Clinical Roundtable Monograph

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Current Management of Thromboembolism in Cancer Patients: Building a Consensus

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Abstract

Venous thromboembolism (VTE) is a common complication of malignancy, recognized in up to 20% of patients with cancer. The disease itself, and the resulting treatment modalities including surgery, hospitalization, and chemotherapy, put these patients at greater risk of VTE than that seen in similar patients without cancer. Not only does VTE cause significant morbidity for patients with cancer, recent studies indicate that the combination of malignancy and VTE reduces survival when compared with malignancy alone, making effective VTE prophylaxis of utmost importance for these patients. This roundtable discussion explores the current data and clinical recommendations on the use of VTE prophylaxis for patients with cancer as it pertains to various settings: surgical patients, hospitalized patients, ambulatory patients, and those with a clinically diagnosed secondary VTE. The appropriateness of various treatment options, such as vitamin K antagonists, unfractionated heparin, low molecular weight heparin, intermittent pneumatic compression devices, and graded compression hose will be discussed, as will the duration of treatment for each patient population.

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in the management of patients with venous thromboembolism (VTE).

Statement of Need/Program Overview: Several new prognostic factors have been identified in VTE, leading to greater specifity of subgroups, prognosis, and treatment options. In addition, many new drugs are being evaluated for the treatment of VTE. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new study findings and clinical trial data in the natural history of venous thromboembolism (VTE) in cancer patients;
- Assess the results of these new study findings including current clinical trials evaluating therapy in the treatment of VTE.
- Integrate into clinical practice the latest knowledge and methods for treating cancer patients with VTE in an effort to improve current prognosis statistics;
- Identify future research directions for all therapies in VTE in cancer patients.

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Venous Thromboembolism in the Patient with Cancer: Risk Factors, Morbidity, and Mortality

Craig M. Kessler, MD

The relationship between venous thromboembolism (VTE) and cancer was first recognized when, in 1865, the French physician Armand Trousseau described the association of migratory thrombophlebitis with underlying cancer.[1] Since that time, a great deal of clinical experience and research has supported his initial observation. VTE is a common complication of cancer patients, causing major morbidity and mortality (Figure 1). VTE affects 4–20% of cancer patients antemortem but has been reported in up to 50% on postmortem examination.[2,3] Indeed, recent data suggest that the incidence of VTE and related complications are actually increasing in frequency.[4]

VTE has also been described as the presenting sign of occult malignancy. For example, Prandoni and colleagues[5] studied the incidence of cancer in 260 consecutive patients with symptomatic, venographically-proved deep vein thrombosis (DVT). Of these patients, 153 had idiopathic venous thrombosis and the other 107 had secondary venous thrombosis, defined as thrombosis associated with a well-recognized risk factor other than cancer. Examination at baseline revealed cancer in 3.3% of patients with idiopathic venous thrombosis, but no cancer was found among the patients with secondary venous thrombosis. During a 2-year follow-up period, overt cancer developed in 1.9% of patients with secondary venous thrombosis and in 7.6% of patients with idiopathic venous thrombosis (P=.043); 17.1% of those with idiopathic first VTE and subsequent confirmed recurrent VTE developed overt carcinoma over the 2-year observation period. From this, we can hypothesize that occult cancer may mediate the development of background hypercoagulability in the host.

Bura and colleagues[6] confirmed these data in their 2004 study in which 103 patients who were hospitalized for bilateral DVT were followed for 12 months. Of these patients, 25.2% were already known to have cancer, 25.2% had a previous history of VTE, and 42.7% had a symptomatic pulmonary embolism (PE). During follow-up, a new cancer was diagnosed in 26% of the 77 patients without known cancer at admission. The investigators found that the risk of cancer was significantly higher for patients with idiopathic thrombosis than it was for patients with secondary thrombosis (40.5% vs 12.5%; odds ratio [OR]=4.8, 95% confidence interval [CI] 1.4–18.8). Based on these data, ruling out the presence of an occult malignancy for patients over the age of 50 who present with an idiopathic DVT can be considered a reasonable course of action.

Risk Factors for VTE in Patients with Cancer

There are a large number of identifiable risk factors for VTE in cancer patients (Table 1). These can be categorized as patient-related factors, cancer-related factors, treatment-related factors, and biomarkers. Patient-related factors include age, sex, race, and comorbid illness. As discussed above, patients who have had previous venous thromboembolic complications prior to their diagnosis of cancer are at greater risk of a subsequent event.

Cancer-related factors include tumor stage, tumor grade, tumor site, and the interval between the diagnosis of cancer and the development of VTE. In regard to disease stage, it is clear that the risk of VTE in the cancer patient is not uniform over the course of the disease.[7] At the time of diagnosis, cancer patients have a 5-fold increase in risk compared to the general population. This increases to a 7-fold increase in risk when cancer patients are hospitalized, because these patients are frequently bedridden or have other complications of cancer and cancer treatment. Certainly treatment, and even some of the supportive care modalities like erythropoietic stimulating agents, increases VTE risk. When a cancer patient enters remission, their level of risk falls close to the baseline risk seen in the general population. The risk will then increase again if their disease recurs or if they develop widespread metastatic disease toward the end of life.

The risk of VTE is also not uniform across cancer sites.[8] Gastrointestinal malignancies, particularly pancreatic cancer, carry the greatest risk, but brain and uterine cancers carry elevated risk as well. Even hematologic malignancies account for as many as one-third of venous thromboembolic events occurring in hospitalized patients.

Treatment-related factors include surgery, hospitalization, chemotherapy, hormonal therapy, therapy with anti-angiogenic agents, and central venous access devices. These factors shall be examined at greater depth later in this roundtable discussion.

Patient-related factors	
• Older age	• Gender
• Race (higher in African Americans, lower in Asians)	• Patient comorbidities
	• History of VTE
Treatment-related factors	
• Major surgery	• Hospitalization
• Chemotherapy	• Hormonal therapy
• Antiangiogenic agents	• ESAs, ?Transfusions
Cancer-related factors	
• Site of cancer	• Advanced stage
• Period between cancer diagnosis and VTE development	
Biomarkers	
• Platelet and leukocyte counts	• Tissue factor
• P-selectin	• D-dimer

Table 1. Risk factors for VTE in patients with cancer.

Adapted from Rao MV, et al. In: Khorana and Francis, eds. *Cancer-Associated Thrombosis*; 2007.

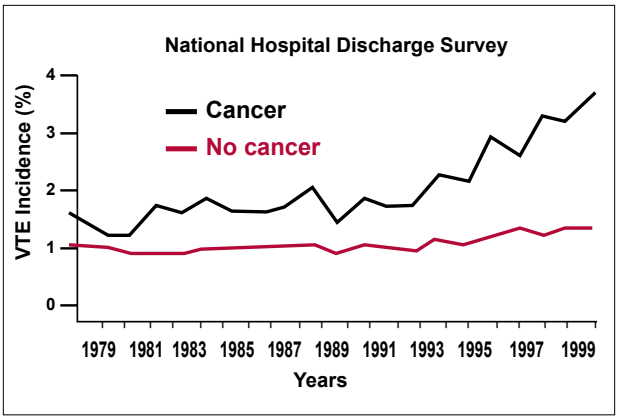

Figure 1. Incidence of VTE in U.S. patients with and without cancer, 1979–1999.

Adapted from Stein PD et al. *Am J Med.* 2006;119:60-68.

VTE-Associated Morbidity and Mortality for Patients with Cancer

The VTE-associated morbidity and mortality in the context of concurrent cancer cannot be overemphasized. The associated morbidity is exacerbated by the need for prolonged anticoagulation and by the pain and limited mobility which occur in conjunction with the development and progression of post-thrombotic syndrome. These patients are also at increased risk for bleeding complications, both because of the cancer and because of the anticoagulation therapy that is generally instituted. A consequence of VTE in cancer patients that is sometimes overlooked is the fact that these complications may often delay or alter the cancer treatment itself. They may hinder the ability to deliver optimal doses of radiation therapy and chemotherapy because of the fear that treatment-induced thrombocytopenia will precipitate more bleeding in the face of concurrent anticoagulation for the venous thromboembolic event.

In terms of mortality, it has been clearly shown that cancer patients who experience thromboembolic events are at increased risk of early death, either from the primary event itself or due to the increased risk for recurrence, even after effective treatment. For example, Komrokji and colleagues[9] retrospectively examined the records for 211 patients with diffuse large B-cell lymphoma to compare the median survival between patients with and without symptomatic VTE (Figure 2). VTE had a significant negative impact upon survival time, which was only 1.04 years for those with symptomatic VTE, compared to 5.2 years for those without symptomatic VTE (*P*=.038). Levitan and colleagues[10] also conducted a retrospective study, analyzing data from the Medicare Provider Analysis and Review Record database between 1988 and 1990. They found that the probability of death within 6 months of an initial hospitalization was 0.94 among those patients with DVT/PE and malignant disease, versus 0.29 among those with DVT/PE and no malignancy (*P*=.001).

Of note, increased mortality is not only confined to patients who have symptomatic thromboses. O'Connell and colleagues[11] performed a case-control study of mortality among 70 cancer patients with unsuspected pulmonary embolism (PE) who were matched with 137 control patients. The unsuspected PE were found on routine cancer staging scans. Using a stratified analysis adjusting for the presence of brain, liver, and lung metastases and for use of erythropoietin, the authors found that proximal unsuspected PE conferred a hazard ratio for death of 1.79 (95% CI, 1.10–2.90; *P*=.018).

These observations are supported by a study by Altinbas and colleagues[12] that showed that the addition of low molecular weight heparin (LMWH) to combination chemotherapy improved survival in patients with small cell lung cancer (SCLC) compared with chemotherapy alone. In this study, 84 patients received cyclophosphamide, epirubicine, and vincristine given at 3-weekly intervals for 6 cycles. These patients were randomized to receive either chemotherapy alone or chemotherapy plus dalteparin 5,000 anti-Xa units once daily. The overall tumor response rates were 42.5% with chemotherapy alone and 69.2% with chemotherapy plus LMWH (*P*=.07). The median progression-free survival was 6.0 months with chemotherapy alone and 10.0 months with chemotherapy plus LMWH (*P*=.01). The median overall survival was 8.0 months with chemotherapy alone

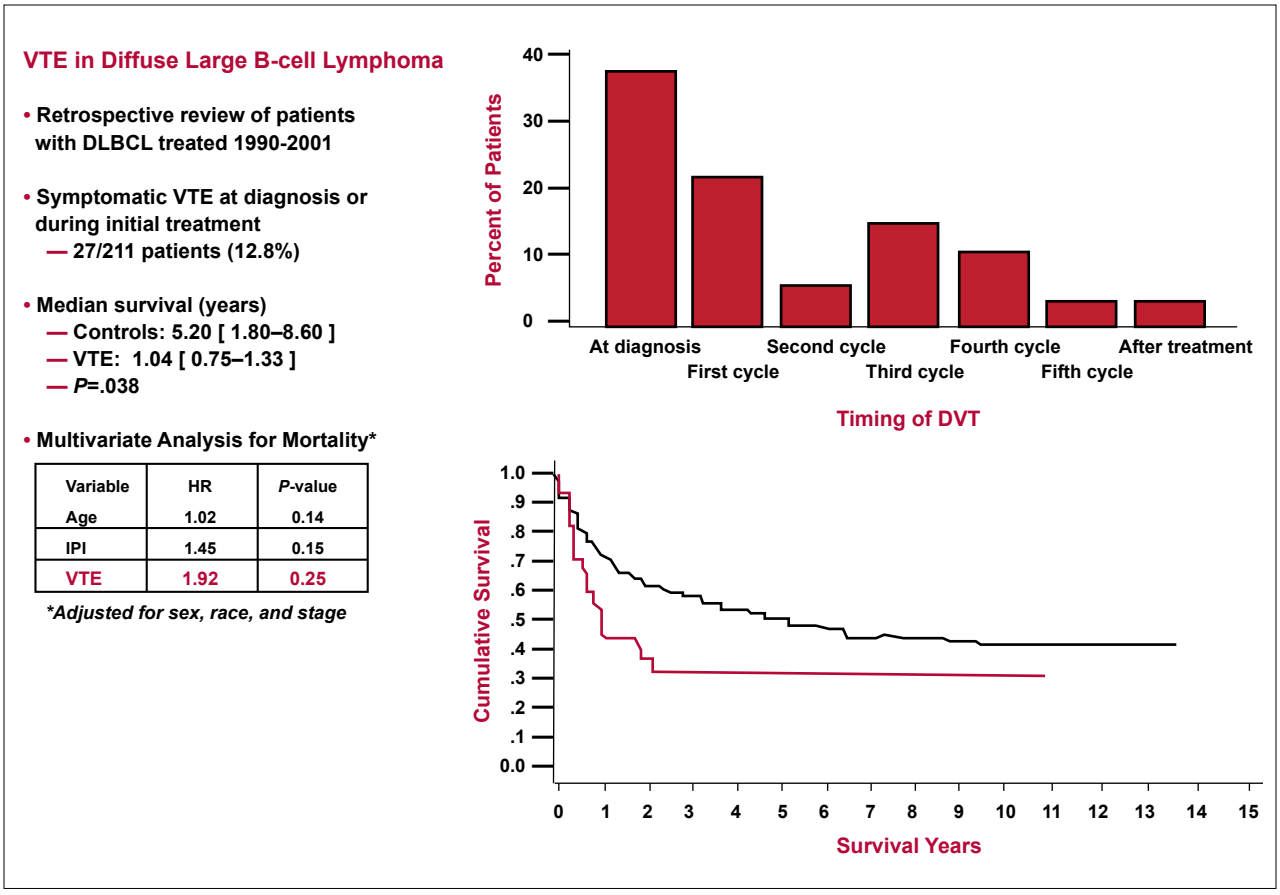

Figure 2. VTE in diffuse large B-cell lymphoma.

and 13.0 months with chemotherapy plus LMWH (*P*=.01). The authors reported that toxicity from the experimental treatment was minimal and that there were no treatment-related deaths. These data were very provocative, suggesting that anticoagulants, and particularly LMWH, may improve clinical outcomes in patients with cancer, possibly even as much as standard chemotherapeutic regimens. Looking forward, future clinical trials of chemotherapy plus LMWH or other anticoagulants will be of great interest.

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Prevention of Venous Thromboembolism in the Non-Surgical Patient with Cancer

Gary H. Lyman, MD, MPH, FRCP (Edin)

The use of VTE prophylaxis and treatment for patients with cancer in the nonsurgical setting has been the subject of some debate. Should hospitalized cancer patients receive VTE prophylaxis? What about ambulatory cancer patients who are receiving chemotherapy or therapy with biologic agents? What is the proper type and duration of treatment for cancer patients with a secondary VTE? A number of randomized clinical trials have been conducted to address these issues.

VTE Prophylaxis for Hospitalized Patients with Cancer

In considering hospitalized cancer patients, there is a question of whether or not they should receive anticoagulation for VTE prophylaxis while hospitalized. Unfortunately, no trials looking at the role of prophylactic anticoagulation have been conducted entirely with cancer patients. Nevertheless, there are a number of useful studies of VTE prophylaxis that have included cancer patients (Figure 3). The first study, called Prophylaxis in Medical Patients with Enoxaparin (MEDENOX),[1] examined the efficacy and safety of thromboprophylaxis with enoxaparin in patients with acute medical illnesses who were at risk of VTE. About 15% of the 1,102 patients in this study had some form of cancer. Patients were randomized to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo subcutaneously once daily for 6 to 14 days. The primary outcome was VTE between days 1 and 14, as detected by bilateral venography or duplex ultrasonography, or documented PE. Patients were followed for 3 months. The authors found that 40 mg of enoxaparin was associated with a relative risk reduction of 63% when compared with placebo (relative risk, 0.37; 97.6% CI, 0.22 –0.63; *P*<.001). The incidence of adverse effects, including bleeding events, did not differ significantly between the placebo group and either enoxaparin group. No significant difference in the primary outcome was seen between the enoxaparin 20 mg group and the placebo group.

The second study, PREVENT, enrolled 3,706 acutely ill medical patients, of which 5% had cancer.[2] In this international, multicenter, randomized, double-blind, placebo-controlled trial, patients were randomly assigned to receive either subcutaneous dalteparin 5,000 IU daily or placebo for 14 days, and were followed up for 3 months. The primary endpoint was VTE, defined as the combination of symptomatic deep vein thrombosis (DVT), symptomatic pulmonary embolism (PE), and asymptomatic proximal DVT detected by compression ultrasound at day 21 and sudden death by day 21. The authors found that dalteparin treatment was associated with a relative risk reduction of 45% when compared with placebo (relative risk, 0.55; 95% CI, 0.38–0.80; *P*=.0015). The authors noted that the

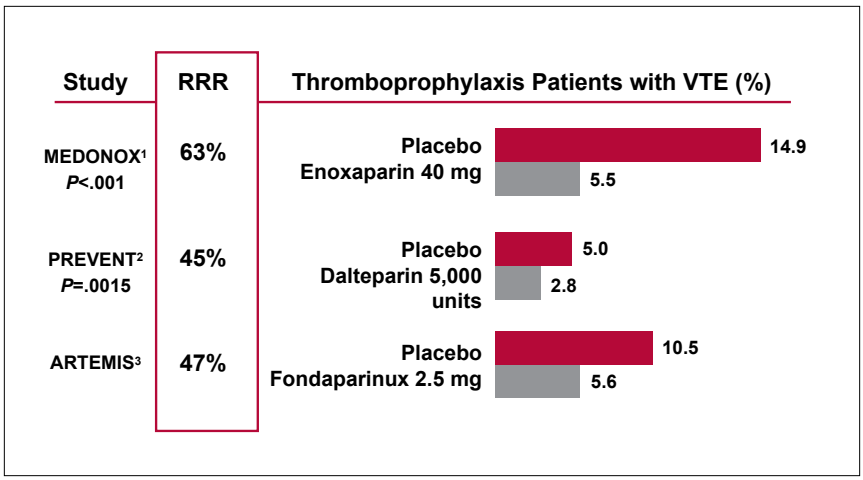

Figure 3. Anticoagulant prophylaxis to prevent screen-detected VTE High risk hospitalized medical patients: VTE.

Adapted from Samama MM et al. *N Engl J Med.* 1999;341:793-800.
Leizorovicz A et al. *Circulation.* 2004;110:874-879.
Cohen AT et al. *BMJ.* 2006; 332: 325-329.

Trial	N	Treatment	Chemo	Duration	VTE	Major Bleeding
FAMOUS Solid tumors (Stage III/IV)	385	Dalteparin Placebo	64%	12 months	2.4% 3.3%	0.5% 0
TOPIC-I Breast (Stage IV)	353	Certoparin Placebo	100%	6 months	4% 4%	1.7% 0
TOPIC-2 NSCLC (Stage IV)	547	Certoparin Placebo	100%	6 months	4.5%† 8.3%	3.7% 2.2%
PRODIGE Giloma	186	Dalteparin Placebo	–	6–12 months	11% 17%	5.1% 1.2%
SIDERAS Solid Tumors (Stage IV)	141	Dalteparin Placebo/Control	54%	Indefinitely	5.9% 7.1%	2.9% 7.1%
PROTECHT Solid Tumors (Stage III/IV)	1166	Nadroparin 2:1 Placebo	100%	< 4 months 2:1 Placebo	1.4% 2.9%	0.7% 0

Table 2. RCTs of Thromboprophylaxis in ambulatory cancer patients. Low molecular weight heparin.

Adapted from Kakkar AK et al. *J Clin Oncol.* 2004;22:1944-1948.
Haas SK et al. *J Thromb Haemost.* 2005;(suppl 1): abstract OR059.
Perry JR et al. *Proc ASCO.* 2007;2011.
Sideras K et al. *Mayo Clin Proc* 2006; 81:758-767.
Agnelli G et al. *Am Soc Hemat.* Sunday December 7, 2008.

risk of bleeding was higher in the dalteparin group compared with the placebo group (0.49% vs 0.16%), although the overall incidence of major bleeding was low.

The third study, ARTEMIS, enrolled 849 medical patients 60 years of age or older, of which 15% were cancer patients.[3] All patients were at high risk for VTE. The patients were randomized to 2.5 mg fondaparinux or placebo subcutaneously once daily for 6 to 14 days, and were followed up at 1 month. The primary outcome was VTE detected by routine bilateral venography along with symptomatic VTE up to day 15. The authors found that fondaparinux was associated with a relative risk reduction of 46.7% (95% CI, 7.7–69.3%; *P*=.029:). Major bleeding occurred in 1 patient (0.2%) in each group.

Based on these data, the most recent American Society of Clinical Oncology (ASCO) clinical guidelines state that hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation.[4]

Ambulatory Patients with Cancer Receiving Systemic Chemotherapy

What about ambulatory cancer patients receiving systemic chemotherapy? A number of randomized, controlled trials[5-9] have looked at the efficacy and safety of various thromboprophylactic agents, but the reduction in risk, if seen, has been usually small or not statistically significant (Table 2). Bleeding events, though rare, were increased with treatment across all studies. Taken together, those of us on the ASCO clinical guidelines panel felt that there were insufficient data from large definitive trials to recommend routine thromboprophylaxis in ambulatory cancer patients, with or without systemic chemotherapy or hormonal therapy.[4]

One specific situation in which the risk of VTE was sufficiently high that the panel felt a recommendation should be made to consider prophylaxis pertains to patients with multiple myeloma who are receiving thalidomide or lenalidomide with chemotherapy or with dexamethasone. Although there have been no direct randomized, controlled trials published that demonstrate the efficacy and safety of thromboprophylaxis in this setting, these patients are at very high risk for thrombosis.[10] Therefore, the panel felt that the risk these patients face would warrant prophylaxis with LMWH or adjusted dose warfarin (international normalized ratio [INR]~1.5). Certainly, randomized clinical trials evaluating antithrombotic agents in this setting are needed.

There has been much concern in the field around the risk of VTE that may be associated with some of the new targeted biologic agents, particularly the anti-angiogenesis agents. A recent major meta-analysis by Nalluri and colleagues[11] that was published in the *Journal of the American Medical Association* summarized the available data from randomized controlled trials about the use of bevacizumab in patients with various cancers. The investigators analyzed data from 15 randomized, controlled trials—a total of 7,956 patients with a variety of advanced solid tumors. They found that patients treated with bevacizumab had a significantly increased risk of VTE, with a relative risk of 1.33 (95% CI, 1.13–1.56; *P*<.001) compared with controls. The risk was not dose-dependent; it was similarly increased at 2.5 mg/kg per week and 5 mg/kg per week. Clearly, further studies in this setting are warranted.

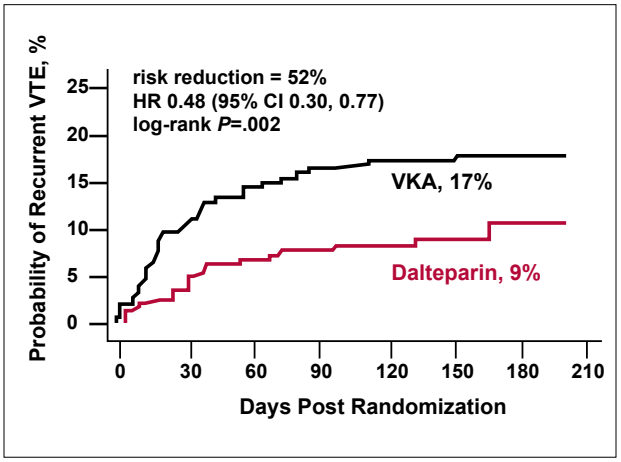

Figure 4. CLOT Trial: Results: symptomatic recurrent VTE.

Adapted from Lee AY et al. *N Engl J Med*. 2003;349:146-153.

Secondary VTE Prophylaxis for Patients with a Previous VTE

Another question that was addressed in the 2007 ASCO clinical guidelines was that of the proper duration and type of secondary VTE prophylaxis in patients who have experienced a thromboembolic event previously in their course of their disease. Based on the work from Prandoni and colleagues, we know that these patients are at triple the risk for a secondary event than are similarly matched patients without cancer.[12] To investigate the question, Lee and colleagues[13] conducted a large randomized, controlled trial, called CLOT, in which a total of 672 patients with cancer who had had an acute, symptomatic proximal DVT, PE, or both were randomly assigned to one of the following groups: dalteparin 200 IU/kg subcutaneously once daily for 5–7 days plus a coumarin derivative (target international normalized ratio, 2.5) for 6 months, or dalteparin 200 IU/kg once daily for 1 month, reduced to approximately 150 IU/kg for 5 months thereafter. During the 6-month study period, 8% of patients in the dalteparin only group had recurrent VTE, compared with 16% of patients in the oral anticoagulant group (HR, 0.48; *P*=.002). Importantly, no statistically significant difference in the rate of major or minor bleeding was seen between the dalteparin group and the oral anticoagulant group, data which can reassure physicians who may feel that long-term dalteparin treatment carries too much of a bleeding risk (Figure 4). The CLOT data paved the way for the United States Food and Drug Administration to approve dalteparin for long-term secondary prophylaxis against DVT and PE in the patient with cancer, the only LMWH that is approved for this indication.

Thus, the ASCO clinical guidelines panel recommended that LMWH be used for an initial 5–10 days of anticoagulant treatment of the patient with cancer with established VTE, then continued for at least 6 months. Because LMWH is not always available, the use of vitamin K antagonists with a targeted INR of 2–3 was also considered acceptable for long-term therapy after the initial 5–10 days of LMWH therapy. After 6 months, indefinite anticoagulant therapy should be considered for patients with active cancer, and clinical trials are now in the works to look at the efficacy and safety of much longer-term LMWH therapy. For patients with contraindications to anticoagulant therapy and in those with recurrent VTE despite adequate long-term therapy, vena cava filters may be used. Of course, careful monitoring of anticoagulation is necessary to limit the risk of hemorrhagic complications, and anticoagulation should be avoided in the presence of active intracranial bleeding or preexisting bleeding diathesis such as thrombocytopenia or coagulopathy.[4]

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Prevention of Venous Thromboembolism in the Surgical Patient with Cancer

Ajay K. Kakkar, MD

Surgery is a major risk factor for VTE.[1] The reported incidence of objectively confirmed, hospital-acquired DVT is approximately 10–40% among medical or general surgical patients who do not receive VTE prophylaxis. Those numbers rise to 40–60% following major orthopedic surgery.[2,3] When surgery is performed on hospitalized patients with cancer, the risk for VTE increases further. After analyzing data from over 1.6 million patients in the California health system, White and colleagues[4] reported that malignancy increases the risk of VTE by approximately 70% in the hospitalized surgical patient population, regardless of the anatomical site of surgery. Indeed, the rate of calf DVT in this population without prophylaxis is 40–80%, and the rate of proximal vein DVT is 10–20%. Clinical PE has been documented in 4–10%, and fatal PE in 1–5%.[1]

Even within the population of patients with cancer undergoing surgery, it is possible to identify subgroups of patients who have an even greater risk for VTE. Agnelli and colleagues[5] conducted a prospective observational study in 2,373 patients undergoing general, urologic, or gynecologic surgery for cancer, and they found that age older than 60 years, previous VTE, anesthesia time greater than 2 hours, advanced stage disease, and bedrest of 4 days or more were all significant predictors of clinically overt VTE occurring up to 1 month after surgery (Table 3).

Variable	Effect	No. of patients VTE / non-VTE	OR	95% CI
Age class	≥60 vs <60 years	≥60 yrs: 42 / 1,516 <60 yrs: 8 / 807	2.6	1.2–5.7
Previous VTE	Yes vs no	Yes: 5 / 36 No: 45 / 2,287	6.0	2.1–16.8
Anesthesia	≥2 vs <2 hours	≥2 hours: 48 / 1,762 <2 hours: 2 / 561	4.5	1.1–19.0
Staging	Advanced vs not advanced	Advanced: 38 / 1,078 Non advanced: 12 / 1,245	2.7	1.4–5.2
Bedrest	≥4 vs <4 days	≥4 days: 25 / 346 <4 days: 25 / 1,977	4.4	2.5–7.8

Table 3. Prognostic risk factors For VTE: multivariable logistic regression analysis.

Adapted from Agnelli G et al. *Ann Surg.* 2006; 243:89-95.

Based on these data, the most recent ASCO clinical guidelines recommend that all patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis, that prophylaxis should be commenced pre-operatively or as early as possible in the postoperative period, and should be continued for at least 7–10 days postoperatively. The panel further recommended that patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes should receive pharmacologic thromboprophylaxis with either low-dose unfractionated heparin or LMWH, unless contraindicated because of a high risk of bleeding or active bleeding. This prophylaxis should begin pre-operatively.[6]

Large clinical trials have provided authoritative evidence for the benefits of pharmacologic prophylaxis in the high-risk surgical population. The first of these studies was a 1975 international, randomized trial investigating the efficacy of low-dose heparin in preventing fatal postoperative PE.[7] In this trial, 4,121 patients over the age of 40 who were undergoing a variety of elective major surgical procedures were enrolled; 23% of the study population was undergoing surgery because of malignancy. The patients were randomized 1:1 to receive either no treatment or 5,000 units of low-dose unfractionated heparin beginning 2 hours prior to surgery and continued 3 times daily in the postoperative period for at least 7 days. The authors found that heparin reduced the mortality rate in the postoperative period from 4.8% in the control group to 3.9% in the treatment group (P<.005). Thus, pharmacologic prophylaxis in this study was demonstrated to save 7 lives for every 1,000 operated patients.

In the subgroup of the 953 patients who underwent surgery with malignant disease in this study, the frequency of fatal PE in the control group of cancer patients (n=491) was 1.6%. Strikingly, this was reduced to 0.4% in the 462 patients randomized to receive low-dose unfractionated heparin, indicating that pharmacological thromboprophylaxis reduces the frequency of fatal PE even in the high-risk cancer population.

A second pivotal study was a 1988 meta-analysis by Clagett and colleagues.[8] This study analyzed data from 29 trials in which patients undergoing major surgical intervention were randomized to control or to low-dose unfractionated

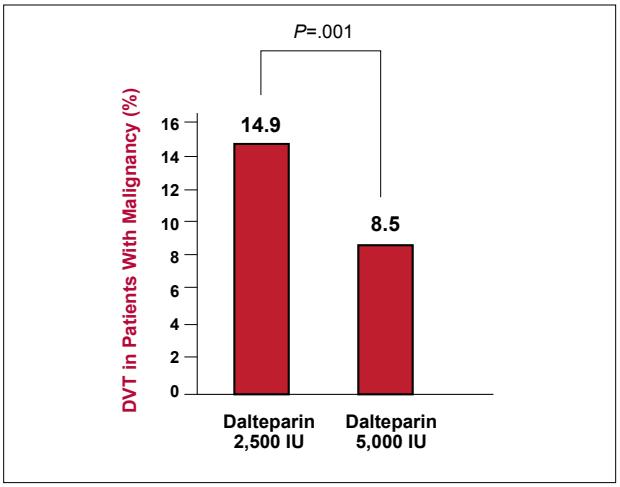

Figure 5. Thromboprophylaxis in cancer surgery. Prospective, randomized, double-blind multicenter trial

Adapted from Bergqvist D et al. *Br J Surg.* 1995;82:496-501.

heparin. In all studies, 5,000 units of unfractionated heparin was given subcutaneously 2 hours before surgery and was continued every 8 or 12 hours for 7 days. The meta-analysis found a 21% reduction in total surgical mortality, a 68% reduction in the frequency of fatal PE, and a 67% reduction in the frequency of DVT among patients who had received unfractionated heparin. Of note, from the 21 trials that included information about bleeding complications, no difference in the overall incidence of major hemorrhage was seen between unfractionated heparin-treated and control patients.

Low Molecular Weight Heparin versus Unfractionated Heparin

In the last 10–15 years, standard practice has moved away from the use of low-dose unfractionated heparin to LMWH for the prevention of VTE in the peri-operative period. One of the most important studies in determining the optimal administration regimen of LMWH was conducted by Berggvist and colleagues[9] (Figure 5). In this randomized, double-blind, multicenter trial, 2,070 patients undergoing surgery for malignant and benign abdominal disease were randomized to receive either 2,500 or 5,000 anti-Xa units of the LMWH dalteparin. Prophylaxis was started in the evening before surgery and given once daily thereafter. Approximately 67% of the patients in this trial were treated for a malignant disorder. The primary endpoint was DVT detected with the fibrinogen uptake test. The investigators found that the incidence of DVT was significantly lower in patients given 5,000 anti-Xa units than that for those given 2,500 anti-Xa units, (6.6% vs 12.7%; *P*<.001), and this was also true for patients with malignant disease (8.5% vs 14.9%; *P*<.001). The overall frequency of bleeding complications was significantly higher in patients randomized to 5,000 anti-Xa units (4.7% vs 2.7%; *P*=.02), although there was no significant difference between the groups for those with malignant disease (4.6% vs 3.6%). These data indicated that patients undergoing operations for malignancies require and can tolerate higher doses of peri-operative LMWH therapy.

Numerous studies have been undertaken to directly compare low-dose unfractionated heparin with LMWH for the prevention of postoperative DVT, with the most thorough being the Canadian Colorectal Surgery DVT Prophylaxis Trial published by McLeod and colleagues in 2001.[10] This study found no difference in efficacy or safety between the agents. The study enrolled 936 patients undergoing resection of part or all of the colon or rectum; they were randomized to receive, by subcutaneous injection, either calcium heparin 5,000 IU every 8 hours or enoxaparin 40 mg once daily (plus 2 additional saline injections). DVT, as assessed by bilateral contrast venography performed between postoperative day 5 and 9, was seen in 9.4% of both groups. The rate of major bleeding events was not significantly different between the groups, although minor bleeding events were more common with enoxaparin (8% vs 5% with unfractionated heparin; *P*=.03).

Mismetti and colleagues[11] reported similar results in a meta-analysis that analyzed data from randomized trials in general surgery comparing LMWH with placebo or no treatment, or with unfractionated heparin. Both agents significantly reduced the risk of asymptomatic DVT, clinical PE, and clinical VTE by about 70%. No significant difference in efficacy was seen between the agents, a finding that held true for the subset of patients undergoing cancer surgery. The authors noted that LMWH at doses below 3,400 anti-Xa units seemed to be as effective as, and safer than, unfractionated heparin, while higher doses yielded slightly superior efficacy but increased hemorrhagic risk, including that of major hemorrhage.

Haas and colleagues[12] undertook a very large study looking at the incidence of fatal PE and death in surgical patients receiving LMWH thromboprophylaxis and, again, found no difference between unfractionated heparin and LMWH. In the double-blind study, 23,078 surgical patients were randomized to received either certoparin 3,000 anti Xa units subcutaneously once daily, or unfractionated heparin 5,000 IU subcutaneously 3 times daily, for a minimum of 5 days. The primary outcome measure was autopsy-proven fatal PE recorded up to 14 days after the end of prophylaxis; this occurred in 0.147% of the certoparin group and 0.156% of the unfractionated heparin group (*P*=.868). No significant difference in mortality rate was seen between groups. The investigators noted that the safety profiles of both treatment groups were similar.

The ASCO clinical guideline panel recommended in 2007 that mechanical methods may be added to pharmacologic methods, but should not be used as a monotherapy

for VTE prevention, unless pharmacologic methods are contraindicated because of active bleeding.[6] There is a good body of evidence indicating that mechanical prophylaxis alone does reduce the risk of DVT, but there is a paucity of data on the relationship between mechanical prophylaxis and the risk of PE. For example, Clagett and colleagues[8] found in their 1988 meta-analysis that intermittent pneumatic compression (IPC) reduced the rate of DVT in cancer patients undergoing surgery from 21% in the control group to 12.8% (P=.04). In the same analysis, graded compression stockings were seen to reduce the rate of DVT from 24.5% in the control group to 9.3% (P<.001). However, there were not enough data in the included studies for any conclusions to be drawn about whether mechanical thromboprophylaxis can reduce the risk for PE in the cancer patient undergoing surgery. For this reason, the ASCO panel was unable to recommend mechanical prophylaxis as a monotherapy.

The combination of mechanical and pharmacologic prophylaxis has been shown to effectively reduce DVT risk. For example, in 4 studies that examined the efficacy of graded compression stockings alone versus in combination with low-dose unfractionated heparin, the overall relative risk reduction was 57% for the combination treatment.[13] Similarly, the overall relative risk reduction seen in 6 studies of low-dose unfractionated heparin alone versus in combination with graded compression stockings was 53% for the combination treatment.[13] IPC devices are also very effective at reducing the risk of DVT when used in combination with pharmacologic prophylaxis. Borow and colleagues[14] compared the efficacy of low-dose unfractionated heparin in combination with IPC versus no prophylaxis in 562 general surgery patients. They found that the DVT rate was 26.8% in the control group, but only 1.5% in the combination group.

Duration of Thromboprophylaxis

The optimal duration of thromboprophylaxis remains one of considerable interest and concern to surgeons. There have been 2 large randomized controlled trials that provide support for at least 7–10 days of treatment. In the first trial, by Bergqvist and colleagues,[15] 332 patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin 40 mg subcutaneously daily for 6–10 days and were then randomly assigned to receive either enoxaparin or placebo for another 21 days. The rates of VTE, as assessed by bilateral venography at the end of the double-blind phase, were 12.0% in the placebo group and 4.8% in the enoxaparin group (P=.02), and this difference persisted at the 3-month follow up. The authors reported that there were no significant differences in the rates of bleeding or other complications during the double-blind or follow-up periods.

The second trial, by Rasmussen and colleagues,[16] was an open-label trial comparing 7 days with 28 days of dalteparin treatment after major abdominal surgery. A total of 427 patients were randomized, and all patients underwent bilateral venography at day 28. The cumulative incidence of VTE was 16.3% with short-term thromboprophylaxis, but was only 7.3% after prolonged thromboprophylaxis, for a relative risk reduction of 55% (P=.012). No increase in bleeding events was seen with prolonged treatment.

Based on these data, the ASCO guidelines recommend that prophylaxis should be continued for at least 7–10 days postoperatively and that prolonged thromboprophylaxis for up to 4 weeks after major abdominal and pelvic surgery should be provided for patients with high-risk features, such as those with residual disease at time of discharge from hospital, obese patients, and those with a previous history of VTE.[6]

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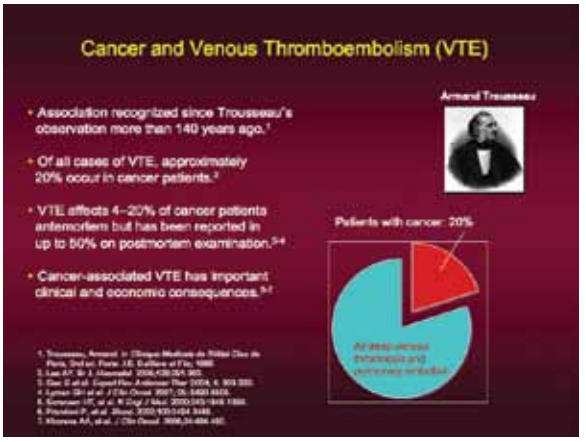

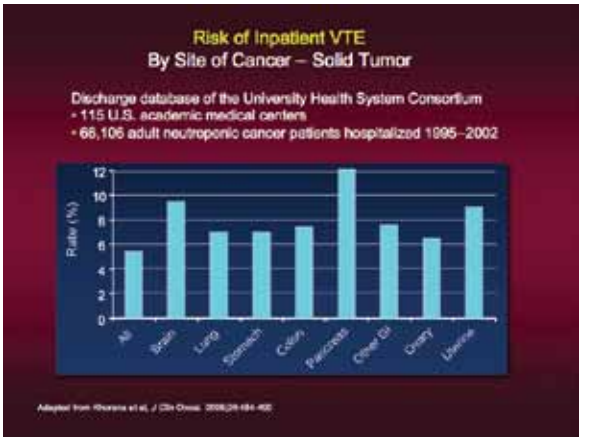

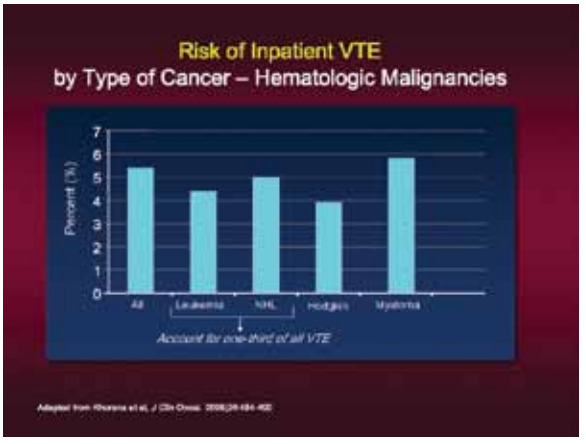

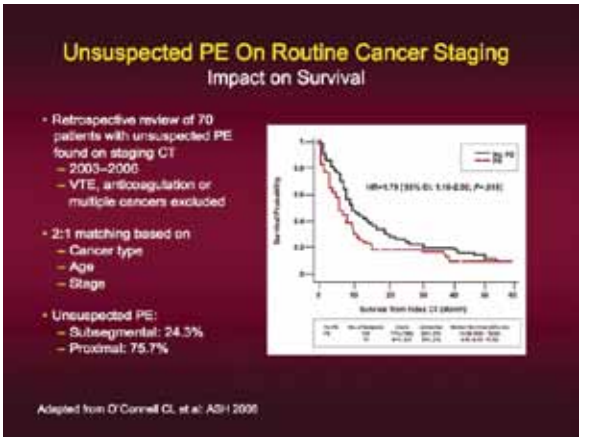

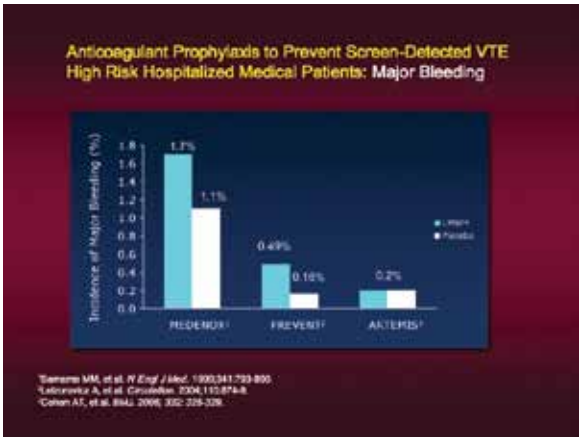

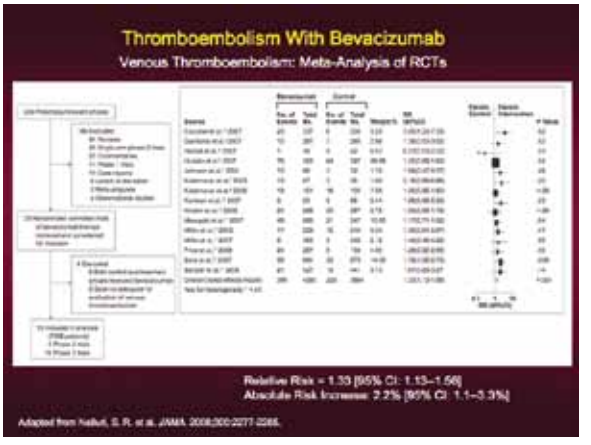

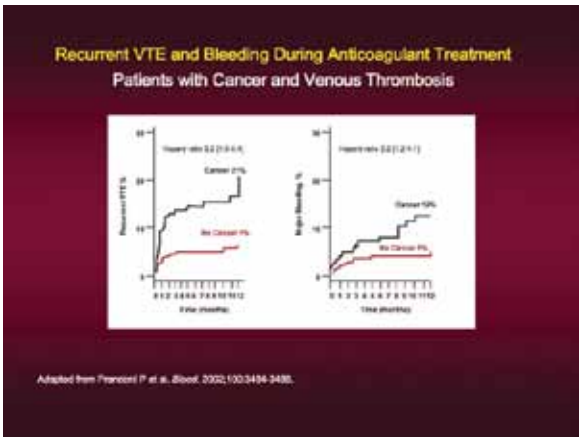

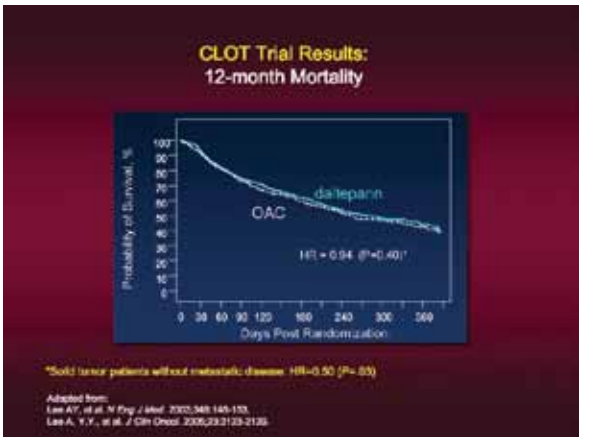

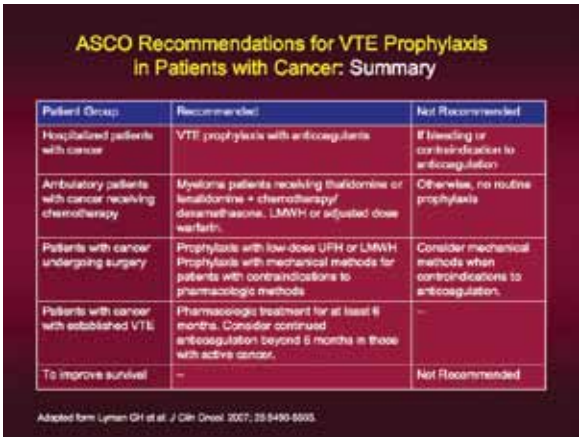

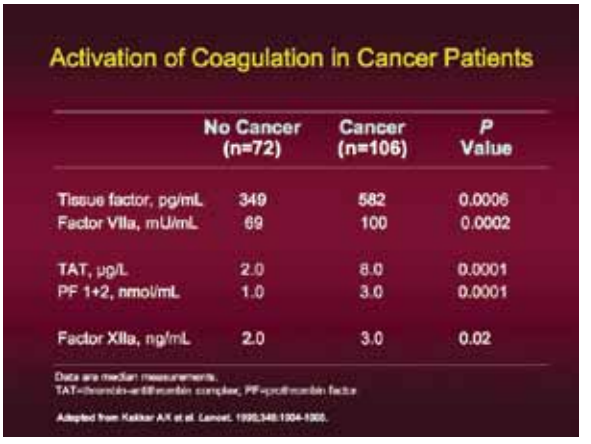

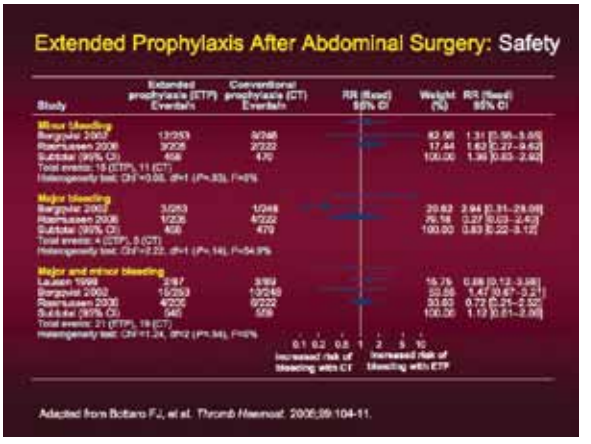

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Current Management of Thromboembolism in Cancer Patients: Building a Consensus

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following is a risk factor for developing VTE in a cancer patient?

   a. Site of cancer
   b. Stage of cancer
   c. Older age
   d. All of the above

2. At which point during the natural history of cancer is a patient at highest risk of VTE?

   a. At diagnosis
   b. During hospitalization
   c. During ambulatory chemotherapy
   d. During remission

3. According to the study by Levitan and colleagues, the probability of death within 6 months of an initial hospitalization was ___ among those patients with DVT/PE and malignant disease, versus 0.29 among those with DVT/PE and no malignancy.

   a. 0.94
   b. 0.87
   c. 0.65
   d. 0.42

4. Which of the following studies indicates that LMWH is effective for VTE prophylaxis in high-risk, hospitalized medical patients?

   a. MEDENOX
   b. PREVENT
   c. ARTEMIS
   d. All of the above

5. According to the American Society of Clinical Oncology Clinical Practice Guidelines, which of the following patient populations should receive VTE prophylaxis?

   a. ambulatory cancer patients receiving hormonal therapy
   b. ambulatory cancer patients not currently receiving chemotherapy
   c. ambulatory multiple myeloma patients receiving thalidomide or lenalidomide with chemotherapy or with dexamethasone
   d. ambulatory cancer patients receiving bevacizumab therapy

6. True or False? The CLOT trial of pharmacologic prophylaxis for secondary VTE showed that long-term treatment with LMWH increased the risk of bleeding compared with long-term treatment with oral anticoagulants.

   a. True
   b. False

7. LMWHs are:

   a. more effective than unfractionated heparin for perioperative VTE prophylaxis
   b. equally as effective as unfractionated heparin for perioperative VTE prophylaxis
   c. less effective than unfractionated heparin for perioperative VTE prophylaxis
   d. not recommended for use in the perioperative period

8. Mechanical VTE prophylaxis:

   a. Has been shown to reduce the rate of PE when used perioperatively
   b. Has not been proven to reduce the rate of DVT when used perioperatively
   c. Is recommended to be used in combination with pharmacological prophylaxis for perioperative VTE prevention
   d. Is recommended for use as a monotherapy for VTE prophylaxis in surgical patients with cancer

9. The study by Bergqvist and colleagues indicates that VTE prophylaxis should be continued for _____ days after surgery.

   a. 1 to 2
   b. 2 to 4
   c. 5 to 7
   d. 7 to 10

10. The study by Rasmussen and colleagues comparing 7 days with 28 days of dalteparin treatment for VTE prophylaxis after major abdominal surgery found that extended treatment was associated with a relative risk reduction of _____.

    a. 25%
    b. 35%
    c. 55%
    d. 75%

Evaluation Form Current Management of Thromboembolism in Cancer Patients: Building a Consensus

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives

After participating this activity, I am now better able to:

1. Describe the importance of new study findings and clinical trial data in the natural history of venous thromboembolism (VTE) in cancer patients. 1 2 3 4 5
2. Assess the results of these new study findings including current clinical trials evaluating therapy in the treatment of VTE. 1 2 3 4 5
3. Integrate into clinical practice the latest knowledge and methods for treating cancer patients with VTE in an effort to improve current prognosis statistics. 1 2 3 4 5
4. Identify future research directions for all therapies in VTE cancer patients.. 1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:

❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

What barriers do you see to making a change in your practice? _____

Which of the following best describes the impact of this activity on your performance?

❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

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