the no-filter group (20.8% vs 11.6%, $P = 0.02$). The difference in occurrence of symptomatic PE between the groups in two years was not significant. The proportion of patients who had died during the two-year follow-up period in the filter and no-filter groups was 21.6% and 20.1%, respectively. The authors concluded that, although their study showed that vena cava filters are initially efficacious for preventing PE in the patient population that they studied, "because of the observed excess rate of recurrent deep-vein thrombosis and the absence of any effect on mortality among patients receiving filters, their systematic use cannot be recommended in this population."

The role of vena cava filters for use in cancer patients has not been clearly defined.[1] However, vena cava filters are the treatment of choice when anticoagulant therapy is contraindicated, such as in patients with brain tumors, central nervous system metastasis, or pericardial tumors.[76]

Quality of Life Issues

The administration of UFH has a variety of negative effects on quality of life. Since the quality of life for patients with cancer is already compromised by their disease and treatments, additional problems from anticoagulant therapy need to be minimized. LMWH has a number of advantages over UFH with regard to quality of life, as can be seen in Table 4, which lists a number of differences between the two agents.

LMWH may also have advantages over warfarin with regard to quality of life issues. Hull et al compared the LMWH tinzaparin with warfarin in a study that assessed quality of life for patients with proximal vein thrombosis who received long-term anticoagulant therapy after hospital discharge.[77] An 11-item questionnaire was used to assess patient satisfaction and convenience. The responses to all items favored tinzaparin, and the overall score was significantly better for tinzaparin compared with warfarin ($P = 0.0024$).

A study of patients with venous thrombosis in which a LMWH administered at home was compared with UFH administered in the hospital used the Medical Outcome Study Short Form 20 to assess quality of life.[78] The responses to the questionnaire showed that patients given LMWH had less impairment of physical activity ($P = 0.002$) and social functioning ($P <0.001$) compared with patients given UFH.

Conclusions

Thrombogenesis is a complex entity in patients with cancer, but the clinical consequences of primary and secondary thromboembolism in these patients make it imperative that clinicians have a grasp of the current etiological theories, as well as treatment options and their associated risks and benefits.

This document has dramatically illustrated these points through the case presentation of S.A., a 70-year-old male with a complex history of non–small cell lung cancer, metastatic to the brain, accompanied by recurrent DVT, heparin-induced thrombocytopenia, and widespread thrombosis following treatment with a vena cava filter.

Current data indicate that although vena cava filters appeared to be initially beneficial for prevention of PE, this effect is outweighed by a later increase in the rate of recurrent DVT. Furthermore, recent studies demonstrate the efficacy of the LMWHs for the prophylaxis of primary and recurrent DVT in cancer patients. There is sufficient data to indicate that they provide a safe and cost-effective alternative which should be considered for prevention of DVT in appropriate cancer patients.

Table 4 Comparing LMWH with UFH in Quality of Life	
UFH	**LMWH**
Continuous, IV infusion	BID or QD subcutaneous injection
Primarily administered in hospital	Administered in hospital, office, or home
Usually administered by healthcare professionals	Administered by patient, caregiver, or professional
Monitoring and dosing adjustments	No monitoring, fixed or weight-based dosing
Frequent dosing errors	More precise dosing
Risk of thrombocytopenia and osteoporosis	Decreased risk of adverse events
Cheap, but not cost-effective	More cost-effective
Requires 5–7 days in hospital	Requires 0–2 days in hospital

From Mousa[20]

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PHARMION

CME QUESTIONS

Management of Thromboembolism in Cancer Patients

1. **Patients with cancer:**
   a. Frequently are in a hypercoagulable state.
   b. Are a very high-risk group for the development of secondary VTE.
   c. Are at increased risk of developing deep venous thrombosis if they have undergone cancer surgery.
   d. All of the above are true.

2. **Which type of cancer is associated with the highest prevalence of VTE?**
   a. Pancreatic
   b. Lung
   c. Colon
   d. All of the above have equal prevalence rates.

3. **Which statement(s) is/are correct:**
   a. There is good evidence that the incidence of DVT/PE recurrence is higher for cancer patients than for other patients.
   b. There are reports of the incidence of recurrent VTE in cancer patients approaching 90%.
   c. In one study reported herein, cancer patients who had an initial episode of DVT were 10 times more likely to have recurrent VTE than those patients without cancer.
   d. All of the above are correct.

4. **Which statement(s) below is/are *incorrect*?**
   a. Malignant tumors are known to express a number of fibrinolytic proteins.
   b. Patients with solid tumors have been found to be impaired with regard to generation of normal fibrinolytic activity.
   c. Malignant tumor cells produce cytokines, but these molecules cannot promote coagulation by acting on the vascular endothelium.
   d. Direct cellular interactions of tumor cells can occur with endothelial cells, monocytes/macrophages, and platelets.

5. **Which of the following statement(s) concerning low-molecular-weight heparins is/are correct?**
   a. The average molecular weight of UFH is 12,000–15,000 Da, whereas the average molecular weight of LMWH is 20,000–40,000 Da.
   b. Low-molecular-weight heparins are produced by chemical or enzymatic depolymerization of unfractionated heparin, a heterogeneous mixture of sulfated polysaccharides.
   c. All of the following are LMWHs currently available to the clinician: tinzaparin, dalteparin, nadroparin, ardeparin, and fondaparinux sodium.
   d. All of the above are correct.

6. **Advantage(s) of LMWHs over UFH include(s):**
   a. Greater bioavailability.
   b. A longer elimination half-life.
   c. Less binding affinity for plasma proteins.
   d. All of the above are correct.

7. **Which statement(s) is/are correct?**
   a. Risk factors for DVT in cancer patients include immobilization, cancer surgery, CVP catheters, chemotherapy, and schizophrenia.
   b. Cancer patients who have undergone surgery have been reported to have lower rates of DVT than patients with nonmalignant conditions who undergo general surgery.
   c. Even when cancer patients are given adequate oral anticoagulant therapy, the rate of recurrent VTE is approximately 10%.
   d. All of the above are correct.

8. **Which statement(s) concerning vena cava filters is/are correct?**
   a. The role of inferior vena cava filters in cancer patients is well defined and they remain the treatment of choice in patients with contraindications for anticoagulant therapy.
   b. The Decousus study of 1998 concluded that in high-risk patients with proximal deep-vein thrombosis the initial beneficial effect of caval filters for the prevention of pulmonary embolism has been shown to be counterbalanced by an excess of recurrent DVT.
   c. Vena caval filters are frequently associated with subarachnoid hemorrhage.
   d. All of the above are correct.

9. **Which of the following statements about quality of life issues in cancer patients receiving the heparins is/are correct?**
   a. UFH must be administered by continuous IV infusion; LMWH is given by SQ injection.
   b. UFH requires careful monitoring and dose adjustments based upon clotting parameters; LMWH requires no monitoring of clotting parameters and the dose is fixed and weight-based.
   c. UFH typically requires 5–7 hospital days to effect therapeutic levels of anticoagulation; LMWH requires considerably less time.
   d. All of the above are correct.

10. **Identify the correct statement(s):**
    a. The NIH controls approved uses for the LMWHs.
    b. Both LMWH and UFH inhibit coagulation primarily by binding to antithrombin III.
    c. A link between cancer and thromboembolic disease was initially reported in the 1800s by Otto Binswanger and is now known as Binswanger's Clotting Hypothesis.
    d. All of the above are correct.

Evaluation Form

Please circle the number that best reflects your opinion of the following statements with regard to this document, using the following rating scale:
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