

Venous Thromboembolism and Cancer: In Brief

Ever since the landmark clinical observations of Trousseau linking venous thrombosis and malignancy, this association has fascinated generations of physicians and other scientists. This monograph has been created to explore many facets of thrombosis and its relationship to malignancy. Venous thromboembolism is an important medical problem which has generally been under-appreciated due to the occult and insidious nature of clinical thrombosis. Patients developing pulmonary emboli often present as sudden death (34%), which makes successful treatment impossible. This problem is uncommon and often masquerades as other conditions such as cardiac events. Furthermore, most fatalities are not subjected to autopsy so the real incidence of this problem may not be apparent. Preventing this disease involves administration of anticoagulants to patients, which can cause bleeding in the surgical patient. Needless to say, this strategy is unpopular among surgeons since often the thrombosis is occult.

Thrombosis prophylaxis has been shown to be very effective in a number of randomized prospective studies done over the past three decades. Based on more than 900 articles in the medical literature, consensus guidelines have been developed and revised every two years for the past two decades. These guidelines are underused for a variety of reasons, including the fact that most thrombosis occurs following discharge and these episodes may be treated by another physician. Large referral centers, for example, are generally unaware of the fate of patients when they return to their local communities. What is particularly troublesome is the fact that 2/3 of all fatalities from pulmonary emboli are seen in medical patients. Surgeons in general have more organized

thrombosis prophylaxis protocols, although they tend to use non-anticoagulant modalities which, in some cases, are ineffective based on the level of patient risk.

One of the authors has worked on a risk assessment schema for the past 25 years in order to provide appropriate thrombosis prophylaxis based on the individual patient's risk. This risk assessment model is based on retrospective incidence data from clinical trials. It represents in some people's minds merely a thorough history and physical. Put another way, it parallels the checklist used by pilots before an aircraft is to fly. The risk factors are also weighted depending on the level of risk. For example, a hernia operation in a 35-year-old without other risk factors is not the same as a recurrent hernia operation in an elderly obese patient with a past history of cancer or DVT. Using this system for providing anticoagulants for the surgical patient, the level of risk for developing serious or fatal thrombosis is much greater than is the risk of bleeding. Surgeons need to realize that sudden fatalities from thrombosis can occur without prophylaxis and this denies the physician any opportunity to treat the problem. If anticoagulants are used, on the other hand, sudden fatalities from bleeding never occur and, although the bleeding can be a serious problem, there is the opportunity to treat the patient. Individuals with high risk scores or limited mobility may need extended out-of-hospital prophylaxis which may involve expensive injections. Using a risk model to identify these individuals may help proper selection of those most likely to benefit from the extended treatment.

Additionally, national organizations and accreditation agencies are embracing the concept of risk assessment linked to appropriate evidence-based prophylaxis.

Patients with malignancy are at increased risk for developing a thrombosis and patients presenting with thrombosis may harbor a hidden malignancy. Malignancy is a

strong risk factor for thrombosis and cancer patients need a greater degree of prophylaxis than do those with benign disease. These individuals have an inherent risk of developing thrombosis because of the hypercoagulable state associated with malignancy. They are also at greater thrombotic risk because of chemotherapy, radiation treatment, central catheters, and prolonged mobility. Thrombosis is considered to be the second most common cause of death in hospitalized patients. One-fifth of all thrombotic episodes are thought to occur in those with active cancer. In one study of patients with a first episode of thrombosis, malignancy was associated with a seven-fold increase in risk compared to no malignancy. In another study looking at discharge codes, the incidence of DVT was 2% in those with malignancy while only a 1% incidence was seen in those with no malignancy. Thrombotic incidence varies with type of cancer, the highest being in those with malignant brain tumors, hematologic malignancies, and a number of visceral adenocarcinomas. Patients with cancer are also more likely to suffer recurrent thrombotic episodes than are those with benign disease. Patients who suffer a thrombosis have been found to present with a malignancy as high as 34% of the time within 5 years. Unfortunately, in many of these cases, the cancer has already spread before it becomes clinically evident. This was observed in one study where 40% of those presenting with a DVT had a metastatic tumor appear within one year. Life expectancy is decreased in patients with thrombosis and malignancy, this combination being associated with a three-fold increase in mortality versus those with thrombosis and benign disease.

The presence of central venous catheters was found in one study to be the highest predictive factor for those with upper extremity DVT. Catheter-related thrombosis is a serious problem which is sub-clinical many times until serious embolization occurs.

When it is discovered, there is always a dilemma regarding removing the catheter and losing access, or just treating the thrombosis. Chemotherapy is another risk factor for thrombosis and the risk is magnified when using certain additional drug combinations such as steroids or erythropoietic drugs.

The importance of risk assessment in cancer patients cannot be overemphasized, including continuing prophylaxis for as long as the patient is at risk. This may entail long-term administration in selected individuals. Several risk assessment models are available and can be used to guide thrombosis prophylaxis regimes. It is important to use anticoagulant prophylaxis and the administration of one of several low molecular weight heparins (LMWH) following discharge has been shown to lower the incidence of thrombosis in cancer patients following abdominal surgical operations. A 50% reduction in recurrent thrombosis in cancer patients at one year was observed when treatment with LMWH for a six-month period was done instead of using only a short period of LMWH treatment and six months of oral anticoagulation. Consensus guidelines currently recommend against using oral anticoagulants for the first six months for treatment of thrombosis in cancer patients.

Even more exciting are the apparent antineoplastic effects of anticoagulants and inhibitors of angiogenesis. A number of studies have shown an improved survival in cancer patients treated with LMWH compared to other anticoagulants or placebo in patients without thrombosis. The combination of prospects for increased survival and reduced chance of recurrent thrombosis have caused some to recommend very long-term LMWH prophylaxis in those with cancer, especially when the disease is still active. Further studies are underway to confirm and refine these observations and, for most

clinicians, more data will be necessary to establish long-term prophylaxis as a widespread approach.

Another exciting concept regarding the pathophysiology of thrombosis is the relationship between inflammation and thrombosis. The contributory roles of microparticles (MP), P-selectin, and Tissue Factor (TF) to vascular inflammation and thrombosis have been a topic of research for one of the authors for at least 20 years. This story begins with Virchow who indicated that cancers tended to occur at sites of chronic inflammation. It has been observed that the development of cancers from inflammation may be driven by inflammatory cells as well as mediators, including cytokines, chemokines, and enzymes, which collectively establish an inflammatory microenvironment. Inflammation involving lymphocytes, plasma cells, macrophages and other inflammatory cells generate a great amount of growth factors, cytokines, reactive oxygen and nitrogen species. These may not only cause DNA damage that leads to tumor growth but they also promote vascular inflammation that sets the stage for thrombosis during the natural history of tumor progression. The selectins represent transmembrane molecules expressed on the surface of leucocytes and endothelial cells. They are important in leukocyte adhesion at the site of inflammation and injury. Microparticles, thought of as cell dust at one time because they are shed from a variety of circulating cells, are a storage pool of biologically important effectors. High levels of endothelial MP's have been reported in hypercoagulable cancer states. MP's have also been seen incorporated into the growing thrombus in association with tissue factor (TF) which is known to be the prime cellular initiator of coagulation.

P-selectin is stored in the platelets and endothelial cells and when released facilitates adhesion of leucocytes to activated platelets, a central event in thrombus formation. P-selectin inhibition has been found to be as effective as low molecular weight heparin in promoting thrombus resolution and in preventing re-occlusion, all without the risk of bleeding. P-selectin inhibition also appears to promote fibrinolysis and to decrease vein wall fibrosis. These observations are based on work done in primates involving major experimental venous thrombosis. We are all eagerly awaiting clinical trials to see if these experimental findings can be duplicated in humans. If this were to be true, one would have a way to prevent thrombosis without bleeding complications. Furthermore, this type of drug may also inhibit the progression of cancer and improve survival without the complications associated with the current anticoagulants.

Improving Thromboprophylaxis: An Individualized Approach to Risk Assessment

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Introduction

Venous thromboembolism (VTE) is a leading, though highly preventable, cause of in-hospital mortality and morbidity among both medical and surgical patients.

Implementation of an effective and targeted thromboprophylaxis strategy has been described as one of the most important steps that hospitals can take to enhance patient safety.¹ Effective assessment of VTE risk is vital for optimizing prophylaxis. However, thrombotic risk varies greatly according to the patient's predisposing risk factors (e.g., age and co-morbid disease) and the risks associated with their clinical situation (e.g., duration and type of surgery), making it difficult to assign patients to one of the categories of VTE risk described in current clinical guidelines.² Furthermore, the available clinical data do not cover every patient situation. Thus, a 'hybrid approach' to risk assessment—combining individualized risk assessment and evidence-based clinical reasoning—provides a logical and effective basis for a prophylaxis strategy. Many have contended that this approach is too complex, yet it is simply based on the patient's medical history and physical examination, both of which are essential parts of the patient encounter. This review summarizes the principles governing effective VTE risk assessment and the data supporting the application of this approach—data that has long been published yet often misinterpreted or overlooked. The application of an example risk-assessment model (RAM) is also presented.

Poor compliance with prophylaxis guidelines

Early studies have shown the clear benefit of prophylaxis: in a randomized multicenter trial conducted over 30 years ago on over 4,000 general surgery patients, subcutaneous heparin yielded a risk reduction of two-thirds for deep vein thrombosis (DVT) and at least half for fatal pulmonary embolism (PE) relative to the control group.³ This was confirmed in a metaanalysis of 16,000 patients some years later.⁴ Since this time, the publication of a substantial body of data across patient groups means that the rationale for prophylaxis is based on solid principles and scientific evidence.² Thus, the guidelines from the American College of Chest Physicians (ACCP) published in 2004 recommend that most surgical patients should have perioperative prophylaxis at an intensity dictated by their level of VTE risk.² However, reports continue to emerge indicating that prophylaxis is suboptimally used in many patients, both surgical and medical.⁵⁻¹⁰ The reported use of prophylaxis in surgical patients in the USA ranges from 38% to 94%, according to the type of procedure.^{7,9,11,12} Notably, a study investigating adherence to 1995 ACCP guidelines in surgical patients reported that a quarter of all patients undergoing high-risk major abdominal surgery were not given VTE prophylaxis of any type.⁹ Furthermore, in a retrospective analysis of VTE cases in a cohort of surgical and medical patients in the USA, it was found that one-sixth of all VTE cases and two-thirds of VTE cases for which prophylaxis was indicated could have been prevented if current ACCP guidelines had been followed.¹⁰ In this study, the authors observe that inadequate prophylaxis was most often due to the fact that no prophylactic measures were prescribed.¹⁰

Why is prophylaxis underused?

Although the data supporting prophylaxis have been available for a long time, its underuse persists. The main reasons underlying the inappropriate use of prophylaxis are summarized in Table 1. VTE is often clinically silent, with the first manifestation being a life-threatening or fatal PE, such that symptomatic VTE is rarely evident in the perioperative period. This, combined with today's short hospital stays, means that the majority of clinically apparent VTE events occurs after hospital discharge.¹³⁻¹⁵ Also, today's trend toward outpatient care, frequently provided by another physician, may make the risks of VTE and the benefits of prophylaxis more difficult to appreciate as the physician may not even be informed that their patient has later been diagnosed and is being treated for DVT. The importance of preventing all thrombi requires an educational process to alert the clinician to the long-term consequences of asymptomatic VTE, including the increased risk of recurrence and the clinical and economic consequences of the post-thrombotic syndrome.

In addition, the fact that VTE has few specific symptoms and is clinically silent in many patients makes diagnosis both difficult and unreliable. Although often minor, the symptoms can be the first (and only) sign of a VTE event. This can be of particular relevance among medical patients, many of whom are at significant risk of thromboembolism. Current ACCP guidelines² include recommendations for prophylaxis in medical patients, as more than two-thirds of cases of fatal PE occur in this patient group.¹⁶ Importantly, in the context of risk assessment, chronic medical illnesses, such as cancer and congestive heart failure, significantly increase VTE risk in patients who are undergoing surgery.^{2,17}

Concern over the associated bleeding risk is often given as a reason for not prescribing pharmacologic prophylaxis. There is, however, a substantial base of clinical evidence from randomized, placebo-controlled, double-blind clinical trials and metaanalyses supporting the safety of heparin-based prophylaxis. In most groups of patients, both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been shown to be very effective in preventing VTE at the expense of no, or a very small, increase in the incidence of major bleeding complications.^{4,18-22}

A significant proportion of patients do not receive appropriate prophylaxis—not because there is a lack of specific clinical evidence to guide prescribing decisions, but because the guidelines are ignored.⁹⁻¹² While there are potential risks associated with pharmacologic prophylaxis, major bleeding complications are extremely rare, and the consequences of not preventing VTE are much more severe.² Patients rarely die from anticoagulant-related bleeding but sudden death as the presenting feature of PE has been observed to occur in an estimated 34% of patients in a large PE population.²³

Individual risk assessment

An individual approach to risk assessment offers a number of benefits (Table 2).

Individualized assessment of thrombotic risk allows physicians to stratify patients according to their overall level of risk and to prescribe appropriate prophylaxis accordingly. There may be occasions where the level of risk is so high that elective quality-of-life procedures should be discouraged or at least require a different level of informed consent than that required for patients at lesser, but still very high risk.

However, VTE risk assessment is complex and must take into account both the patient's unique set of characteristics, such as age, chronic illness, history of VTE, and any

‘exposing risk factors,’ such as the type and length of operation. Many patients have multiple risk factors, which are considered to increase thrombotic risk due to their cumulative effect.²⁴ To be effective, therefore, a RAM must offer a simple and standardized method of scoring VTE risk.

Risk assessment models

One might consider a RAM as nothing more than a thorough patient medical history and physical examination where factors known to be associated with the development of thrombosis are tabulated and scored according to their relative risk of thrombosis. One such RAM is presented in Fig. 1.²⁵ This RAM is implemented using a ‘hybrid’ approach—applying the results of risk assessment to the current clinical guidelines. The model has clear lists of exposing and predisposing risk factors and a simple scoring system that allows patients to be assigned to one of four VTE risk categories described in the 2004 ACCP guidelines (low, moderate, high, very high).² Based on this stratification of patient risk, appropriate prophylaxis regimens can be recommended for both surgical and medical patients (Tables 3 and 4, respectively).

Risk-factor weighting

While the need for a practical, straightforward RAMs exists, oversimplification of the risk-assessment process could lead to an inaccurate assessment of an individual’s true risk. Thus a key element of the above RAM is the weighting of risk factors in accordance with the associated risk for VTE. Weighting is evidence-based using data from the scientific literature (Fig. 1). Where multivariate analysis has identified an independent risk factor for VTE, the data are clear. For risk factors showing an association with

increased risk, we assess the body of retrospective incidence data to assign an appropriate risk weighting. The examples of age, surgery duration, and malignancy will be discussed here.

Early work from Borow et al.²⁶ showed that increasing patient age and duration of surgery are both associated with an increased risk for DVT. Age over 60 years was shown to dramatically increase the incidence of thrombosis, with venographic DVT rising from 20.1% in patients aged 40 to 60 years, to 36.4% in patients aged over 60 years and 65.2% in those over 71.²⁶ Further studies have confirmed that the risk of VTE is increased in those over the age of 75,^{27,28} explaining why such individuals are assigned a greater point score in this RAM than those aged under 40. In the same study from Borow et al., the incidence of DVT was also shown to increase with surgery duration; an incidence of 20% was observed after procedures of 1 to 2 hours compared with 62.5% in operations lasting 3 or more hours.

For patients with a malignancy, there is up to a 6-fold increase in the incidence of VTE compared with those without a malignancy.²⁹ Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than 3 times the risk of fatal PE compared with non-cancer patients undergoing a similar procedure.² It thus appears logical to assign a greater weight to the cancer patient. The risk of VTE in these patients also steadily increases with the number of risk factors present. In a study of 507 patients with active cancer, hospitalization, prior DVT, DVT in the family, chemotherapy, fever, and elevated C-reactive protein were predictive of an increased VTE risk. In the absence of all these factors, the predicted risk was 2.3%, rising to 72% if all were present.³⁰

Case example

The impact of advancing age as a risk factor for VTE could mean that a minor operation, such as inguinal hernia, may confer substantial risk when performed on a person aged >75 years, yet minimal risk to a patient aged less than 40. Similarly, consider the case of a patient aged >75 years with no risk factors for VTE other than age, and undergoing a laparoscopic or arthroscopic procedure lasting more than one hour. This elderly patient will be at risk for postoperative VTE, especially if confined to bed or not fully mobile. There is no prospective trial covering this exact situation to help guide therapy, but assessment of VTE risk indicates that this patient may benefit from anticoagulant therapy, perhaps even for 5-7 days post-procedure as prescribed in the past on an inpatient basis. Such patients are now going home earlier or not being admitted at all. Is it justifiable to ignore the proven 5-7 day prophylaxis period simply on the basis of a change in setting?

Medical patients

Risk factors in medical patients are very similar to those in surgical patients, although the decision tree for thrombosis prophylaxis is much simpler (Table 4). Three large randomized prospective trials, MEDENOX,³¹ PREVENT,³² and ARTEMIS,³³ have demonstrated the value in acutely ill medical patients of anticoagulant thromboprophylaxis compared with placebo. In all these trials, the inclusion criteria included age over 40 (>60 years for ARTEMIS) at hospital admission and at least one other risk factor. It is clear from these studies that appropriate anticoagulant prophylaxis is effective in reducing VTE, with a reported relative risk reduction of between 45% and 63%. The use of graduated compression stockings (GCS) alone has not been shown to

provide this level of protection in these “at risk” patients,² but as demonstrated in surgical patients, there are data to support the addition of GCS to enhance the prophylactic effects of anticoagulants in medical patients.^{34,35} Further analysis of the MEDENOX trial showed that an acute infectious disease, age older than 75 years, cancer, and a history of VTE are independent risk factors for the development of VTE.²⁷ The previously mentioned data from Kröger et al.³⁰ indicate that in patients with cancer, the level of risk for VTE increases as the number of risk factors increases. We would view such patients, with cancer and additional risk factors, as having extremely high risk for VTE, and suggest that they receive both physical and pharmacologic modalities. Patients with a contraindication to anticoagulants should receive GCS and intermittent pneumatic compression (IPC) devices for prophylaxis. Recommendations for prophylaxis in medical patients are summarized in Table 4.

RAMs in practice: too complex?

Although RAMs are developed with the aim of offering a simple and standardized method of VTE risk scoring, implementation has thus far been poor. Critics of this approach have said that the length of the checklist or complexity of the scoring system may make them impractical for everyday use. However, as we have shown, a RAM should be considered simply as a thorough medical history and physical examination, with a comprehensive list of weighted risk factors guiding treatment. The ACCP guidelines on the other hand classify surgical patients into four broad risk groups (low, moderate, high, highest) based on type of surgery (major or minor), age, and presence of additional risk factors.² According to this schema, a patient aged 60 years and having a colon resection for cancer would be categorized as high risk (3 factors: cancer, abdominal

surgery, and age) with IPC recommended as a suitable alternative to anticoagulant therapy. But IPC is not an acceptable sole means of prophylaxis given an increased incidence of VTE in cancer patients of up to 6 times that of individuals without a malignancy. In the RAM presented here, the patient would be classified with 6 points, 2 each for age, cancer, and surgery, thus placing the patient in the very high risk category. The resulting recommendation would be for combined prophylaxis with anticoagulants post-operatively unless contraindicated.

Critics of the point system argue that if the patient in the above example should receive combined prophylaxis by scoring ≥ 5 , then a higher points total (i.e., through the addition of other risk factors) may be irrelevant. However, the type, onset, duration, and intensity of prophylaxis may be geared to the patient's score. Some patients may need to continue prophylaxis after hospital discharge, or those with very high scores may be counseled about the wisdom of undergoing an elective or quality-of-life procedure given their high degree of thrombotic risk.

The introduction of computerization is also simplifying the implementation of RAMs. Weighted VTE risk factors were employed in an electronic alert system developed to identify hospitalized patients at risk for VTE.³⁶ Implementation of the alert program increased physicians' use of prophylaxis and significantly reduced the 90-day incidence of venographic VTE by 41% ($P = 0.001$).³⁶ We are integrating the above RAM (Fig. 1) into our hospital patient database and including a similar 'alert' to improve prophylaxis prescribing patterns.

Furthermore, we recommend that the patient becomes an active partner in the prophylaxis decision-making process. Table 5 represents a simple questionnaire that can be completed

by the patient at the time of the initial encounter. Collecting information in this manner can greatly simplify the process of data collection and analysis.

In conclusion, individualized VTE risk assessment offers a way of integrating current prophylaxis guidelines and clinical judgment. If a carefully validated, practical RAM is implemented throughout a hospital, it can improve prophylaxis rates and ensure that the prophylaxis prescribed is appropriate to the patient's thrombotic risk. This is of particular relevance in the light of recent quality improvement initiatives that identify VTE risk assessment as a priority issue for increasing patient safety. In the USA, the National Quality Forum, with support from the Agency for Healthcare Research and Quality, has identified VTE risk assessment for all patients on admission to hospital, and regularly thereafter, as one of 30 evidence-based safe practices to reduce or prevent adverse events and medical errors.³⁷ Implementation of a RAM may help to simplify this process. We plan to prospectively validate and refine the thrombosis prophylaxis model presented here using appropriate 90-day clinical endpoints in inpatients and outpatients from both medical and surgical populations.

Cancer-Associated Thrombosis: Epidemiology and Methods for

Defining Risk

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Introduction

Thrombosis is considered to be the second most common cause of death in hospitalized patients with cancer, after death from cancer itself.³⁸ Patients with cancer have an inherent increased risk of developing venous thromboembolism (VTE) because of the hypercoagulable state associated with malignancy.³⁹ Cancer therapies (chemotherapy, hormonal therapy, radiotherapy), surgery, the prolonged use of central venous catheters (CVCs), and prolonged immobility all add to this risk.^{39,40} For the hospitalized cancer patient, particularly those facing surgery, adequate assessment of the risk of VTE and a management plan to reduce those risks is vital.² This article reviews the epidemiology of thrombosis in the cancer patient population and the role of risk assessment in optimizing preventive measures.

Thrombosis risk in patients with cancer

Incidence

The true incidence of VTE in patients with a malignancy is uncertain because of the heterogeneity of the cancer patient population, the presence of many confounding factors, and the difficulties conducting large epidemiological studies in patients with diverse diseases and variable prognoses. Two population-based estimates collected from Olmsted

County, Minnesota,^{40,41} yield a combined annual incidence of a first VTE of approximately 1 in every 200 cancer patients.⁴² With an estimated 1,399,790 new cases of cancer in 2006 in the USA, this would result in approximately 7,000 cases of VTE.⁴³ The results of a population-based, case-control study suggest that almost one-fifth of VTE cases are attributable to active cancer.⁴⁴ Cancer is an independent risk factor for VTE, increasing the risk by more than 4-fold, and rising up to 6.5-fold in cancer patients receiving chemotherapy.⁴⁰ An even greater risk was reported in a recent population-based, case-control study: for 3,220 patients with a first diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) malignancy was associated with a 6.7-fold (95% confidence interval [CI] 5.2-8.6) increased risk compared with no malignancy.⁴⁵

The association between VTE and cancer was highlighted by Stein et al.⁴⁶ in a study of discharge codes from the US National Hospital Discharge Survey. For more than 700 million patients over the period 1979-1999, the incidence of VTE in patients with malignancy was 2% compared with 1% in patients with no malignancy. This doubling of risk appeared to be reflected with incidences of DVT and PE of 1.6% and 0.6% respectively in cancer patients, compared with 0.8% and 0.3% in non-cancer patients.⁴⁶

Patterns of disease

The incidence of VTE among patients with cancer varies according to tumor type. Malignant brain tumors, hematological malignancies, and adenocarcinomas of the pancreas, uterus, ovary, stomach, and kidney are considered to confer highest risk of VTE.⁴⁵⁻⁴⁹ Data from the recently published US National Hospital Discharge Survey,

spanning 20 years and including 827,000 cancer patients with VTE, showed that the highest incidence of VTE, a rate of 4.3%, occurred in hospitalized patients with carcinoma of the pancreas.⁴⁶ The next highest incidence was 3.5% in patients with brain tumors. In a study by Blom et al., hematological malignancies were reported to confer the highest risk of VTE with a 28.0-fold (95% CI 4.0-199.7) increase over healthy controls.⁴⁵ While certain cancers are clearly associated with an increased risk of VTE, there are less data on the incidence of VTE according to stage of disease. Data that are available suggest that advanced metastatic cancer is associated with increased risk of VTE. Patients with solid tumors with distant metastases were reported to have a 19.8-fold (95% CI 2.6-149.1) increased risk of VTE versus cancer patients without metastases, representing a 58.0-fold (95% CI 9.7-346.7) increased thrombotic risk compared with the patient without cancer.⁴⁵ A study in 281 women undergoing surgery for cervical or uterine cancer reported that an advanced clinical stage of malignancy led to an increased risk of VTE. The incidence of VTE was 6.7% in clinical stage I disease compared with 30.7% in patients with clinical stage II ($P < 0.01$).⁵⁰ For women with breast cancer on chemotherapy, higher rates of thrombosis have been observed in those who are postmenopausal.⁵¹

Patients with cancer also have an increased risk of recurrent thromboembolic events compared with those without an underlying malignancy.^{47,52} The cumulative incidence of recurrent VTE in patients after a first episode of DVT rises from 17.5% (95% CI 13.6-22.2%) after 2 years to 30.3% (95% CI 23.6-37.0%) after 8 years.⁵² The concurrent presence of cancer further increases the risk of recurrent VTE by a factor of 1.72 (95% CI 1.31-2.25).⁵²

Cancer risk in patients with VTE

The incidence of cancer in patients with a primary diagnosis of VTE is reported to range from 7% in the first 6 months to 2 years after detection of VTE^{53,54} to as high as 34% over 5 years.⁵⁵ Several studies have reported that an unexplained thrombotic event may be an early indicator of an occult cancer.⁵³⁻⁵⁷ For example, Monreal et al. reported that in a consecutive series of 674 patients with idiopathic VTE, the diagnosis of an occult cancer was made in 15 patients at admission and in 8 further patients during follow-up, with the cancer typically at an early stage when discovered.⁵⁶

A retrospective analysis of data from two Danish registries collected over a 15-year period provides information on the risk of a diagnosis of cancer after VTE.⁵⁸ For 15,348 patients with DVT, there were 1,737 cases of cancer. Cancer risk linked with a VTE diagnosis was shown to be greatest in the first 6 months of patient follow-up.

Furthermore, 40% of patients who received a diagnosis of cancer within a year of VTE already had distant metastases at the time of cancer diagnosis. As in other studies, there were strong associations between VTE and a diagnosis of cancer of the pancreas, ovary, liver, and brain.⁵⁸

Impact of cancer-associated thrombosis on mortality

With the increased risk of VTE comes reduced life expectancy. Data relating to over 12 million Medicare patient admissions per year in the USA and evidence from prospective studies and national registries show that the combination of VTE and malignant disease is associated with at least a 3-fold increase in mortality.^{47,59,60} In long-term follow-up

studies, patients with cancer who develop VTE have an 8.1-fold (95% CI 3.6-18.1) higher risk of dying after an acute thrombotic event than patients without cancer.⁵² In addition, cancer patients with VTE have a 12% survival rate at 1 year in contrast to a 36% survival rate in patients with cancer and no VTE ($P < 0.001$).⁶¹ Levitan et al. demonstrated that the probability of death was highest for patients with concurrent DVT/PE and malignant disease compared with those with either malignancy or VTE alone (Fig. 2).⁴⁷

It has also been reported that as many as one in seven hospitalized cancer patients die of PE rather than cancer itself. As many as 60% of all cancer patients who died of PE had localized or limited metastatic cancer that would have allowed for reasonably long survival in the absence of PE.⁶²

Risk factors for thrombosis in cancer patients

Cancer is an independent risk factor for thrombosis.^{2,44,63} In addition to the recognized risk factors for VTE that apply across patient groups, such as age, obesity, and a history of VTE,² patients with cancer may have risk factors associated with their condition or treatment that further increases their risk of VTE.

Central venous catheters

Many patients with cancer require placement of CVCs for delivery of anticancer therapy and parenteral nutrition, to aid transfusion, and facilitate blood sampling. Long-term catheter placement has been associated with an increased risk of DVT. However, the reported incidence of clinically overt DVT in adult cancer patients with an indwelling CVC is conflicting, ranging from 0.3% to 28%, and rising to between 27% and 66%

when accounting for asymptomatic thrombi assessed by venography.⁶⁴ It has been suggested that changes in the way that newer generations of catheters are inserted or maintained have resulted in a lower risk of VTE.⁶⁵ Due to conflicting evidence, the risk of VTE with indwelling CVCs in cancer patients and the efficacy of VTE prophylaxis remain controversial.⁶⁶ Therefore, evidence-based guidelines do not recommend routine prophylaxis in cancer patients with CVCs.^{2,65}

Hormonal and cytotoxic chemotherapy

Chemotherapy is an independent risk factor for VTE.^{40,67} In the Olmsted county population-based study, the risk of VTE was increased 6.5-fold (95% CI 2.1-20.2) in patients with malignancy receiving chemotherapy and 4.1-fold (95% CI 1.9-8.5) in patients with malignancy not receiving chemotherapy, compared to patients without malignancy.⁴⁰ Data from two randomized controlled studies in patients with multiple myeloma indicate that the anticancer drug lenalidomide, an analog of thalidomide, given in combination with high-dose dexamethasone, resulted in a 3.5-fold (95% CI 1.77-6.97) increase in the rate of VTE. Concomitant administration of erythropoietic drugs further increased VTE rates.⁶⁸ An elevated prechemotherapy platelet count is also associated with a high incidence of VTE.⁶⁷

Hypercoagulable state associated with cancer

Tumor cells induce a hypercoagulable or prothrombotic state through a variety of mechanisms including the release of procoagulant substances, fibrinolytics, proinflammatory cytokines, and through angiogenesis and interaction with other blood

cells.³⁹ There may also be physical effects of an enlarging tumor, such as vessel compression, that can predispose to hemostasis and an increased risk of thromboembolism.

Surgery

Surgical intervention places patients with cancer at a 2-fold increased risk of postoperative VTE compared with non-cancer patients undergoing the same procedure.⁵¹ In addition to factors relating to the malignancy, the risk of VTE is elevated following cancer surgery through accumulation of other risk factors, such as advanced age, debility, prolonged or difficult surgery, and an often lengthy and complicated postoperative course.⁶⁹

Underuse of prophylaxis

There is strong rationale and evidence supporting the use of VTE prophylaxis in patients with malignant disease.^{2,65,70} Despite this evidence, many hospitalized patients at risk of VTE are prescribed suboptimal or inappropriate prophylaxis.⁹ In a retrospective record review from 10 US hospitals, only 50% of high-risk major abdominal surgery patients—of whom 71% had concurrent cancer—received VTE prophylaxis that conformed with American College of Chest Physicians (ACCP) guidelines.⁹ The problem of prophylaxis underuse extends to non-surgical cancer patients. In a worldwide survey of perceptions and practices regarding VTE risk among 3,891 oncologists, 52% would employ prophylaxis routinely in cancer patients requiring surgery, but in fewer than 5% of cases where surgery was not planned.⁷¹

Reasons for the underuse of thromboprophylaxis in surgical patients include the opinion that VTE risk is low, perhaps because this risk can differ by up to 10-fold between different patient diagnoses.⁴⁹ In addition, concerns may exist about the risk of hemorrhagic complications, especially that the use of anticoagulants may unmask the bleeding tendency caused by chronic disseminated intravascular coagulopathy.⁷² The primary objective of thromboprophylaxis in the cancer patient is to reduce the incidence of fatal PE since many patients may not live long enough to suffer post-thrombotic complications.⁷² To aid identification of patients most likely to benefit from VTE prophylaxis, a risk stratification approach can be used to classify patients in terms of their thromboembolic risk.

Risk assessment

Although it is clear that a large number of cancer patients will benefit from VTE prophylaxis due to their high risk of VTE, there may be a limited rationale for indiscriminately providing routine thromboprophylaxis to all cancer patients. However, the balance is tipped firmly in favor of prophylactic intervention in cases where there is a prior history of VTE, additional risk factor for thrombosis, or when surgery is planned. Thus, according to the National Quality Forum-Endorsed Set of Safe Practices, all patients should be assessed for thrombosis risk upon admission to hospital and periodically during hospitalization (Safe Practice 17).³⁷

A number of approaches to patient-risk assessment are available to ensure that an accurate evaluation can be made of cancer patients' VTE risk at various stages during their cancer management. The ACCP guidelines' approach to risk assessment (Table 6)² stratifies patients into one of four broad categories—low risk, moderate risk, high risk,

and highest risk—according to factors such as type and severity of surgery, age, history of VTE, and presence of other risk factors for VTE. Cancer is considered a key risk factor for VTE in the ACCP guidelines and can move a patient from a low-risk up to a higher risk category, particularly when surgery is indicated.² The ACCP provides evidence-based recommendations for the use of physical, pharmacologic and combined modalities of thromboprophylaxis according to risk category. Specific recommendations are made regarding time of initiation, dosing, and duration of prophylaxis.²

Another option for risk assessment is the common risk-factor approach, which is based on eight weighted risk factors as defined in Table 7. When a patient achieves a score of 4 or more they are identified as candidates for thromboprophylaxis.³⁶ In this common risk-factor system, cancer ranks among the major risk factors meriting the highest score (3 points). By simple arithmetic it can be seen that a cancer patient requiring major surgery (an intermediate risk factor scoring 2 points) is immediately eligible for VTE prophylaxis.³⁶ This approach was implemented in an electronic alert system linked to hospital patient databases that was designed to alert physicians and surgeons to a patient's risk of VTE. In the study testing the use of this system, physicians' use of prophylaxis was increased and the 90-day incidence of venographically confirmed VTE was reduced by 41% ($P = 0.001$).³⁶

It is also possible to apply a more detailed risk-factor assessment approach as shown in Fig. 3.²⁵ Drawing from currently available risk-assessment models, the detailed risk-factor assessment approach described by Caprini et al. considers a patient's predisposing and exposing risk factors for VTE, such as age, malignancy, surgery, immobilization, and CVC. Weighting of these risk factors is based on historical incidence data from prior

randomized trials. The sum of the risks is used to assign the patient to a risk group that broadly reflects the four risk categories defined by the ACCP, and recommend prophylaxis according to risk category. An accompanying safety assessment determines cases in which alternative prophylaxis should be considered (Fig. 3).

Benefits of anticoagulation

Antithrombotic effects

For the primary prevention of VTE, the benefits of prophylaxis in surgical oncology patients are supported by strong evidence.² Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) have shown equal efficacy and safety in reducing the risk of postoperative VTE in surgical cancer patients.² The Enoxaparin and Cancer (ENOXACAN) II study demonstrated the importance of continued prophylaxis for the period of ongoing VTE risk in 332 patients requiring surgery for abdominal or pelvic cancer. This study showed a VTE rate of 4.8% in patients receiving 30 days of enoxaparin (40 mg once daily) compared with 12.0% in those patients receiving enoxaparin for only 6-10 days ($P = 0.02$).⁷³ Less data are available for medical patients with cancer. Very-low-dose warfarin prophylaxis, constituting of 1 mg daily for the first 6 weeks, then adjusted to an International Normalized Ratio (INR) of 1.3-1.9 and continued throughout a mean duration of 181 days of chemotherapy, reduced the relative risk of VTE by 85% compared with placebo ($P = 0.031$) in patients with metastatic breast cancer. This reduction in VTE risk was observed without an increase in the bleeding risk in these patients.⁷⁴

In the secondary prevention of VTE, a number of studies show the promise of LMWH in reducing the incidence of VTE in cancer patients with a history of thrombosis. In a group of 772 cancer patients, the Randomized Comparison of LMWH versus Oral Anticoagulant Therapy for the Prevention of Recurrent VTE in Patients with Cancer (CLOT) trial showed that 5 months of dalteparin (200 U/kg for the first month, 150 U/kg thereafter) prophylaxis was associated with an 8% rate of recurrent VTE. This was half the rate of 16% for dalteparin given for 5-7 days followed by 6 months of therapy with a vitamin K antagonist adjusted to an INR of 2-3 ($P = 0.002$).⁷⁵ Long-term LMWH may also offer a survival benefit. In a post hoc analysis of follow-up data from the CLOT trial, the probability of death at 12 months was 20% in the LMWH group compared with 36% in the vitamin K antagonist group ($P = 0.03$).⁷⁶

Anti-neoplastic effects

Drugs that inhibit angiogenesis are currently creating interest as potential anticancer drugs through their actions to deprive tumors of the blood necessary for growth and metastases.⁷⁷ There is some evidence that anticoagulant therapies may also have some anti-neoplastic properties. Heparin inhibits the actions of procoagulant factors including tissue factor and factor VII, which are known to be released by certain tumors.³⁹ Animal models have demonstrated that heparin can also inhibit the so-called “platelet cloaks” that form around certain tumors.⁷⁸ Through such actions it has been postulated that heparin treatment may help attenuate tumor metastases.⁷⁸

A regimen of 5 weeks of subcutaneous UFH, initially 500 U/kg/day given in 2 or 3 doses and then adjusted by clotting times, has been tested in patients with small cell lung

cancer. In this patient population, UFH improves complete response (disappearance of all malignant lesions) rates from 23% to 37% ($P = 0.004$) and increases median survival from 261 days to 317 days ($P = 0.01$).⁷⁹ A 6-week course of the LMWH nadroparin, dosed according to weight class, also improves survival in patients with advanced solid malignant tumors. Nadroparin increased median survival from 6.6 months with placebo to 8 months (Mortality hazard ratio 0.75, 95% CI 0.59-0.96).⁸⁰ Dalteparin 5,000 U once daily during an 18-week course of chemotherapy also improved tumor response rates in patients with small cell lung cancer, from 42.5% for chemotherapy alone to 69.2% for chemotherapy plus LMWH ($P = 0.07$). Median progression-free survival was improved from 6 months to 10 months ($P = 0.01$) and median overall survival from 8 months to 13 months ($P = 0.01$).⁸¹ Warfarin-based anticoagulation has also been associated with prolongation in time to first evidence of disease progression in patients with small cell lung cancer ($P = 0.016$) and improvements in patient survival from a median of 23.0 weeks to 49.5 weeks ($P = 0.018$).⁸²

Conclusions

Patients with cancer have a high risk of VTE, estimated to be at least 4- to 7-fold higher than patients without evidence of malignant disease. Certain cancers, such as those affecting the brain, ovary, pancreas, colon, stomach, lung and prostate, and hematological malignancies are identified as conferring a very high risk of VTE. For any patient found to have DVT or PE, the impact on outcome is significant. It has been suggested that VTE may even serve as an early sign of occult cancer. VTE in cancer increases mortality risk; thus patients with malignant disease who could have responded reasonably to cancer management may die not of the cancer itself but of cancer-related VTE. Cancer induces a

hypercoagulable state, which can be worsened by anticancer therapies, thereby heightening patients' risk factors for VTE. In particular, surgery in the cancer patient confers a high additional risk, and there is a clear rationale and strong evidence to support thromboprophylaxis to prevent VTE in such patients. There is a wealth of guidance to support physicians and surgeons in assessing patient risk at admission and periodically during hospitalization, and to direct the choice of appropriate and optimal prophylactic management to prevent VTE. In addition to the proven benefits of anticoagulant therapy to reduce the risk and incidence of VTE in cancer patients, there is emerging evidence that anticoagulant prophylaxis may confer malignant disease benefits in the form of anti-neoplastic effects and survival benefits.

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Prevention of Venous Thromboembolism in Cancer Surgical Patients

David Bergqvist, MD, PhD, FRCS

Introduction

Since Armand Trousseau in 1865 described the association between thrombosis and cancer, this relationship has been repeatedly reported.⁸³ He meant, that so strong was the association, that in a patient with thrombosis, who was not pregnant or had tuberculosis, cancer should be strongly suspected. Ironically enough he himself died in gastric cancer half a year after having had a left-sided arm thrombophlebitis. This association later became known as Trousseau's syndrome.

There are many factors in cancer patients, which could be of pathogenetic importance for the development of thrombosis, a summary being given in Table 8. The purpose of this paper is, however, not to discuss those factors. Suffice it to say that the thrombogenic process in cancer patients is complex. The surgical procedure in cancer patients is also often more extensive than in non-cancer patients, and when it comes to operations within the lower abdomen and pelvis, there may be vein injuries as well. In most studies the duration of the operation is significantly prolonged compared to surgery for benign diseases. Patients with colorectal cancer have been associated with an increased frequency of thrombophilia, and in one study there was an increased frequency of resistance to activated protein C relative to a control group⁸⁴. In a recent multivariate analysis, five factors were identified as important to increase the risk of venous thromboembolism after cancer surgery: age above 60 years, previous venous thromboembolism, advanced cancer, anesthesia lasting more than two hours and bed rest for longer than three days.⁸⁵

Data from large epidemiological population based studies have now verified the original observation by Trousseau, that there is an association between malignant disease and thrombosis.^{58,86-88} The malignancies most frequently diagnosed in patients who present with deep vein thrombosis are localized to prostate, lung, colon, pancreas and stomach. Vice versa, there is also an increased risk of patients with a malignant diagnosis to develop thrombosis within the next few years, most prevalent malignancies being localized to lung, hematological and gastrointestinal organs, breast and brain.⁴⁵ Not only is there an association between the two disease types, but in patients having the combined diagnosis of a malignant disorder and venous thromboembolism the survival is significantly reduced compared with having either.⁴⁷ Cancer after an episode of venous thromboembolism has a worse prognosis than cancer without venous thromboembolism.¹¹⁴ In cancer patients who are carriers of the factor V Leiden mutation the risk of venous thrombosis is 12-fold that of patients with the mutation but no cancer.⁴⁵ In a large population-based autopsy study of 23796 patients, the risk of pulmonary embolism was significantly increased in patients with gastrointestinal and pulmonary adenocarcinoma, pancreatic cancer being the most aggressive in this respect.⁸⁸ Whether or not, an extensive cancer screening should be undertaken in patients with “idiopathic” venous thromboembolism has yet to be shown.⁸⁹

Postoperative thrombosis after cancer surgery

Today it is rare that patients are operated on for cancer without receiving thromboprophylaxis as cancer is placing the patient in a high risk group, of a similar risk as major orthopedic surgery (for instance ACCP (American College of Chest Physicians) guidelines 2004, Geerts et al., Table 9). From older studies using the fibrinogen uptake

test for thrombosis diagnosis, it can be concluded that abdominal surgery for cancer almost doubles the frequency of postoperative deep vein thrombosis in patients without prophylaxis (Table 10). Not only that, but in patients operated on for cancer this diagnosis is an independent risk factor for developing major postoperative thromboembolism despite “adequate” prophylaxis,^{13,17} an observation which is true also for fatal pulmonary embolism.⁹⁰ A high proportion of venous thromboembolism occurs after more than one month after the surgical treatment of cancer.^{13,85} The relative risk increase is about 70-75% and of the same order of magnitude as having had previous venous thromboembolism or a previous major orthopedic event.¹⁷ The highest rates of fatal pulmonary embolism is seen after surgery for malignancies in the small intestine, large bowel and pancreas.⁹⁰ Moreover, the thromboembolic events seem to be clinically overt to a higher degree in patients operated on for cancer.⁹¹ In patients undergoing colorectal surgery postoperative wound infection is an important risk factor for the development of deep vein thrombosis.⁹²⁻⁹⁴ Colorectal surgery implies a specific high risk for postoperative thromboembolic complications relative to other general surgery.^{13,95} The fact that these operations tend to be major, requiring pelvic dissection and the perioperative positioning of the patients, are likely contributing factors.

Prophylaxis

Many of the prophylactic studies in so called general surgery have included various proportions of patients with different forms of cancer. Most frequently the malignancies have been localized to the abdominal cavity or pelvis. That low dose unfractionated heparin has a thromboprophylactic effect is not disputed any longer and has been repeatedly shown.^{3,4,91} When low molecular weight heparins had been shown effective in

various surgical situations, a large randomized trial in cancer surgery showed enoxaparin to be equally effective as unfractionated heparin, using venographic surveillance for detection of deep vein thrombosis.⁹⁶ However, data pointed to the need of a higher dose of low molecular weight heparin in abdominal/pelvic cancer patients than in patients with similar operations for benign diseases, and in spite of the higher dose the prophylactic effect could be obtained without increasing the risk of bleeding complications.⁹⁷ So 5000 Xa inhibitor units of dalteparin gave a significantly lower frequency of thrombosis of 8.5% versus 14.9% with 2500 XaI units, the frequency of bleeding complications being without difference, 4.7 and 2.7% respectively. This dose dependent effect is one reason to place cancer patients in the highest risk group together with major orthopedic surgery, where also the higher dose is required.² In Table 11 studies on low molecular weight heparins in abdominal cancer surgery are summarized, the effect being significantly better than no prophylaxis and equal to that of unfractionated heparin. However, low molecular weight heparins have a number of advantages over unfractionated heparin such as a more predictable pharmacokinetic profile, a higher bioavailability after subcutaneous injection and a longer plasma half-life after subcutaneous injection allowing once-daily dosing.⁹⁸ Low molecular weight heparins also go with lower risks for heparin induced thrombocytopenia and osteoporosis.

There has been a concern on the potential risk to induce spinal hematoma when combining pharmacological prophylaxis and spinal/epidural catheters.^{2,99,100} Measures to reduce the risk should be taken as indicated in Table 12.

Duration of prophylaxis

In the mid 1990's it was demonstrated that clinically relevant thromboembolism was significantly reduced by prolonging prophylaxis from one to four weeks after elective hip surgery.¹⁰¹ Already in 1988, however, Scurr et al¹⁰² had demonstrated that a substantial proportion of patients (around 25%) undergoing major abdominal surgery developed thrombosis when they had left hospital, recently supported in the @RISTOS project.⁸⁵ Levine⁷⁴ could show that warfarin for 15 months (compared to placebo) significantly decreased the risk of thromboembolism in patients with advanced breast cancer. With this background it was logical to investigate the duration of prophylaxis also after abdominal cancer surgery, where many of the background factors could indicate an increased risk of venous thromboembolism also after weeks. So, in the first study in patients undergoing abdominal or pelvic surgery for malignancy all patients received enoxaparin for around one week and were then randomized to placebo or to continued enoxaparin, the so called ENOXACAN III study.⁷³ At phlebography after ca 4 weeks the group with prolonged prophylaxis had a significant reduction in venographic deep vein thrombosis (4.8 vs 12%). The effect was similar (5.5 vs 13.8%) after three months, excluding a rebound phenomenon after stopping prophylaxis. Supporting data were found in two small studies with tinzaparin and in an interim analysis from an open study with dalteparin.¹⁰³ Further studies on optimal duration of thromboprophylaxis in cancer patients are needed, but I would be surprised if this group would not benefit from prolonged prophylaxis just as hip surgery patients do. Another problem connected to prolonged prophylaxis which has to be addressed, is the health economic influence of the regimen.

Low molecular weight heparins and survival in cancer patients

For decades and with irregular intervals there has been a discussion whether anticoagulant therapy may reduce the morbidity and mortality from cancer.¹⁰⁴ This discussion has become revitalized and more focused after the development of low molecular weight heparins. There are indications from treatment as well as prophylaxis trials that low molecular weight heparins may give a survival benefit, at least in patients with a better prognosis.^{80,81,105-108} Apart from their anticoagulant and antithrombotic effects there are several other mechanisms which may play an important role explaining an effect of anticoagulant substances in cancer such as antiangiogenesis, modulation of the immune system, inhibition of tissue factor expression, antitumor effects by effect on extracellular matrix, on growth factors, on cell surface adhesion of circulating tumor cells and on smooth muscle cell proliferation.^{103,109-111}

New prophylactic substances

Any new prophylactic substance has to be compared with low molecular weight heparins and either be more effective or safer or have a simpler mode of administration and at least be as cost effective. There are two new principles in various stages of clinical testing and approval: Xa inhibition and IIa inhibition. A problem when new potential thromboprophylactic substances are tested is that major orthopedic surgery is often used as a model in the first run, which means that so called general surgery indications are delayed for perhaps several years. This can induce logistical problems when clinical introduction of the new substance is planned.

The Xa inhibitor fondaparinux, shown to be at least as effective as enoxaparin in major orthopedic surgery,¹¹² is effective also in high risk abdominal surgery.¹¹³ Once-daily dose

of 2.5 mg was started postoperatively. In a subgroup analysis in cancer patients (1408 of the 2048 randomized patients) fondaparinux was significantly more effective than dalteparin (4.7 vs 7.7% of venographically detected deep vein thrombosis).

The IIa inhibitor ximelagatran, also effective in major orthopedic surgery,¹⁰⁷ is adequately absorbed early after abdominal cancer surgery.¹¹⁴ Although this study was primarily aimed at analyzing pharmacodynamic effects, ximelagatran was at least as effective as dalteparin and seemed to have a better effect when prolonging the prophylaxis from one week to four weeks. This observation is important as the substance can be administered orally. A caveat, at present analyzed in detail, is an increase in liver enzymes after 2-3 months of treatment, almost all within 6 months.¹¹⁵ The reaction seems to be benign and reversible and is obviously of limited importance when postoperative prophylaxis is concerned, but the finding motivated rejection by FDA in September 2004¹¹⁶ and has recently made the pharmaceutical company Astra Zeneca to withdraw ximelagatran from further use.

Guidelines

In the 7th ACCP guidelines for 2004² the recommendations in cancer patients are:

7.0.1. We recommend that cancer patients undergoing surgical procedures receive prophylaxis that is appropriate for their current risk state (Grade 1A). Refer to the recommendations in the relevant surgical subsections.

7.0.2. We recommend that hospitalized cancer patients who are bedridden with an acute medical illness receive prophylaxis that is appropriate for their current risk state (Grade 1A). Refer to the recommendations in the section dealing with medical patients.

To summarize, the ACCP guidelines recommend “aggressive” thromboprophylaxis to cancer patients undergoing surgery.

Similar recommendations can be found in guidelines from the Swedish health care authorities (Swedish Social Board of Health and Welfare 2004), where regarding cancer patients is written: Low molecular weight heparins for one week are the first option. Prolonged prophylaxis for another 3 weeks may be indicated after abdominal cancer surgery, especially if other risk factors are present.

Conclusions

- Surgery for abdominal/pelvic cancer is a high risk situation for VTE
- Pharmacological prophylaxis is indicated
- Low molecular weight heparins are effective
- Extended post-operative prophylaxis should be considered but more studies are needed
- Thrombin inhibitors and factor Xa inhibitors are promising but more studies are needed
- Low molecular weight heparins may have a survival benefit in cancer patients

Treatment of Venous Thromboembolism in Cancer Patients

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Introduction

Venous thromboembolism (VTE) is a common complication of cancer⁷¹ and represents an important component of the total VTE burden accounting for around 20% of all cases.⁴⁴ The relative risk for VTE in cancer appears to be about 4- to 6-times that of the non cancer population,^{29,45} with cancer patients who have developed a thrombotic episode having a poorer survival than those who have never experienced this complication.^{61,87} Despite these epidemiological observations, VTE diagnosis and management is often neglected.¹²⁷

Managing the cancer patient with thrombosis is attended by a number of additional challenges. These include difficulties in achieving consistent anticoagulant control, drug interactions between cancer therapies and vitamin K antagonists (VKA), the more frequent need for interruption of therapy for invasive procedures or in response to thrombocytopenia and a less consistent anticoagulant response in poorly nourished cancer patients.^{128,129} Cancer patients experience both greater rates of recurrent thrombosis whilst receiving therapy and bleeding associated with their therapy^{130,131} with the resultant detrimental effect on quality of life.^{132,133} The treatment of VTE is considered in two phases, initial therapy with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and long term secondary prevention usually with a VKA.

Initial therapy

Irrespective of cause for thrombosis, the treatment aims for deep venous thrombosis (DVT) are to prevent fatal pulmonary embolism (PE) and treat the morbidity associated with the acute event, whilst preventing medium term recurrence of VTE and reducing the long term sequelae of the post phlebotic syndrome.² This is achieved in the initial treatment phase with either LMWH administered subcutaneously on a body weight adjusted basis without need for formal anticoagulant monitoring or with dose adjusted intravenous UFH according to monitoring of the activated partial thromboplastin time (aPTT) to achieve in 1.5-2.0 times the control value.¹³³⁻¹³⁶ Such therapy is administered for 5-7 days during which time treatment with VKA (warfarin or another coumarin) is commenced. These are dosed to achieve an international normalised ratio (INR) of 2.0-3.0.¹³⁵ Meta analysis of studies comparing intravenous UFH with subcutaneous LMWH indicated both initial treatment methods to be as effective in terms of preventing recurrent VTE with LMWH being safer.^{137,138} These studies also suggest that therapy with LMWH for initial treatment of VTE may be provided to patients at home.¹³⁹⁻¹⁴¹

Although there has been no formal evaluation of UFH versus LMWH for initial VTE treatment in cancer patients the results of meta-analyses suggest the use of LMWHs^{37,38,142-145} to be preferable, with a recent Cochrane review demonstrating both a lower risk of recurrent thrombosis and a lower risk of a major bleeding in patients who were treated with LMWHs.¹⁴⁵ The outcomes for cancer patients and non cancer patients in trials reported in these analyses indicate that although overall recurrence rates and bleeding rates were higher in cancer patients, the behaviour of LMWH and UFH within either cancer or non cancer populations was the same. Thus it seems appropriate to

extrapolate data obtained from the “general” population to the cancer patients group.^{142–145}

A frequently asked question with regard to initial VTE treatment with LMWH is what is the optimal LMWH regimen - once or twice daily? For the general VTE population a few studies have compared once-daily versus twice-daily LMWH therapy where cancer patients with thrombosis have been included and where outcomes in these patients have been reported.¹⁴⁶ Cancer patients receiving once-daily injections of the LMWH enoxaparin (1.5 mg/kg) had two-fold risk of recurrent VTE compared with those patients who were treated with twice-daily enoxaparin injections (1.0 mg/kg with each injection), although the difference was not statistically significant. A second study also found higher efficacy for twice-daily administered LMWH reviparin compared to a once-daily regimen in patients with malignancy and VTE.¹⁴⁷

The use of vena caval filters for treatment of VTE is in general only considered when full-dose anticoagulation is contraindicated or unsuccessful.¹³⁵ Although initially effective in preventing pulmonary embolism, in the longer term such filters are associated with more thrombotic episodes and as such require the utilization of oral anticoagulants potentially indefinitely.¹⁴⁸ Recently, the use of temporary caval filters has been advocated. These have the advantage that they can be removed after days or weeks of use, but have not been formally evaluated in cancer patients.¹⁴⁹

Long-term therapy

Conventional long-term anticoagulant therapy for DVT consists of warfarin or other VKA for a minimum duration of 3 to 6 months. In general such strategies are

followed in cancer patients, although continuation of anticoagulation beyond six months for those with active cancer or receiving anti cancer therapy has been advocated. Compared to non-cancer patients, the long-term secondary VTE prophylaxis approach with VKA is often sub-optimal for cancer population in regards of both efficacy and safety. It has been reported, that during warfarin treatment cancer patients experienced a 3- to 4-times higher risk of VTE recurrence and a 2- to 6-times higher risk of major bleeding as compared to non-cancer population on the same anticoagulation regimen.^{130,131} It appears that the recurrence risk is related to the extent of malignant disease.¹¹⁰ it might be suggested that more intensive anticoagulant regimens be adopted to overcome this higher recurrence rate seen in cancer patients but the risk of bleeding makes such an approach unattractive. Furthermore, in cancer population unlike non-cancer groups, the risk of bleeding during VKA therapy has a tendency to increase over time.¹³¹

In view of these difficulties, an alternative approach has been to use LMWH over 3 to 6 months to prevent recurrent VTE in cancer patients. Several LMWHs (dalteparin, tinzaparin and enoxaparin) have been investigated in randomized clinical trials as alternatives to VKA for long-term therapy in cancer patients.^{75, 150-152}

The ONCENOX study evaluated feasibility of LMWH therapy for prevention of recurrent VTE in cancer patients with compliance as a primary end-point.¹⁵⁰ The study included 102 cancer patients with DVT, PE, or both and compared three regimens: two doses of LMWH enoxaparin administered at a dose of either 1.0 mg/kg and 1.5 mg/kg once-daily by subcutaneous injection or a standard warfarin regimen, with all patients receiving initial LMWH twice daily for five days. No statistically significant difference

in the rate of recurrent VTE or bleeding during treatment period was found between the treatment arms; the trial terminated early.

The LITE study randomised 737 patients with proximal DVT to either the LMWH tinzaparin at a dose of 175 U/kg once-daily or intravenous UFH followed by full dose anticoagulation with warfarin over 3 months.¹⁵¹ Data were reported on the outcome of the 167 patients with cancer associated thrombosis, in whom was found a significant benefit of tinzaparin therapy over intravenous UFH/warfarin in terms of a reduction in the frequency of recurrent VTE. During the treatment period the rate of major bleeding in tinzaparin group was 6.3% versus 8.0% in warfarin group.

A third study – the CANTHANOX trial¹⁵²– randomised cancer patients with DVT, PE or both to either enoxaparin (1.5 mg/kg in once-daily subcutaneous injections) or warfarin; patients allocated to this group receiving 5-7 days of enoxaparin 1.5 mg/kg once-daily and receiving warfarin at a target INR of 2-3. The trial was closed prematurely with 147 patients. No significant difference in the primary end-point (combined outcome of recurrent VTE and/or major bleeding within 3 months treatment period) was detected between the groups: of those 75 patients randomised to warfarin, 21.1% had a major haemorrhage or recurrent VTE, compared with 10.5% of those 71 patients who received enoxaparin therapy (p=0.09).

The CLOT trial (Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulation Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer)⁷⁵ randomised 676 patients with a cancer associated proximal DVT and/or PE to either LMWH dalteparin initially 200 U/kg once daily for 5-7 days and then for the following 6 months – acenocoumarol (VKA) anticoagulation (INR 2-3) or

LMWH dalteparin in the dose of 200 U/kg for the first month and then 75-80% of this full-dose for the next 5 months. The primary outcome was that of objectively documented symptomatic recurrent DVT, PE or both, and secondary outcomes of major bleeding, all bleeding, and death. Over the 6-months period of treatment 27 of 338 patients in LMWH arm and 53 of 338 patients, in VKA arm had developed primary outcome event with the cumulative risk of recurrent VTE being 17% in acenocoumarol group to 9% in dalteparin group, a 52% risk reduction ($p=0.002$). Major bleeding was reported in 6% of patients in the dalteparin arm and in 4% in the VKA arm ($p=ns$).

Data from these studies suggests that LMWH therapy may offer an attractive alternative to oral anticoagulation for the long term secondary prevention of recurrent VTE in cancer patients. LMWH injections appear to be well tolerated with a recent quality of life survey suggesting that long-term thromboprophylaxis with LMWHs in the palliative care setting was preferable to warfarin having a positive impact on the overall quality of life.¹⁵³

The question of the duration of anticoagulation for cancer patients beyond six months remains controversial. Epidemiological evidence from prospective cohort and population-based studies indicates that cancer patients who suffered VTE as compared to non-cancer patients with thrombotic episode had approximately twice-fold higher risk of VTE recurrence after warfarin discontinuation.¹³⁵ It is well appreciated that the heightened risk of recurrent VTE in cancer may persist for many years after the initial event.¹³³ The prospective cohort study had shown that the figures of cumulative incidence of recurrent VTE in cancer patients were increasing over time after the initial event: at 2 years post-event - 17.5%, at 5 years – 24.6% and at 8 years – 30.3%.⁵² For those with

active cancer or those receiving active cancer therapy some form of anticoagulation should be considered beyond six months, although its nature and duration have yet to be formally evaluated in clinical trials.

An interesting observation of DVT treatment studies conducted over the past 15 years has been the survival advantage associated with LMWH therapy in cancer patients who have received thrombosis treatment. The question of whether long-term anticoagulant therapy with LMWHs could prolong survival in cancer patients has been addressed in a number of prospective clinical studies in which cancer patients received LMWH with mortality as a primary end-point.^{106,80,81} The first randomized placebo-controlled double-blind study Fragmin Advanced Malignancy Outcome Study (FAMOUS) aimed to evaluate the LMWH dalteparin in its impact on survival in 385 patients with advanced solid tumor malignancy.¹⁰⁶ The study failed to detect the prespecified 15% difference in mortality at 12 months after randomization, for which it was powered; the post-hoc analysis of a group of patients having good prognosis (those who survived beyond 17 months) demonstrated benefits of dalteparin therapy over placebo (p=0.03). The study suggested a persistent and increasing benefit in terms of survival for patients who received dalteparin.

A survival benefit in cancer patients was also reported in two further randomized studies.^{80,81} In one, patients with small-cell lung cancer receiving standard chemotherapy with or without the LMWH dalteparin for 18 weeks demonstrated a significant survival advantage at up to 36 months of follow up.⁸¹ A second study recruited patients with a variety of solid tumor malignancies and found a significant difference in probability of survival with the LMWH nadroparin compared with placebo administered for six

weeks.⁸⁰ In both these studies the investigators have detected more pronounced LMWH effect for patients with better prognosis at the time of randomization.

Conclusions

The management of VTE in cancer patients remains a challenge. It is a common complication and conventional methods for its treatment and long term secondary prevention which can be adopted successfully in the general population are less effective in the cancer population. LMWH therapy both for initial treatment and potentially for long term secondary prevention of recurrent episodes provides important therapeutic advantages.

The Pathophysiology of Thrombosis and Inflammation and its Relationship to the Cancer Patient

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Thrombosis in cancer: scope of the clinical problem

The first description of a definite relationship between cancer and the occurrence of thromboembolic disease dates to Troussseau's description in 1865.⁸³ This observation has since been well confirmed in several reports highlighting the increased risk of developing both venous and arterial thrombosis in patients with malignant disease.¹⁵⁴⁻¹⁵⁸ Cancer is associated with a hypercoagulable state manifesting as either clinical thrombosis or biochemical abnormalities in coagulation parameters¹¹⁰ and thought to account for a significant increase in the morbidity and mortality of malignant disease.³⁹ Hemostatic disorders in malignancy range from the occurrence of venous thromboembolism (VTE) typically in association with primary solid tumors to disseminated intravascular coagulation (DIC) predominantly seen in patients with hematological malignancies.⁵¹ While many thrombotic events are spontaneous in the absence of malignancy, patients with tumors have a high incidence and risk of VTE in the early months after diagnosis and this risk is further augmented following the development of metastatic disease.^{45,159} VTE is likely the second leading cause of death in cancer patients; approximately 20% of new cases of symptomatic VTE occur in cancer patients.^{42,52,160,161}

Although the autopsy documented incidence of VTE in cancer patients is approximately 50%, this may not reflect the true incidence of cancer associated VTE since these patients receive chemotherapy or hormonal treatment which could themselves directly predispose

to VTE.¹⁶² Incidence of clinically important thrombosis ranges from 5% to 60%. Cancer patients have a 4-fold increased chance of developing symptomatic VTE compared to patients without cancer.²⁹ In men, pancreatic and lung cancers are particularly involved, while in women gynecologic, pancreatic and colorectal cancers are most frequently associated with risk for thrombosis. Hematologic malignancies seem to carry a lower risk.¹⁶⁰ Cancers of the pancreas, ovary and brain are most strongly associated with thrombotic complications.¹⁶³

Active cancer and chemotherapy increase the risk of VTE and from a clinical standpoint it is noteworthy that procoagulant effects are also contributed in part by anticancer chemotherapy and radiotherapy.¹¹⁰ Both venous and arterial thromboembolism is commonly seen in breast cancer patients undergoing chemotherapy.^{164–166} The rates tend to be higher with upper gastrointestinal tract cancer and lung cancer, although in one study lymphoma was also associated, especially with cancer treated with at least one round of chemotherapy.⁶⁷ The rate of VTE also varied with pretherapy platelet count. By multivariate analyses, a prechemotherapy platelet count $\geq 350,000$, site of cancer, hemoglobin < 10 g/dl or use of erythropoietin, and use of white cell growth factors were associated with VTE.

There is a statistically significant and important association between idiopathic DVT and cancer.^{51,53} The development of cancer among patients with bilateral DVT is more frequent than patients with unilateral DVT, especially when the DVT is idiopathic.¹⁶⁷ The incidence of occult cancer in those patients who present with primary (idiopathic) DVT is between 6.5% to 16.6%, a 2 to 3-fold increase, especially in the first 6 to 12 months after presentation.¹⁶⁰ Risk of DVT with all types of cancers decreases with

time.⁵⁸ Patients with thrombosis have a poorer prognosis and a shorter survival than patients who do not present with thrombosis. Cancer diagnosed at the same time or within one year after an episode of DVT is associated with an advanced stage of cancer and poor prognosis.^{61,168}

Patients undergoing surgery are at increased risk of DVT/PE. Cancer surgery doubles the risk of postoperative DVT and triples the risk of fatal pulmonary embolism (PE), and is the most common cause of death at 30 days after surgery.^{2,13,20,69,85,169} The presence of indwelling central venous catheters⁶⁴ and prolonged immobilization in debilitated diseased patients may further increase in the risk of VTE in cancer patients.^{2,63,160,170,171}

A recent study evaluated the incidence of clinically evident VTE in patients undergoing cancer surgery.⁸⁵ A total of 2373 patients undergoing general surgery, urologic surgery, and gynecologic surgery were studied with greater than 4/5 of patients receiving VTE prophylaxis. The incidence of VTE was 2.83% in general surgery, 2.0% in gynecology surgery, and 0.87% in urologic surgery. Forty percent of these events occurred after the third postoperative week. Half of deaths (1.72%) were caused by the VTE. Factors associated with VTE were age >60 and had previous VTE, advanced cancer, anesthesia >2 hours, and bed rest >3 days.

Recently we¹⁷² investigated risk factors associated with VTE events in patients with malignancy. In this study of 566 patients with VTE and 416 without VTE with malignancy admitted to the University of Michigan between 1992 and 2000, we found a number of factors to be associated with VTE (Table 13).¹⁷² These included increasing age, solid tumor, leukopenia, infection, and advanced stage. Neutropenia, radiation, and

chemotherapy were not associated with VTE. Patient survival was also decreased in those with VTE. Factors associated with decreased survival included solid tumor, advanced stage, increasing age, neutrophil count, the presence of infection and the use of an antimetabolite (Table 14).¹⁷² Another recent study found that in cancer patients, risk factors for VTE were inpatient treatment, prior deep vein thrombosis (DVT), DVT in the family, chemotherapy, fever and C-reactive protein (CRP). In both inpatients and outpatients, the number of factors present predicted risk. Without factors, the incidence of VTE was 2.3% but if all factors were present, the incidence of VTE was 72%.³⁰ Another study has identified hospitalized neutropenic cancer patients to be increased risk of venous thrombosis.¹⁷³ We have also looked at these factors important for recurrent VTE in patients with cancer. In a series of 99 patients, recurrent VTE occurred in 40% of patients with significant risk factors including new metastases (OR 3.3) and history of VTE (OR 10.6). Although a single episode of neutropenia did not reach significance, multiple neutropenic episodes did reach significance for recurrent DVT. Mean survival was 30 months.¹⁶⁸

Overview of currently understood mechanisms of thrombosis in the cancer patient

The pathophysiology of VTE, DVT and PE in cancer patients depends on tumor type, extent of disease, host response, therapies used, and risk factors. Many tumors express tissue factor-like material, including gastric and pancreatic (often with Trousseau syndrome). Tumor infiltrating macrophages express tissue factor activity; activated macrophages produce interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF α) stimulating endothelial cell tissue factor (TF), downregulating endothelial cell anticoagulant activity, and stimulating releases of fibrinogen/fVIII.^{160, 174,175}

Subclinical activation of prothrombotic mechanisms reflects the host response to the growing cancer, and illustrates the ability of cancer cells to activate hemostatic mechanisms in a complex, multifactorial manner. In general, cancer cells initiate and promote the development of thrombosis by influencing procoagulant, fibrinolytic and proaggregating pathways; by augmenting proinflammatory cytokines; and by direct interactions with the blood vessel wall as well as with circulating blood cells. Notably, in cancer patients fibrin formation and dissolution is continuously ongoing at different rates putting the patients at risk of secondary thrombosis, and the increased fibrin formation is also implicated in the metastatic process.¹⁷⁶

Proposed prothrombotic mechanisms operative in cancer include: 1) the production of procoagulants (e.g., TF), inflammatory cytokines and the interaction between cancer cells and blood cells (monocytes, platelets) as well as endothelial cells; 2) thrombus promotion via host responses such as acute phase, inflammation and angiogenesis; 3) decrease in the levels of inhibitors of coagulation; and 4) impairment of fibrinolytic pathways.¹⁷⁷ From a clinical standpoint it is noteworthy that procoagulant effects are also contributed in part by anticancer treatment.¹¹⁰

Whereas multiple mechanisms are likely operative in the pathophysiology of thrombosis in cancer, it is important to recognize that the basic mechanisms for hypercoagulability in cancer also likely mediate metastasis. Therefore, an advanced understanding of the intimate relationship between thrombosis and cancer underscores that targeting effective control of coagulation in the cancer patient can not only prevent vascular complications but also has the potential to reduce metastasis, and possibly prolong survival.

As our understanding of the pathophysiology of thrombosis has advanced, the relationship of this in the cancer patient is beginning to emerge. In particular the role of inflammation and thrombosis, the contributory roles of Microparticles (MP), P-selectin and TF in this process are areas of ongoing investigation. The prothrombotic state of malignancy is complex and multifactorial.¹⁷⁷ Broadly, interactions between cancer and the hemostatic system disrupt the balance of procoagulants versus anticoagulants owing to tumor production of procoagulant substances. The net result is activation of the clotting cascade directly or indirectly by inducing an inflammatory response which in turn feeds back on tumor cells and stimulates further procoagulant release.^{157,158,161} This cycle may be further accentuated owing to the procoagulant effects triggered by chemotherapeutic drugs.¹³³

In the following sections we have summarized the role of these key players in the pathophysiology of DVT, with emphasis on the evidence for the cross talk between vascular inflammation and thrombosis and how this relates to the pathogenesis of DVT in the cancer patient.

Thrombosis and inflammation in the pathophysiology of thrombosis in cancer

Although the relationship between inflammation and cancer has received recent attention, the link between inflammation and cancers was noticed ~150 years when as early as 1863, Virchow indicated that cancers tended to occur at sites of chronic inflammation. Indeed, the development of cancers from inflammation may be driven by inflammatory cells as well as mediators, including cytokines, chemokines, and enzymes, which collectively establish an inflammatory microenvironment.⁷⁸ Inflammation involving lymphocytes, plasma cells, macrophages and other inflammatory cells generate

a great amount of growth factors, cytokines, reactive oxygen and nitrogen species. These may not only cause DNA damage that leads to tumor growth but they also promote vascular inflammation that sets the stage for thrombosis during the natural history of tumor progression.

Adhesion and cellular migration play a pivotal role in a number of physiological and pathological processes, including lymphocyte trafficking, leukocyte recruitment, hemostasis, wound healing, tumor angiogenesis and cancer metastasis. These fundamental cellular interactions are precisely regulated by temporal and spatial presentation of various cell adhesion molecules.⁷⁹ During inflammation associated with cancer progression the upregulation of adhesion molecules in concert with several of the mechanisms discussed below likely contributes to the increased risk for the development of venous thrombosis.

The role of microparticles in thrombogenesis

Thrombosis can be viewed as an inflammatory process. One aspect of this process revolves around selectin and MP biology, two interdependent fields. The selectins are transmembrane molecules expressed on the surface of leukocytes and endothelial cells. They play a critical role in leukocyte rolling and adhesion to areas of vascular injury and inflammation.¹⁸⁰ MPs are small submicron (≤ 1 micrometer) phospholipid vesicles shed from a variety of cell types including platelets, leukocytes and endothelial cells, vascular muscle cells and erythrocytes.¹⁸¹⁻¹⁸⁴ They are normal constituents of blood and can be isolated from plasma by ultracentrifugation. MPs lack DNA and RNA but are protein rich. The protein expression profile of MPs depends on the cell of origin and the conditions influencing their production. The protein and phospholipid content of MPs

determines their biologic activity. Subpopulations of MPs rich in TF and phosphatidylserine have been identified.^{185,186}

Although MPs, were initially recognized in the 1940's as a subcellular factor that facilitated fibrin formation, for long they were considered "cell dust". In 1967 MPs were described as small vesicles of platelet dust with procoagulant activity¹⁸⁷. Due to the recognition that MPs can act as diffusible messengers that interact with circulating blood cells as well as the blood vessel wall and supported by recent investigations, MPs are now thought of as a disseminated storage pool of physiological bioactive vascular effectors.¹⁸⁸ A challenging problem in this emerging area of research is delineation of the functional role played by endothelial MPs (EMP) and other MPs in health and disease.¹⁸⁹ High levels of MPs-associated TF have been reported in cancer hypercoagulable states^{190,191} and MPs carry a large-multimer von Willebrand Factor (vWF) which interacts with platelets to yield stable platelet aggregates.¹⁹² EMPs appear to play a role in hemostasis, thrombosis and inflammation. Furthermore, EMPs bind and activate leukocytes and enhance their transmigration.^{183,192}

More recently experimental and clinical studies indicate that, significant changes in MPs may contribute to the pathophysiology of vascular disease, inflammation and immunity.^{186,188,193-195} The interest in MPs has grown in recent years not only due to their procoagulant potential but because of their putative proinflammatory role. Furthermore, the association of increased MPs with inflammatory vasculopathy in atherosclerotic disease and increased thromboembolic risk emphasizes that reducing MPs formation and/or its target interactions may be a novel strategy to reduce proinflammatory and thrombotic risks. In particular, the association of TF with MPs and the incorporation of

MPs into the growing thrombus¹⁹⁶ have prompted intense investigation among vascular scientists, since TF is a prime cellular initiator of coagulation.

Pathological dysregulations leading to variations in the nature or proportion of circulating MPs (qualitative and quantitative aspects), and perhaps more frequently an augmentation of the number of circulating procoagulant MPs can result in an increased thrombotic propensity.¹⁸⁶ Elevated levels of circulating MPs have been reported in various disorders characterized by thrombotic complications particularly in cardiovascular diseases. The implication of MPs in inflammation is also well documented. Interleukin-1 β (IL-1 β) is observed in shed MPs, and MPs are a source of aminophospholipid substrates of secretory phospholipase A₂ for the generation of lysophosphatidic acid, a potent proinflammatory mediator and platelet agonist. Additionally, MPs favor endothelial activation and monocyte-endothelium interactions. Blood-derived MPs stimulate release of cytokines from EC and upregulation of TF expression at their surface. Platelet-derived MPs also enhance expression of cell adhesion molecules in monocytic and EC. Thus, MPs are key actors of blood coagulation.

MPs derived from platelets, endothelial cells and leukocytes have been shown to exhibit procoagulant properties.¹⁹⁷ The first demonstration of tumor shedding of MPs and a link to the hypercoagulable state of cancer was made in 1981.¹⁹⁸ Procoagulant activity has been observed in a guinea pig hepatocarcinoma cell line as well as a mouse breast carcinoma cell line both *in vitro* in tissue culture and also *in vivo*. Furthermore, procoagulant activity was associated with the shedding of membrane-derived microvesicles.¹⁹⁹ Despite the demonstration that MPs associated TF have been implicated in the prothrombotic state in patients, MPs have also been shown to facilitate blood

coagulation in the absence of TF as illustrated by membrane vesicles shed from guinea pig and human tumor cells in culture that promote functional prothrombinase activity.²⁰⁰

Collectively these observations indicate that MPs may both initiate blood coagulation and also allow thrombin generation by providing a surface for the generation of fibrin. Recent preliminary evidence from the literature suggests a possible role for TF-bearing MPs in cancer-associated thrombosis.^{197,210–203} We have demonstrated the association of leukocyte-derived MPs with venous thrombosis experimentally, and have also noted that measuring MPs combined with other markers such as d-dimer and soluble P-selectin increases the sensitivity of biomarkers for the diagnosis of DVT.^{204,205}

The role of P-selectin in thrombogenesis

P-selectin (CD62P), is the largest of the selectins, with a mass of 140 kDa. It extends approximately 40 nm from the endothelial surface and like the other members of the selectin family, has an N-terminal lectin domain, an epidermal growth factor motif, nine regulatory protein repeats, a transmembrane section and a short intracytoplasmic tail.²⁰⁶ P-selectin is stored in the alpha granules of platelets and in the Weibel-Palade bodies of endothelial cells. Exposure to an activating stimulus results in rapid translocation of P-selectin to the cell surface.²⁰⁷ E-selectin is upregulated after the initiation of thrombosis in a transcription dependent fashion. P-selectin can be secreted into the circulation as a component of endothelial cell and platelet derived MPs or, in small quantities, as a free, alternatively spliced version lacking a transmembrane domain (soluble P-selectin).²⁰⁸

Binding of anti P-selectin monoclonal antibodies to stimulated EC *in vitro* induces increased intracellular Ca^{2+} (mimicking polymorphonuclear leukocyte

adherence) and implies a possible role of P-selectin as a signaling receptor.²⁰⁹ However, a definitive role for P-selectin in downstream cellular signal transduction remains unexplored.²¹⁰ Binding of P-selectin to its receptor PSGL-1 primes leukocytes intracellularly for cytokine and chemoattractant-induced beta (2)-integrin activation for adhesion of leukocytes, and P-selectin mediates heterotypic aggregation of activated platelets to cancer cells and adhesion of cancer cells to stimulated endothelial cells.²¹¹

P-selectin facilitates adhesion of leukocytes to activated platelets and EC and is increasingly considered a key player linking thrombosis and vascular inflammation. P-selectin, is rapidly translocated to the plasma membrane upon cell activation and serves as the initial point of contact for adhesion of leukocytes to activated platelets or EC.²¹² Activation of platelets, a central event in thrombus formation, recruits leukocytes at the site of vascular injury²¹³ which may augment fibrin deposition within the thrombus. Several lines of evidence have demonstrated that platelet activation leads to exposure of P-selectin and interaction of P-selectin with its ligand PSGL-1.²¹⁴

Expression of P-selectin on EC can occur in response to inflammatory mediators such as thrombin, phorbol esters, or hypoxia, rapidly (occurring within minutes), generally reaching its peak at 10 minutes and declining to baseline after 3hr.²¹⁵⁻²¹⁷ Further P-selectin expression occurs within hours in response to inflammatory cytokines such as TNF α and IL-1.²¹⁶⁻²¹⁸ Likewise, there is increased P-selectin expression on platelets upon incubation with adenosine or epinephrine and increased platelet expression of this molecule is a marker of platelet activation.^{219,220} Nitric oxide (NO) regulates P-selectin expression as evidenced by increased P-selectin on EC in response to NO

synthase inhibition²²¹ and this reciprocal relationship between low NO metabolites and high P-selectin expression may be clinically important.²²²

Although the primary ligand for P-selectin is P-selectin glycoprotein ligand-1 (PSGL-1), a dimeric molecule rich in O- and N-glycans, P-selectin can also bind to heparin sulfate and fucoidan.²¹⁰ PSGL-1 is constitutively expressed on hemopoietic cells such as neutrophils, lymphocytes, eosinophils, monocytes and other myeloid progenitor cells where it mediates tethering and adhesion.^{223,224} Mice expressing elevated levels of P-selectin are thrombophilic, and P-selectin based therapy has been demonstrated to correct a mouse model of hemophilia.²²⁵ We have found that mice with a deletion of the P-selectin transmembrane domain, resulting in high levels of circulating P-selectin, have elevated thrombotic potential.²⁰⁴ In animal models of DVT, P-selectin expression regulates fibrin deposition and thrombus size.^{226,227} We have also demonstrated that P- and E-selectin deletions are associated with decreased thrombosis and the thrombi have decreased fibrin.^{228,229} In a primate model of stasis induced DVT, antibodies against P-selectin or antibodies directed toward the P-selectin receptor PSGL-1 inhibit thrombosis and promote recanalization.^{230,231} We have also demonstrated that P-selectin inhibition is an effective treatment for established primate iliofemoral DVT.²²⁸ P-selectin inhibition has been found to be as effective as low molecular weight heparin in promoting thrombus resolution and in preventing re-occlusion, all without the risk of bleeding. P-selectin inhibition also appears to promote fibrinolysis and to decrease vein wall fibrosis.²³²

P-selectin dependent tissue factor accumulation and fibrin deposition begins within the first 20 minutes of injury, before leukocyte rolling occurs. P-selectin is critical for the localization of MPs to areas of injury and inflammation.^{233,234} The PSGL-1: P-

selectin interaction promotes leukocyte and platelet rolling in areas of injury. P-selectin also stimulates the generation of thrombogenic MPs from leukocytes.^{225,235} These pro-thrombotic MPs express TF and possess an anionic surface.^{236,237} On the surface prothrombinase, tenase and factor V/Va assemble.²³⁸ MPs have been shown to accumulate in growing thrombi in a PSGL-1:P-selectin dependent fashion. Of interest, additionally, the anti-metastatic effects of anticoagulants reflect their action on P-selectin-mediated binding, further linking the P-selectin system, cancer, and thrombosis.²³⁹ In fact, different heparin preparations demonstrate vastly different potency to inhibit metastasis by inhibiting P-selectin dependent tumor cell interactions.

Role of tissue factor in the procoagulant state in cancer

TF previously known as thromboplastin, is a 47-kDa protein expressed in vascular and nonvascular cells. Tissue factor is localized to the outer aspects of the vein wall. Following vascular injury, TF is constitutively expressed in subendothelial cells such as vascular smooth muscle. TF is a prime initiator of coagulation and its expression is not restricted to the subendothelium but could also originate from stimulated monocytes and endothelial cells. Intravascular TF activity localized on injured endothelium is dependent on neutrophil, platelet, and MP adhesion, leukocyte-derived MP being readily associated with venous thrombosis.²⁴⁰ Colocalization of platelets and leukocytes on growing fibrin clot, and the reported generation of TF-bearing MP induced by soluble P-selectin point to the central role of inflammation during thrombogenesis.²⁴¹

Although TF is constitutively expressed on the surface of most non-vascular cells there is significant upregulation of TF in cancer cells. Moreover, in normal cells responding to inflammatory stimuli initiation of blood coagulation by TF occurs either

directly via TF expressed on the surface of cancer cells or indirectly via TF on endothelial cells, monocytes, macrophages and fibroblasts in response to inflammation.¹⁹⁷ Evidence supports that mononuclear cells are induced to express TF in certain forms of cancer.^{242,243} TF can promote tumor growth through two distinct mechanisms. First, TF initiates blood coagulation, resulting in generation of thrombin which is a potent mitogen that accentuates the growth and metastatic potential of cancer cells. Increased expression of protease activated receptor-1 (PAR1), the thrombin receptor, is shown to correlate with the malignant phenotype in breast cancer and the cytoplasmic tail of TF may be involved in vascular remodeling, angiogenesis as well as metastasis.²⁴⁴⁻²⁴⁶ Furthermore, the hemostatic pathway promotes TF-mediated vascular inflammation which indirectly increases thrombogenicity. TF-initiated coagulation generates thrombin, and this protease signals through activation of a unique class of G protein-coupled PAR 1, 3 and 4.²⁴⁷ Importantly, signaling activities of TF may occur before or even independently of thrombin and fibrin generation, platelet activation, and blood clot formation.²⁴⁸

Activation of coagulation facilitates adhesive spreading of cancer and demonstration of TF-ligation-induced cellular metastasis indicates that TF modulates cell adhesion.^{249,250} Tumor cell-expressed TF that forms thrombin is the precursor to fibrin generation involved in hematogenous tumor dissemination.²⁵¹ Thrombin regulates at least two important pathways in tumor cells. Thrombin-dependent PAR1 signaling induces proliferation of metastatic tumor cells,²⁵² and at low doses thrombin augments tumor cell survival consistent with findings in other cells.²⁵³ Thrombin signaling via PAR1 regulates tumor cell motility and thrombin has been demonstrated to decrease breast cancer cell motility.²⁵⁴

TF-triggered pathways contribute to changes in the tumor microenvironment.²⁵⁵ Furthermore, activation of coagulation produces proteolytic fragments of proteases, inhibitors, and extracellular matrix proteins which are potent regulators of tumor angiogenesis.²⁵⁶ One of the well illustrated mechanisms of TF influence on angiogenic pathways is via an upregulation of vascular endothelial growth factor (VEGF) and downregulation of thrombospondin.^{210,257,258} Local thrombin production induces VEGF signaling indirectly via either paracrine PAR1 stromal cell signaling or by autocrine activation of cancer cells. Moreover, suppression of antiangiogenic thrombospondins in TF-positive cancer cells could facilitate the action of angiogenic factors.²⁵⁵

Thus, elevated levels of circulating TF observed in cancer patients²⁵⁹ may contribute not only to the hypercoagulable state in cancer, but likely are intimately related with the tumor microenvironment and its dissemination. TF's role in tumor metastasis may be linked to TF procoagulant activity in the blood which could originate from many sources such as membrane-derived MP^{199,260} and leukocytes.²⁶¹ More recently shedding of TF-containing MP has been implicated as the main source of TF activity released from human cancer cells²¹⁰ and this source of TF could contribute to the prothrombotic state associated with cancer.

Indeed MP derived from monocytes are major carriers for blood borne TF.²⁴¹ Moreover, MP are procoagulant because of exposure of negatively charged surface phospholipids (principally phosphatidyl serine) and a subfraction of MPs which express PS and TF are highly procoagulant.²⁶² Monocyte-derived MPs are proposed to be a sign of vascular complication in patients with lung cancer, and elevated levels of circulating

platelet MPs are observed in gastric cancer with a potential role for MPs as metastasis predictors.²⁶³

Clinical implications, summary, and conclusions

A strong link between cancer and thrombosis is well recognized by the high frequency of tumor diagnosis in patients presenting with signs and symptoms of thromboembolism. Extrinsic factors such as chemotherapy, radiation, hormonal therapy, posturgical immobilization and the presence of long-dwelling central venous catheters augment this risk in cancer patients. The hypercoagulable state in the cancer patient presents a special challenge for treatment and also increases the risk of surgical complications and complications due to other invasive procedures.¹⁷⁷ Importantly, the dysregulation of hemostatic mechanisms via complex multiple pathways including procoagulant activity of tumor cells and host inflammatory response are intimately linked not only to the cancer associated thrombosis, but also likely operative in tumor progression and metastatic disease dissemination.²⁶⁴

Generally speaking, thromboembolic disease in patients with cancer is managed by standard antithrombotic therapy with unfractionated or low molecular weight heparin and warfarin as first line treatment. The primary aims are to treat the acute event, prevent death due to PE, and reduce the risk of recurrent VTE.^{69,265,266} However, the clinical management of VTE in the cancer patient may be complex and challenging and the occurrence of VTE contributes to a reduction in the quality of life of the cancer patient.

Remarkably, despite strong biochemical and clinical association between cancer and thrombosis observed in the literature, laboratory markers have not conclusively shown to be predictive of thromboembolic disease in cancer patients and are currently not

clinically useful in guiding thromboprophylaxis in cancer patients²⁶⁷ and the actual risk of VTE in a given cancer patient is difficult to determine. Currently it is challenging to assign the exact significance of a given factor/mechanism in the overall paradigm of thrombogenesis due to cancer and it is likely that perturbation of several factors is necessary for clinical thrombosis to develop. Since many mechanisms that have emerged to aid our understanding of the pathophysiology of thrombosis in cancer are derived from animal tumor models and *in vitro* cell culture investigations, the exact contribution of these in the context of thrombosis development in patients remains to be fully established. Nevertheless these advancements provide an opportunity to address the clinical problem by testing new targeted therapeutics to prevent and treat clinical thrombosis in the cancer patient. Furthermore, the reciprocal association between cancer induced thrombosis and tumor progression via growth angiogenesis and metastatic spread evokes consideration of antithrombotic therapeutic strategies to limit these processes.^{176,267}

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Table 1. Reasons for underuse of prophylaxis

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- Lack of awareness of problem, particularly in medical patients
 - Failure to recognize the many clinical signs that may be associated with thromboembolism
 - Misconception of risk levels
 - Concerns over safety of pharmacologic prophylaxis (bleeding risks, immune reactions)
 - Lack of awareness of consensus guidelines
 - Insufficient clear clinical evidence covering all patient groups
 - Cost concerns (pharmacologic prophylaxis)
-

Table 2. Benefits of the individualized approach to thrombotic risk assessment

-
- Includes both predisposing (patient) factors and exposing (clinical) factors
 - Offers a simple, clinically relevant, and easy-to-use format
 - Clearly stratifies patients according to established ACCP risk categories
 - Facilitates implementation of appropriate thromboprophylactic strategies
 - Standardizes assessment of VTE risk
 - Allows thromboprophylactic regimens to be determined for patient groups in whom there is insufficient clinical evidence per se
 - Guards against excessive use of prophylaxis in lower-risk settings (IPC works as well as anticoagulants in moderate-risk patients without bleeding side effects)
 - Cancer patients need more than just IPC based on the level of increased risk of VTE in cancer patients compared to benign disease

ACCP, American College of Chest Physicians; IPC, intermittent pneumatic compression, VTE, venous thromboembolism.

Table 3. Prophylaxis decision-making tool for surgical patients, based on VTE risk scores. The total risk score guides the physician to the most appropriate prophylactic treatment; risk categories correspond to the ACCP guidelines.² (Adapted from Geerts et al.²)

Total VTE risk score*	Risk level**	Incidence of DVT without prophylaxis (%)		Incidence of PE without prophylaxis (%)		Recommended prevention strategies
		Calf	Proximal	Clinical	Fatal	
0-1	Low	2	0.4	0.2	<0.01	No specific measures; early ambulation
2	Moderate	10-20	2-4	1-2	0.1-0.4	LWMH ($\leq 3,400$ U once daily) or LDUH, (5,000 U bid) or GCS* or IPC
3-4	High	20-40	4-8	2-4	0.4-1.0	LMWH ($> 3,400$ U daily), LDUH (5,000 U tid) or IPC
≥ 5	Highest	40-80	10-20	4-10	0.2-5.0	LMWH ($> 3,400$ U daily), fondaparinux 2.5 mg once daily, warfarin (INR 2-3), or GCS/IPC plus LDUH/LMWH

Combining GCS with other prophylactic methods (LDUH, LMWH, or IPC) may give better protection.⁵⁷⁻⁵⁹

ACCP, American College of Chest Physicians; bid, twice daily; DVT, deep-vein thrombosis; GCS, graduated compression stockings; INR, International Normalized Ratio; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated

heparin; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; tid, three times daily; VTE, venous thromboembolism.

Table 4. Thrombosis prophylaxis in the medical patient

Category of patient	Recommended prevention strategy
Medical patient over the age of 40 yrs + 1 risk factor (score 2)	LDUH 5000 U tid* OR LMWH: Enoxaparin 40 mg once daily OR Dalteparin 5000 U once daily
Medical patient with a score of > 4	One of the above anticoagulant regimes + GCS and IPC
Medical patient with contraindication to anticoagulants	GCS + IPC

Combining GCS with other prophylactic methods (LDUH, LMWH, or IPC) may give better protection.^{60,61}

GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low dose unfractionated heparin; LMWH, low-molecular-weight heparin; tid, three times daily.

Table 5. DVT risk-assessment questionnaire to be completed by the patient

Risk factor		Response and score			
1	Personal history of DVT or PE	No = 0	Yes = 3	NA = 0	
2	Family history of DVT or PE (any blood relative)	No = 0	Yes = 3	NA = 0	
3	Malignancy	No = 0	Yes active = 3	Yes previous = 2	NA = 0
4.	Personal history of recent MI or stroke (≤ 1 month)	No = 0	Yes = 1	NA = 0	
5	Recent major surgery (≤ 1 month)	No = 0	Yes = 1	NA = 0	
6	Currently on BCP, HRT, or hormonal therapy for breast or prostate cancer	No = 0	Yes = 1	NA = 0	
7	Current or recent acute inflammatory or infectious process (< 1 month)	No = 0	Yes = 1	NA = 0	
8	Currently immobile (unable to ambulate in the inpatient setting)	No = 0	Yes = 1	NA = 0	
9	History of unexplained stillborn infant, recurrent spontaneous abortion, premature birth with preeclampsia, or growth-restricted infant	No = 0	Yes = 1	NA = 0	
10	Swollen legs	No = 0	Yes = 1		
11	Varicose veins	No = 0	Yes = 1		
12	Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$)	No = 0	Yes = 1		
13	Age	$\leq 40 = 0$	41-60 = 1	61-74 = 2	$\geq 75 = 3$
Total DVT risk score					

BCP, birth-control pill; BMI, body-mass index; DVT, deep-vein thrombosis; HRT, hormone-replacement therapy; MI, myocardial infarction; NA, not applicable; PE, pulmonary embolism.

Table 6. ACCP guidelines approach to risk assessment: categorizing incidence of venous thromboembolism according to level of risk (data from Geerts WH, et al.²)

Risk category	Definition			Risk without prophylaxis (%)		Prevention strategy*
	Surgery	Age (years)	Additional risk factors	Calf-vein thrombosis	Clinical PE	
Low	Minor	<40	No	2	0.2	1
Moderate	Minor	40-60	No	10-20	1-2	1 or 2
	Minor	<40	Yes			
	Major	<40	No			
High	Minor	>60	No	20-40	2-4	2 or 1
	Minor	40-60	Yes			
	Major	40-60	No			
	Major	<40	Yes			
Highest	Major	>60	No	40-80	4-10	3
	Major	>40	Yes			
	Major		Multiple			

*1 = physical; 2 = pharmacologic; 3 = both.

ACCP, American College of Chest Physicians; PE, pulmonary embolism.

Table 7. The common risk-factor approach to risk assessment using risk factor weighting.⁶⁵ A score of 4 or more requires prophylaxis.

- Major risk factors (3 points each)
 - Cancer
 - Prior VTE
 - Hypercoagulable states
- Intermediate risk factor (2 points)
 - Major surgery
- Minor risk factors (1 point each)
 - Advanced age (>70 years)
 - Obesity (BMI >29 kg/m²)
 - Hormone replacement therapy or oral contraceptives
 - Bed rest (active order not related to surgery)

BMI; body mass index; VTE; venous thromboembolism.

Table 9. Highest thromboembolic risk in surgical patients without prophylaxis.(Modified from Geerts et al.²)

	Percent thromboembolism			
	Calf DVT	Proximal DVT	Clinical PE	Fatal PE
Major surgery in patients >40 years plus prior VTE, cancer or molecular hypercoaguable state; major orthopedic surgery or injuries	40-80	10-20	4-10	0.2-5

Table 10. Risk of postoperative DVT in patients undergoing general abdominal surgery (diagnosis with fibrinogen uptake test): the influence of cancer

		Number and frequency of DVT			
		With cancer		Without cancer	
		n	(%)	n	(%)
Kakkar et al. ¹¹⁷	1970	24/59	(41)	38/144	(26)
Walsh et al. ¹¹⁸	1974	16/45	(35)	212/217	(10)
Rosenberg et al. ¹¹⁹	1975	28/66	(42)	291/128	(23)
Allan et al. ¹²⁰	1983	31/100	(31)	21/100	(21)
Sue-Ling et al. ¹²¹	1986	12/23	(52)	16/62	(26)
Total			38		19

Table 11. Low molecular weight heparin (LMWH) prophylaxis in abdominal cancer surgery

Author	Trial design	No	LMWH vs comparator	Results	Comments
Bergqvist 1995 ⁹⁷	DB, MCT	2070	Dalteparin 5000 vs 2500 U	5000 superior	67% cancer venography
ENOXACAN 1997 ⁹⁶	DB, MCT	631	Enox vs UFH	No diff.	Venography
Fricke 1988 ¹²²	Open	80	Dalte vs UFH	No diff.	FUT
Ho 1999 ¹²³	Open	320	Enox vs no proph.	Enox. Superior	Colorectal surgery Object. Verification
Baykal 2001 ¹²⁴	DB	102	Enox vs UFH	No diff.	High risk gyn Clin diagm. Nadro
Boncinelli 2001 ¹²⁵	Open	50	Nadro vs UFH	No diff.	High risk gyn. Clin. Diagn. Nadro
McLeod 2001 ¹²⁶	DB, MCT	936	Enox vs UFH	No diff.	Colorectal surg. Venography

Table 12. Suggestions to improve safety of neuraxial block in patients with pharmacological thromboprophylaxis. (Modified after ACCP guidelines, Geerts et al. 2004²)

1. Neuraxial anesthesia should be avoided in patients with known bleeding disorders.
2. Neuraxial anesthesia should be avoided when hemostasis is impaired by pharmacological substances.
3. Pharmacological prophylaxis should be delayed in patients with “bloody tap”.
4. Removal of epidural catheters should be done when the anticoagulant effect is at a minimum.
5. Anticoagulant prophylaxis should be delayed for at least 2 h after spinal needle or epidural catheter removal.
6. If prophylaxis with vitamin-K antagonists is used epidural analgesia should not be used for more than 1-2 days. INR should be <1.5 at catheter removal.
7. Because of the long half-life of fondaparinux it should not be administered along with continuous epidural analgesia.

Table 13. Factors associated with venous thromboembolic events in patients with malignancy by multivariate analysis. (Used by permission from Lin J et al.¹⁷²)

	Odds Ratio	95% Confidence Interval	P Value
Increasing Age	1.05	1.03 – 1.08	<.001
Solid Tumor	5.0	1.7 – 14.9	.004
Leukopenia	4.2	1.20– 14.6	.02
Infection	4.9	1.20 – 19.80	.03
Stage III/IV Cancer	1.5	.99 – 2.10	.06
Neutropenia	.05	.01 - .19	< .001
Radiation	.16	.06 - .46	< .001
Chemotherapy	.07	.03 - .18	< .001

Table 14. Factors associated with decreased survival in patients with VTE and malignancy. (Used by permission from Lin et al.¹⁷²)

	Odds Ratio	95% Confidence Interval	P Value
Solid Tumor	3.9	1.8 – 8.4	.001
Stage III/IV	1.6	1.2 – 2.1	.001
Increasing Age	1.02	1.0 – 1.04	.01
Neutrophil Count	1.1	1.02 – 1.2	.02
Infection	3.3	1.1 – 9.9	.03
Antimetabolite	4.6	.70 – 30.6	.11

Fig 1. An example of an easy-to-use risk-assessment model. Retrospective incidence data are shown for all risk factors (information included here for explanatory purposes only; not included on the RAM intended for physician use). (Updated from Caprini et al.²⁵)

Fig. 2. Probability of death within 183 days of hospital admission. (From Levitan et al.⁷; reproduced with permission)

Fig. 3. A detailed risk-factor approach to risk assessment. (Updated from Caprini et al.²⁵)