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Venous Thromboembolism Prophylaxis:

Considerations *for* Medical, Surgical, *and* Cancer Patients

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CME and Faculty Information

CME INFORMATION

Needs Statement/Target Audience: This activity is intended to provide hospitalists, oncologists, emergency medicine physicians, and other health care professionals with clinical education to improve appropriate thromboprophylaxis in at-risk patients.

Educational Activity Objectives: Upon completion of this activity, the participants should be able to:

- List the risk factors for VTE in surgical and medically ill hospitalized patients
- Describe which groups of patients should receive thromboprophylaxis
- Demonstrate awareness of the benefits and risks of current and emerging pharmacotherapies for thromboprophylaxis
- Describe recent guidelines for VTE prophylaxis and the most effective means of ensuring appropriate thromboprophylaxis

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INTRODUCTION

Venous thromboembolism (VTE) is a serious complication that presents in a wide variety of clinical circumstances. The objective of this primer is to present current information on VTE risk and thromboprophylaxis from clinical studies as well as the recently published guidelines from American Society of Clinical Oncologists (ASCO) and American College of Chest Physicians (ACCP). The intended audience consists of hospitalists, oncologists, emergency physicians, and other health care professionals who might care for patients at risk for VTE.

New VTE occurs at a rate of about 100 per 100,000 people in the United States per year, and the risk increases from fewer than 5 cases per 100,000 at age 15 to about 500 cases per 100,000 at age 80.[1] VTE is a major complication of cancer, with clinical rates of 4% to 20%,[2] and the rate increases with advanced disease.[3]

RISK FACTORS

Various conditions increase the risk for VTE, and this risk is especially acute in hospitalized patients. In this section, information about the risks of VTE is presented along with a simplified system to help evaluation.

Table 1 shows the deep vein thrombosis (DVT) prevalence in various hospitalized patient groups. Joint arthroplasty, major trauma, spinal cord injury (SCI) and critical care patients are at special risk.

Table 1: Risks of DVT in hospitalized patients.

Patient Group	DVT Prevalence, %
Medical patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip or knee arthroplasty, hip fracture surgery (HFS)	40–60
Major trauma	40–80
SCI	60–80
Critical care patients	10–80

The rates are based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.[4]

Table 2 shows the characteristics of patients with acute DVT and/or pulmonary embolism (PE). Most patients are older than 40 years, and approximately one-third are obese. More than one-third of the patients have 3 or more risk factors.

Table 2: Risk factors observed in 1231 consecutive patients treated for acute DVT and/or PE.[5]

Risk Factor	Patients (%)
Age ≥ 40 years	88.5
Obesity	37.8
History of venous thromboembolism	26.0
Cancer	22.3
Bed rest ≥ 5 days	12.0
Major surgery	11.2
Congestive heart failure	8.2
Varicose veins	5.8
Fracture (hip or leg)	3.7
Estrogen treatment	2.0
Stroke	1.8
Multiple trauma	1.1
Childbirth	1.1
Myocardial infarction	0.7
1 or more risks	96.3
2 or more risks	76.0
3 or more risks	39.0

Table 3: Levels of thromboembolism risk and recommended thromboprophylaxis in hospital patients.

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis, %†	Suggested Thromboprophylaxis Options
Low risk		
Minor surgery in mobile patients	< 10	No specific thromboprophylaxis Early and "aggressive" ambulation
Medical patients who are fully mobile		
Moderate risk		
Most general, open gynecologic or urologic surgery patients	10–40	LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Medical patients, bed rest or sick		
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§
High risk		
Hip or knee arthroplasty, HFS	40–80	LMWH, fondaparinux, oral vitamin K antagonist (VKA, INR 2–3)
Major trauma, SCI		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§

The descriptive terms are purposely left undefined to allow individual clinician interpretation. †Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis. §Mechanical thromboprophylaxis includes intermittent pneumatic compression (IPC) or venous foot pump and/or graduated compression stockings; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.[4] LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; INR, international normalized ratio

Since the risk for an individual patient is difficult to assess and the interaction of multiple factors is not known, a tiered system has been proposed to simplify evaluation. It is based on the primary reason for hospitalization and its associated risk of DVT, and recommends an initial thromboprophylactic strategy **(Table 3)**.[4]

The connection between VTE and malignancy has been recognized for a long time. The pathogenesis of thrombosis in patients with malignancy is complex, and some of the cancer-related factors that may be functionally involved in increased VTE are listed in **Table 4**.

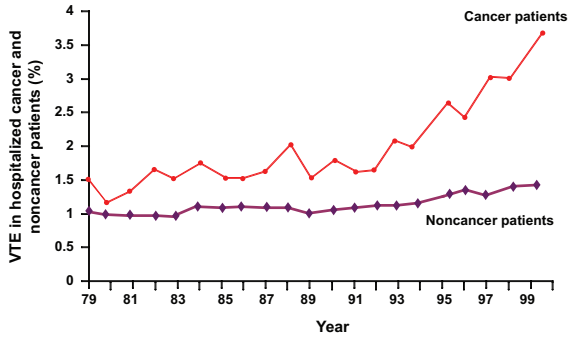
Table 4: Cancer-associated factors that may increase the risk of VTE.[6,7]

Immobilization
Surgery
Chemotherapy and catheter-associated blood vessel damage
Procoagulant proteins: Increased levels Reduction of natural anticoagulants Release from tumor cells
Suppression of fibrinolytic activity
Increased platelet reactivity and activation
Enhanced adhesion of neutrophils
Down-regulation of thrombomodulin
Release of cytokines from tumor cells

The eighth edition of the ACCP guidelines[4] and the ASCO VTE guidelines[8] summarize the data showing elevated risk of VTE in patients with cancer. Multivariate analysis of data from the Olmsted County case-control study suggests that malignant neoplasm alone was associated with a 4-fold increased risk of VTE, and cytotoxic or immunosuppressive chemotherapy increased the risk to more than 6-fold.[9] The risk of VTE varies by cancer type and extent, and is especially high among patients with malignant brain tumors; adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, and kidney; and hematologic malignancies.

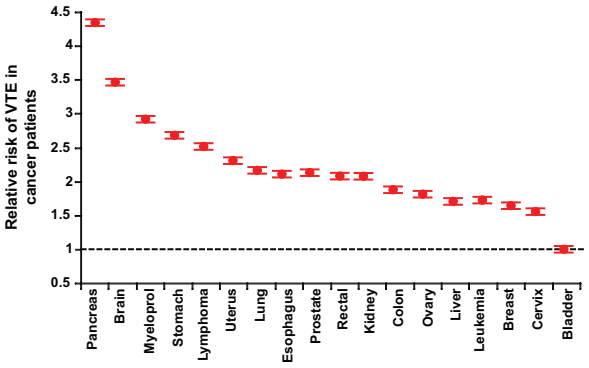
A retrospective study of more than 40 million patients discharged from hospitals with diagnostic codes for malignancies, PE, and DVT found that patients with cancer have about twice the rate of VTE than hospitalized patients without cancer.[10] In addition, the rate of increase observed in recent years is higher among patients with cancer **(Figure 1)**. The authors suggest that the increase in VTE is due to higher diagnostic sensitivity and increased awareness of the association between VTE and cancer.

Figure 1: From 1989 through 1999 the incidence of VTE in hospitalized patients with cancer increased faster than in patients without cancer.[10]



The distribution of VTE is not uniform among different types of cancer. Pancreas and brain cancer are associated with particularly high rates of VTE (4.3 and 3.5 diagnoses/100 hospitalizations, respectively).

Figure 2. Relative risk of VTE in patients with different types of cancer ranged from 1.02 to 4.34.[10]



Myeloprol signifies myeloproliferative and other lymphatic/hematopoietic cancers. Lymphoma includes lymphoma, lymphosarcoma and reticulosarcoma.

Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE encountered by noncancer patients who are undergoing similar procedures **(Figure 2)**. Cancer is also an independent predictor of thromboprophylaxis failure.[8] The @RISTOS Project[11] looked at 2373 patients undergoing general (n = 1238, 52%), urologic (n = 685, 29%), or gynecologic (n = 450, 19%) surgery for cancer. The incidence of clinically overt VTE was 2.1% (DVT, 0.42%; nonfatal PE, 0.88%; death attributed to VTE

Table 5: Prognostic risk factors for VTE: multivariable logistic regression analysis.[11]

Variable	Effect	No. of Patients VTE/Non-VTE	OR	95% CI
Age class	≥ 60 vs < 60 yrs	≥ 60 yrs: 42/1516 < 60 yrs: 8/807	2.6	1.2–5.7
Previous VTE	Yes vs No	Yes: 5/36 No: 45/2287	6.0	2.1–16.8
Anesthesia	≥ 2 vs < 2 hrs	≥ 2 hrs: 48/1762 < 2 hrs: 2/561	4.5	1.1–19.0
Staging	Advanced vs Not Advanced	Advanced: 38/1078 Not advanced: 12/1245	2.7	1.4–5.2
Bed rest	≥ 4 vs < 4 days	≥ 4 days: 25/346 < 4 days: 25/1977	4.4	2.5–7.8

0.80%). The overall death rate was 1.72%; VTE was the most common cause of death, occurring in 46% of the fatalities. A large number (40%) of the VTE events occurred more than 21 days after surgery. Multivariate analysis revealed 5 risk factors for VTE after cancer surgery **(Table 5)**.

DIAGNOSIS

Diagnostic tools for detection of DVT and PE are clinical presentation, biochemical detection of elevated D-dimer, and confirmation with ultrasound. None of these tests is ideal, and a stepwise diagnostic strategy is discussed in this section.

Table 6: The Wells clinical model for assessing the PTP of DVT.[12]

Clinical characteristic†	Score
Active cancer (treatment ongoing, administered within previous 6 mo or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 d or major surgery within previous 12 wks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Swelling of entire leg	1
Calf swelling > 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

A score of 2 or higher indicates that the probability of DVT is "likely"; a score of less than 2 indicates that the probability is "unlikely." †In patients who have symptoms in both legs, the more symptomatic leg is used.[13]

The clinical symptoms of DVT (unilateral calf, leg, or thigh swelling or pain)[8] and PE (shortness of breath, tachypnea, pleuritic chest pain, a pleural rub, hypoxia, hemoptysis, tachycardia, syncope along with accompanying symptoms), and signs of a DVT or right heart failure[8] are nonspecific. Wells and colleagues have developed a clinical model to evaluate the pretest probability (PTP) of DVT **(Table 6)**.[12,13] This system accounts for signs, symptoms and risk factors of DVT that result in a high negative predictive value (NPV).

D-dimer is a fragment of cross-linked fibrin. While D-dimer is often elevated in VTE, the test is not specific, as D-dimer is also elevated in conditions such as infection, inflammation, cancer, surgery, cardiac or renal failure, acute coronary syndromes, acute nonlacunar stroke, peripheral artery disease, ruptured aneurism or aortic dissection, pregnancy, cerebral sinus thrombosis, and sickle cell crises.[14,15] Age has a negative effect on the specificity of the D-dimer assay, though the sensitivity is high and independent of age **(Table 7)**.

Table 7: Performance characteristics of an ELISA test in different age strata at a cutoff value of 500 ng/mL in 671 outpatients investigated for suspected PE.[14]

Age	Sensitivity, %	Specificity, %
< 30	100	60
30-39	100	72
40-49	100	60
50-59	100	54
60-69	100	32
70-79	98	22
≥ 80	100	9

Several immunoassays are available in ELISA and agglutination formats.[15] The best test is determined by the clinical setting and by the sensitivity/specificity requirements of the diagnostic sequence.[15] In cases where the D-dimer levels are very high, the test might have positive predictive value[16] but the largest benefit appears to be from its NPV, excluding DVT as a diagnosis.[13]

Patients with cancer have elevated risk of VTE and therefore the test performance is different.[15] A review of studies of suspected DVT reveals a DVT prevalence of 11% to 25% in patients without cancer, but 37% to 52% in patients

with cancer. The D-dimer test sensitivity in these studies is high for both patient groups, but the specificity is higher in the noncancer patient group. Studies with a high DVT prevalence also had a lower NPV (70% to 80%). In cancer patients, the D-dimer can be elevated because of the inflammatory reaction to the cancer, resulting in a low positive predictive value (PPV) for VTE.

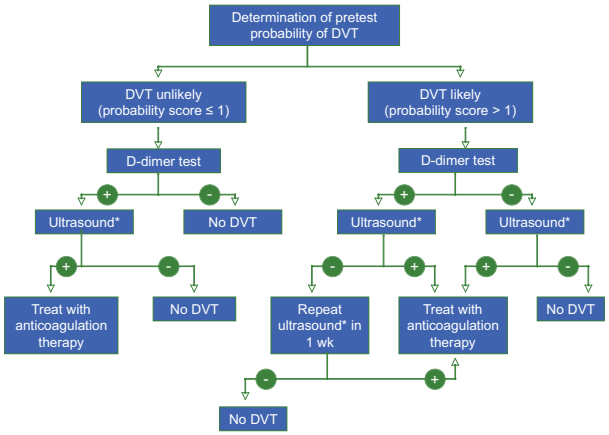
Another way to approach the diagnosis of VTE is with a combination of tests. Ljungqvist et al[17] studied the use of the Wells PTP score in combination with the D-dimer test in emergency departments by doctors without much experience in thromboembolic diseases. They asked whether a low clinical probability together with a normal D-dimer level safely excludes VTE. Patients (n = 374) with suspected VTE were screened; patients with a Wells PTP score of 1.5 or higher or a D-dimer level of 0.5 mg/L or higher were excluded. The study included 118 patients with suspected DVT and 33 with suspected PE. After 3 months, the investigators contacted the 151 study subjects and none reported symptoms or diagnosis of VTE. The NPV of the D-dimer test for all patients, irrespective of their Wells PTP score, was 99.5% and the PPV was 24.2%. The NPV for low scores (irrespective of the D-dimer) was 93.3% and the PPV was 27.3%. A follow-up D-dimer test 3 to 7 days after the initial investigation did not add any further information. The authors conclude that a low Wells PTP score in combination with a low D-dimer level safely excludes VTE at the emergency department, and that follow up D-dimer after 3 to 7 days adds no further information.

Patients with risk factors leading to a PTP score > 1 and patients with a PTP score < 1 with a positive D-dimer test should be tested for DVT with ultrasound, illustrated in **Figure 3**. Scarvelis and Wells emphasize that the D-dimer test should not be used to exclude DVT in the presence of a high PTP.[13] Sometimes the imaging is not practical in a timely manner; if there is a strong clinical suspicion of DVT, LMWH can be initiated prior to obtaining the ultrasound result.

VTE PROPHYLAXIS

Though prophylactic anticoagulation has been demonstrated to be effective in reducing the risk of VTE in at-risk patients, a substantial proportion of these patients do not receive prophylaxis. This section describes screening for patients with asymptomatic DVT, several studies supporting the use of VTE prophylaxis, a computer alert system that was shown to reduce the risk of DVT or PE, and key prophylaxis recommendations from the most recent ACCP and ASCO guidelines.

Figure 3. Diagnostic algorithm using D-dimer testing and ultrasound imaging in patients with suspected DVT.



Pregnant women were not included in the development of this algorithm. Comorbidities associated with high D-dimer levels diminish the usefulness of the test for diagnosis DVT.[13]

*Imaging done from proximal veins to calf trifurcation.

Certain patient populations at high risk for asymptomatic DVT are also at high risk of bleeding. Use of a screening ultrasound to help decide which patients should receive treatment has been proposed for these groups. Unfortunately, ultrasound as a screening tool was found to be neither specific nor sensitive for the diagnosis of DVT. In a thromboprophylaxis trial of trauma patients,[18,4] 215 SCI patients underwent both contrast venography and ultrasound approximately 14 days after injury; 53% of the abnormal ultrasound scan results were proven to be false positive, while the ultrasound missed 71% of the DVTs detected by contrast venography. The cost, accessibility, and accuracy of ultrasound in this setting suggest that it might not be a useful routine test prior to thromboprophylaxis.

In a trial with hip and knee arthroplasty patients, ultrasound screening detected DVT in 2.5% of patients, who then received therapeutic anticoagulation.[19] However, both the ultrasound and sham groups had a total event outcome (proximal DVT or PE or major bleeding) rate of 1%. These findings were confirmed in another trial,[20] in which 346 hip and knee arthroplasty patients received LMWH thromboprophylaxis for

10 days and were then randomized to continue LMWH for another 3 weeks, or to have prehospital discharge ultrasound screening with anticoagulant therapy if the findings were positive. Ultrasound screening identified proximal thrombi but did not reduce the rate of symptomatic VTE in the 3-month follow-up period. These studies and others[4] suggest that prehospital discharge screening using contrast venography or ultrasound does not predict which patients require posthospital discharge thromboprophylaxis.[4] The absence of an effective and inexpensive screening test for asymptomatic DVT supports the practice of extended postdischarge thromboprophylaxis as the best means to prevent thromboembolic complications in major orthopedic surgery. The eighth edition of the ACCP guidelines recommends against the routine use of ultrasound screening before hospital discharge.[4] Though ultrasound does not appear to be a good screening test, it has been used as an endpoint measure of DVT in clinical trials.

ENDORSE was a major, retrospective multicenter study looking at the prevalence of VTE risk in the acute hospital care setting, and the proportion of at-risk patients who receive effective prophylaxis.[21] All hospital inpatients aged 40 years or older and admitted to a medical ward, or those aged 18 years or older and admitted to a surgical ward, in 358 hospitals across 32 countries were assessed for risk of VTE on the basis of hospital chart review. Of the 68,183 enrolled patients, 45% were surgical and 55% were medical. Almost 52% were judged to be at risk for VTE. Only 58% of the at-risk surgical patients and 40% of the at-risk medical patients received thromboprophylaxis.

Several random-controlled trials (RCTs) of anticoagulants for VTE prophylaxis in acutely ill hospitalized medical patients report significant reduction in VTE with pharmacologic prophylaxis.[8] In MEDENOX[22] (Prophylaxis in Medical Patients with Enoxaparin), the primary efficacy outcome was VTE between days 1 and 14. Patients were examined for DVT by mandatory venography. The primary efficacy end point in PREVENT[23] (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial) was the incidence of VTE by day 21, a composite of objectively confirmed symptomatic DVT (proximal or distal), fatal or symptomatic nonfatal PE, sudden death, and asymptomatic proximal DVT detected by systematic compression ultrasound at day 21. The primary efficacy outcome of ARTEMIS[24] (ARixtra for ThromboEmbolism Prevention in a Medical Indications Study) was the composite of DVT detected by routine bilateral venography on days 6 to 15, and symptomatic VTE up to day 15. The results summarized in **Table 8** show relative risks (RR) for VTE of 0.37 with enoxaparin, 0.55 with dalteparin, and 0.47 with fondaparinux.

A meta-analysis of the use of LMWH in general surgical patients found that compared to placebo or no treatment, LMWH lowered the RR for asymptomatic DVT (RR = 0.28, $P < 0.001$), clinical PE (RR = 0.25, $P = 0.018$), and clinical thromboembolism (RR = 0.29, $P = 0.009$), and was associated with a trend toward reduced mortality (RR = 0.54, $P = 0.09$).[25] The results also support the use of asymptomatic DVT as a surrogate marker for clinical outcome.

Table 8: Trials of anticoagulants for VTE prophylaxis in acutely ill hospitalized medical patients.[8]

		Cancer Patients		Placebo Events		Treatment Events				
Reference	Total # of Patients	#	%	#	%	#	%	Relative Risk	*P*	95% CI
MEDENOX	579*	72	12.4	43/288 8/41†	14.9 19.5	16/291 3/31†	5.5 9.7	0.37	< 0.001	0.22 to 0.63
PREVENT	3706	190	5.1	73/1473	4.96	42/1518	2.77	0.55	0.0015	0.38 to 0.8
ARTEMIS	849‡	131	15.4	34/323	10.5	18/321	5.6	0.47	0.029	0.08 to 0.69

* MEDENOX included a 20 mg enoxaparin arm of 287 patients with event rates equivalent to placebo. Number includes only placebo and patients receiving 40 mg treatment. †Number of patients with cancer treated with placebo and 40 mg treatment arms. There is no statistical difference ($P = 0.4$).
‡Total patients assessable for safety analysis; only 644 patients were assessable for primary end point.

Venous Thromboembolism Prophylaxis:

Mechanical methods of thromboprophylaxis should be used primarily in patients at high risk for bleeding, or possibly as an adjunct to anticoagulant-based thromboprophylaxis.[4] Since poor fitting of devices and poor patient compliance are common, careful attention should be directed toward the proper use of these methods.

In June 2008, the ACCP released the eighth edition of the clinical practice guidelines for antithrombotic and thrombolytic therapy. Among the key evidence-based recommendations in the chapter on prophylaxis[4] are the following:

- Every hospital should develop a formal strategy that addresses the prevention of VTE. The use of aspirin alone as thromboprophylaxis is not recommended for any patient group and mechanical methods of thromboprophylaxis should be used primarily for patients at high bleeding risk or possibly as an adjunct to anticoagulant thromboprophylaxis;
- Thromboprophylaxis with a LMWH, LDUH, or fondaparinux is recommended for patients undergoing major general surgery;
- Routine thromboprophylaxis with LMWH, LDUH, fondaparinux, or IPC is recommended for all patients undergoing major gynecologic surgery or major, open urologic procedures;
- An anticoagulant agent (LMWH, fondaparinux, or a VKA [target INR, 2.5; range, 2.0 to 3.0]) is recommended for patients undergoing elective hip or knee arthroplasty;
- The routine use of fondaparinux, LMWH, a VKA (target INR, 2.5; range, 2.0 to 3.0) or LDUH is recommended for patients undergoing HFS;
- Patients undergoing hip or knee arthroplasty or HFS should receive thromboprophylaxis for a minimum of 10 days; for hip arthroplasty and HFS, thromboprophylaxis should continue for > 10 days and up to 35 days;
- All major trauma and all SCI patients should receive thromboprophylaxis;
- Thromboprophylaxis with LMWH, LDUH, or fondaparinux is recommended for patients admitted to hospital with an acute medical illness;
- On admission to the ICU, all patients should be assessed for risk of VTE, and most should receive thromboprophylaxis.

In 2007, ASCO published recommendations for VTE prophylaxis and treatment in patients with cancer.[8] These guidelines address 5 critical questions:

1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

- Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation.

2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systematic chemotherapy?

- Routine prophylaxis with an antithrombotic agent is not recommended.
- Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis. Until such time as data are available from RCTs, LMWH or adjusted-dose warfarin (INR ~1.5) is recommended in myeloma patients receiving thalidomide plus chemotherapy or dexamethasone. This recommendation is based on extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer.
- RCTs evaluating antithrombotic agents are needed in patients with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone.
- Research identifying better markers of ambulatory patients with cancer most likely to develop VTE is urgently needed.

3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

- All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis.
- Patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes should receive pharmacologic thromboprophylaxis with either LDUH or LMWH unless contraindicated because of a highrisk of bleeding or active bleeding.
- Prophylaxis should be commenced preoperatively, or as early as possible in the postoperative period.
- Mechanical methods may be added to pharmacologic methods, but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding.

- A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest risk patients.
- Prophylaxis should be continued for at least 7 to 10 days postoperatively. Prolonged prophylaxis for up to 4 weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features such as residual malignant disease after operation, obese patients, and those with a previous history of VTE.

Question 4 addresses prevention of recurrent VTE and Question 5 addresses the use of anticoagulants to improve survival in cancer patients in the absence of established VTE.

Both sets of guidelines emphasize the necessity of weighing the benefit of thromboprophylaxis with the risk of bleeding. The ACCP guidelines conclude that the risk of bleeding associated with IV UFH in patients with acute VTE is less than 3%, though it may rise with increasing heparin dosages and age (> 70 years). LMWH is associated with less major bleeding compared with UFH in acute VTE. The risk of major bleeding with a prophylactic dose (2.5 mg/d) of fondaparinux in patients undergoing surgery for hip fracture and medically ill patients is very small; the risk of bleeding at the therapeutic dose of 7.5 mg/d has not been evaluated. VKA therapy can be monitored with an INR to reduce the risk of bleeding.[26]

ADHERENCE

Thromboprophylaxis is underutilized.[27] One barrier is fear of bleeding. Underestimation of the risk of VTE and caution about heparin-induced thrombocytopenia (HIT) also contribute. The effect of successful prophylaxis is not readily apparent, while the adverse events of bleeding or HIT are dramatic. The perceptions of potential outcomes may influence clinicians to not use prophylaxis. Several studies suggest that institutional strategies can increase the rate of prophylaxis.

A meta-analysis by Tooher et al[28] examined the success of various strategies aimed at improving thromboprophylaxis utilization. Adherence to guidelines and the provision of adequate prophylaxis were poor in studies that relied on passive dissemination of guidelines. In general, the use of multiple strategies was more effective than a single strategy. The most effective strategies incorporated a system for reminding clinicians to assess patients for VTE risk, either electronic decision-support systems or paper-based reminders, and used audit and feedback to facilitate the iterative refinement of the intervention. Outcomes data for VTE, cost and utilization of resources were not available.

The BEHAVE study[29] assessed methods for improving patient safety by increasing heparin thromboprophylaxis for medical-surgical ICU patients. After a 3-month baseline period, guidelines were implemented using a) interactive multidisciplinary educational inservices; b) verbal reminders to the intensive care unit team; c) daily computerized documentations of thromboprophylaxis by nursing staff; d) weekly graphic reports to individual intensivists on guideline adherence; and e) public displays of graphic feedback on group performance. There was a 3-month thromboprophylaxis assessment period 10 months later. ICU and hospital mortality rates were similar across phases. Heparin thromboprophylaxis increased by 50% during the implementation and assessment phases ($P = 0.01$).

Choosing the appropriate patients for prophylaxis is important. A computer alert system based on 8 factors was tested in an outcomes study in hospitalized patients.[30] Consecutive patients were evaluated for VTE risk according to the system shown in Table 9.

Table 9: Criteria for selection of medically ill patients for VTE prophylaxis used in conjunction with electronic alerts.

1 point each:
Age > 70
Obesity (body mass index > 29)
Bed rest
Hormone replacement therapy or combined oral contraceptives
2 points each:
Major surgery
3 points each:
Cancer
Prior VTE
Hypercoagulability
Patients with a score of at least 4 points were considered at increased risk.

Alternate patients with a computed risk of 4 points or greater were assigned to intervention or control groups. Physicians treating patients in the intervention group were electronically alerted to the VTE risk status of the patient, while no alert

was issued for the control group. More patients in the intervention group than in the control group received mechanical prophylaxis (10% vs 1.5%, $P < 0.001$) or pharmacologic prophylaxis (24% vs 13%, $P < 0.001$). The primary end point of DVT or PE at 90 days occurred in 61 patients (4.9%) in the intervention group, compared with 103 (8.2%) in the control group. The computer alert reduced the risk of DVT or PE at 90 days by 41% (HR, 0.59; $P = 0.001$).

Several initiatives have addressed the question of how to implement guidelines and increase appropriate thromboprophylaxis. The Society for Hospital Medicine has a VTE implementation guide entitled *Preventing Hospital-Acquired Venous-Thromboembolism, A Guide for Effective Quality Improvement* available on its Web site,[31] and the National Quality Forum has National Consensus Standards for the Prevention and Care of Venous Thromboembolism (including Deep Vein Thrombosis and Pulmonary Embolism) available on its Web site.[32]

EMERGING THERAPIES

Rivaroxaban, an orally active direct factor Xa inhibitor, was compared to LMWH for prevention of VTE in patients undergoing hip or total knee arthroplasty in 2 recent studies. RECORD1[33] was a randomized, double-blind study of 4541 patients who were scheduled to undergo elective total hip arthroplasty. Patients received either 10 mg of oral rivaroxaban qd, beginning after surgery, or 40 mg of enoxaparin SC qd, beginning the evening before surgery, plus a placebo tablet or injection. The primary efficacy outcome was the composite of DVT, nonfatal PE, or death from any cause at 36 days. DVT was assessed by venography. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group (absolute risk reduction, 2.6%; $P < 0.001$). Major VTE occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group (absolute risk reduction, 1.7%; $P < 0.001$). Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin group ($P = 0.18$).

RECORD3[34] was a randomized, double-blind trial of 2531 total knee arthroplasty patients who received either oral rivaroxaban, 10 mg once daily, beginning 6 to 8 hours after surgery, or enoxaparin, 40 mg SC qd, beginning 12 hours before surgery. The primary efficacy outcome was the composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days after surgery. DVT was assessed by venography. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 79 of 824 patients (9.6%) who received rivaroxaban and in 166 of 878 (18.9%) who received enoxaparin (absolute risk reduction, 9.2%; $P < 0.001$). Major VTE occurred in 9 of 908 patients (1.0%) given rivaroxaban and 24 of 925 (2.6%) given enoxaparin (absolute risk reduction, 1.6%; $P = 0.01$). Symptomatic events occurred less frequently with rivaroxaban than with enoxaparin ($P = 0.005$). Major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% of patients in the enoxaparin group. On the basis of these trials, rivaroxaban was superior to enoxaparin for thromboprophylaxis after hip or total knee arthroplasty; the drugs were associated with similar rates of bleeding.

Other compounds in development include apixaban, an oral Xa inhibitor, and dabigatran, an oral IIa inhibitor. These compounds are in phase 3 clinical evaluation for a variety of VTE prevention and treatment indications.

SUMMARY

The risk of VTE in cancer, surgical and medical patients is underappreciated. The new ACCP and ASCO guidelines that delineate the appropriate use of thromboprophylactic agents may increase this awareness if they are used in conjunction with one of the strategies that promotes adherence. The danger of bleeding due to overadministration of anticoagulants does not appear to be a safety concern with the new generation of LMWHs and emerging therapies.

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Attestation/Evaluation Form

To obtain *AMA PRA Category 1 Credit*™, participants are required to:

1. Read the learning objectives, review the activity, and complete the posttest.
2. Complete this Attestation/Evaluation form.
3. Mail or fax these forms to: The France Foundation
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Indicate the number of *AMA PRA Category 1 Credits*™ you are claiming ____ (Max 1 credit)

Signature:_____ Date:_____

I certify that I have completed this CME activity as designated.

BIAS, FAIR BALANCE

Was this activity fair, balanced, objective, and free from commercial bias? ❑ Yes ❑ No

If no, please state reason(s)_____

PRACTICAL APPLICATION

4 = strongly agree; 3 = agree; 2 = disagree; 1 = strongly disagree

a)____ What I learned at this activity has increased my confidence in managing patients with VTE

b)____ What I learned in this activity will improve my ability to provide thromboprophylaxis to patients at risk for VTE

c)____ What I learned in this activity will result in an improvement in my patients' health status

d)____ Do you intend to make changes or apply new information to your practice as a result of this activity?

____ Yes, I plan to make changes*

____ I'm not sure, but I'm considering changes*

____ No, I already practice these recommendations

____ No, I don't think this applies to my practice

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*If yes or you are considering changes, please check off what you intend to do differently or incorporate into your clinical practice as a result of this educational activity

____ Better recognize high-risk patients that should receive thromboprophylaxis as a matter of standard clinical management

____ Improve guideline adherence to reduce thromboembolic risk in my practice setting

____ Other: _____

BARRIERS

What are the top 3 barriers that might inhibit your ability to incorporate any of the above changes into your clinical practice?

1._____ 2._____ 3._____

DEMOGRAPHIC QUESTIONS

How did you hear about this CME activity?

❑ Received via mail ❑ Downloaded from www.VTEeducation.com™ ❑ Received copy from colleague

❑ Other: _____

Number of years in practice: ❑ ≤ 5 ❑ 6–10 ❑ 11–15 ❑ 16–20 ❑ 21–25 ❑ 25+

What percentage of your patients are at risk for VTE? ❑ ≤ 5 ❑ 6–20 ❑ 21–40 ❑ 41–60 ❑ 60+

May we contact you in the future with a brief survey to assess how you have used the information presented in this activity or to assess other educational needs? ❑ Yes ❑ No

ACTIVITY EVALUATION

4 = strongly agree; 3 = agree; 2 = disagree; 1 = strongly disagree

Upon completion of this activity, I will be able to:

a)____ Describe which groups of high risk patients should receive thromboprophylaxis as a matter of standard clinical management

b)____ Demonstrate awareness of the benefits and risks of current and emerging pharmacotherapies for thromboprophylaxis

c)____ Develop a strategy for improving guideline adherence and reducing thromboembolic risk in the at-risk patients

Please rate the overall content presented in this activity: ❑ Too basic ❑ Appropriate ❑ Too complex

ONGOING UNMET EDUCATIONAL NEEDS

Recommendations for future CME topics in this disease area: _____

_____

_____

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Posttest

1. **Which of the following is not a risk factor for VTE?**
   A. Age > 40
   B. Obesity
   C. Diabetes
   D. Congestive heart failure
   E. Trauma

2. **Which of the following is a risk factor for VTE in cancer patients?**
   A. Chemotherapy
   B. Hospitalization
   C. Older age
   D. Surgery
   E. A, B, and D only
   F. A-D

3. **According to the @RISTOS Project, the risk of VTE is highest immediately after surgery and decreases until day 20. After this window of danger, the risk remains low.**
   A. True
   B. False

4. **In 2008, Cohen et al reported in *Lancet* that the percentage of hospitalized medical patients at risk for VTE who received appropriate prophylaxis was_____%.**
   A. 88%
   B. 65%
   C. 40%
   D. 18%

5. **The 2008 ACCP guidelines recommend aspirin as a low-cost effective agent for thromboprophylaxis.**
   A. True
   B. False

6. **Which of the following is NOT a barrier to effective VTE prophylaxis?**
   A. Fear of bleeding
   B. Lack of quantitative patient evaluation tools
   C. Failure to treat
   D. Lack of effective agents

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Notes

Notes