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A Call to Action:

Practical Guidance *in Support of* New Standards
for VTE Prophylaxis

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CME and Faculty Information

CME INFORMATION

Needs Statement/Target Audience

This activity is intended to provide hospitalists, critical care specialists, critical care nurses, general surgeons, health system pharmacists, oncologists, 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 and how to assess overall risk in each hospitalized patient
- Demonstrate awareness of the most recent guidelines for risk assessment and prophylaxis in VTE and identify potential gaps in relation to current practice
- Develop a strategy for improving guideline adherence and reducing thromboembolic risk within the hospital setting

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Commercial Support Acknowledgment: This educational activity is supported by an educational grant from GlaxoSmithKline.

Release/Expiration Dates: This activity is eligible for CME credit from **October 2009 through October 31, 2010.**

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INTRODUCTION

Venous thromboembolism (VTE) is a serious cardiovascular complication of multiple surgical and medical conditions. This primer is an update on VTE risk and thromboprophylaxis based on registry and clinical studies as well as the recently published guidelines from American Society of Clinical Oncologists (ASCO), the National Comprehensive Cancer Network (NCCN), and American College of Chest Physicians (ACCP). Common barriers to proper VTE prophylaxis and successful strategies are discussed. The intended audience consists of hospitalists, oncologists, emergency physicians, critical care nurses, general surgeons, health system specialists, and other health care professionals who might manage 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; the rate increases with advanced disease.

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.

Deep vein thrombosis (DVT) is highly prevalent in various hospitalized patients, and almost all have at least 1 risk factor for VTE.³ Joint arthroplasty, major trauma, spinal cord injury (SCI), and critical care patients are at special risk. **Table 1** shows the rates of asymptomatic DVT in various patient groups. The ratio of asymptomatic DVT to

Table 1: Risks of DVT in hospitalized patients.³

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
Spinal cord injury	60–80
Critical care patients	10–80

symptomatic VTE varies in different conditions. For example, total knee replacement patients and total hip replacement patients had ratios of 21:1 and 5:1, respectively.⁴

Among patients with acute DVT and/or pulmonary embolism (PE), most patients are older than 40 years, and approximately one-third are obese.⁵ More than one-third of the patients have 3 or more risk factors (**Table 2**).

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 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

The connection between VTE and malignancy is well recognized, and multiple factors contribute to its pathogenesis, including immobilization, surgery, chemotherapy, catheters, and dysregulation of coagulation.⁶

The eighth edition of the ACCP guidelines³ and the ASCO VTE guidelines⁷ 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.⁸ 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



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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.⁹ In addition, the rate of increase observed in recent years is higher among patients with cancer. The authors suggest that the increase in VTE is due to higher diagnostic sensitivity and increased awareness of the association between VTE and cancer. 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). Solid tumors are not unique in being associated with a high risk of VTE.

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. Cancer is also an independent predictor of thromboprophylaxis failure.⁷ The @RISTOS Project¹⁰ looked at 2373 patients undergoing general, urologic, or gynecologic surgery for cancer. The incidence of clinically overt VTE was 2.1% (DVT, 0.42%; nonfatal PE, 0.88%; death attributed to VTE 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 3).

Table 3: Prognostic risk factors for VTE: multivariable logistic regression analysis.¹⁰

Variable	Effect	OR	95% CI
Age class	≥ 60 vs < 60 yrs	2.6	1.2–5.7
Previous VTE	Yes vs No	6.0	2.1–16.8
Anesthesia	≥ 2 vs < 2 hrs	4.5	1.1–19.0
Staging	Advanced vs Not Advanced	2.7	1.4–5.2
Bed rest	≥ 4 vs < 4 days	4.4	2.5–7.8

The observational RIETE study also found a high coincidence between cancer and VTE.¹¹ Of 14,391 patients with symptomatic acute VTE, 2945 (20%) also had cancer. The incidence of fatal PE within 3

months in these cancer patients was 2.6% and the incidence of fatal bleeding was 1.0%, significantly higher than the rates in patients without cancer (1.4% and 0.3%, respectively). The odds ratios for fatal PE and fatal bleeding for patients with both cancer and VTE are shown in Table 4. There were differences in the rate of prophylaxis; for example, 69% of surgical patients had received prior prophylaxis, in contrast to only 26% of patients who had been immobilized.

Table 4. Multivariate analysis of the risk of developing fatal pulmonary embolism (PE) or fatal bleeding in cancer patients with VTE.¹¹

Variables	Fatal PE OR (95% CI)	Fatal bleeding OR (95% CI)
Body weight < 60 kg	-	2.5 (1.1-5.3)
Recent major bleeding	2.8 (1.2-6.3)	3.0 (0.96-9.1)
Serum creatinine > 1.2 mg/dL	2.6 (1.6-4.3)	2.8 (1.3-5.8)
Immobility ≥ 4 days	1.9 (1.1-3.2)	4.1 (1.9-8.7)
Surgery	0.6 (0.2-1.4)	-
Symptomatic PE	13.9 (6.3-30)	-
Metastatic cancer	2.9 (1.8-4.8)	3.1 (1.4-7.1)

The RIETE investigators also looked at the effect of white blood cell count at baseline in patients with cancer and acute VTE on recurrent VTE, major bleeding, and death during a 3 month period. Patients with an elevated WBC count at baseline had increased incidence of recurrent VTE (OR 1.6; 95% CI 1.2–2.2), major bleeding (OR 1.5; 95% CI 1.1–2.1), or death (OR 2.7; 95% CI 2.3–3.2). These differences persisted after multivariate adjustment, and the authors suggest that WBC counts might become a component of prognosis in these patients.

There are several therapy-related risk factors for VTE. These include estrogen-containing oral contraceptives or hormone replacement therapy (HRT), selective estrogen receptor modulators, and erythropoiesis-stimulating agents.³ The selective estrogen receptor modulator tamoxifen is associated with a 2 to 5-fold increased rate of VTE among women with breast cancer. This risk was increased in postmenopausal women and when tamoxifen was combined with chemotherapy. Aromatase inhibitors such as anastrozole, letrozole, or exemestane are associated with approximately half the risk of VTE compared with tamoxifen. Angiogenesis inhibitors are also associated with increased thromboembolic



complications in cancer patients. Thalidomide and lenalidomide are associated with VTE, especially when they are combined with chemotherapy and/or high-dose dexamethasone. The presence of a central venous catheter (CVC) in cancer patients predisposes to upper-extremity DVT and is reviewed in the guidelines publication.³

Several registry studies describe the state of patient care. The DVT-FREE study was a prospective study of 5451 patients with ultrasound-confirmed DVT.¹² It found that among the 2726 patients who were diagnosed with DVT in the hospital, only 42% had received prophylaxis within 30 days prior to diagnosis. Cancer was reported in 1768 (39%), of whom 1096 (62.0%) had active cancer. Cancer patients less often received VTE prophylaxis prior to development of DVT compared to those with no cancer (308 of 1096, 28.2% vs. 1196 of 3444, 34.6%; $P < 0.0001$).¹³

The NABOR study retrospectively examined the medical records of 3778 patients and found low rates of appropriate prophylaxis.¹⁴ After orthopedic surgery procedures, more than 90% of patients received some prophylaxis, though 8% received only aspirin. In secondary prevention, almost half of the patients with VTE receiving UFH or LMWH had their anticoagulation discontinued before an INR of 2.0 or greater was achieved for 2 consecutive days.

The IMPROVE study surveyed rates of VTE prophylaxis in acutely ill medical patients in 52 hospitals in 12 countries.¹⁵ Approximately 60% of eligible patients received prophylaxis. Intermittent pneumatic compression was the most common treatment in the US (22%), though it was used considerably less (0.2%) in other countries. Patients in US hospitals received UFH as the most frequent pharmacologic agent (21%), while LMWH was most frequently used in other countries (40%).

The CURVE study of acutely ill medical patients in Canadian hospitals found that in 90% of the cases prophylaxis was indicated.¹⁶ However, only 23% received any prophylaxis, and 16% received appropriate thromboprophylaxis.

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.¹⁷ All hospital inpatients aged 40 years or older admitted to a medical ward, or those aged 18 years or older 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.

GUIDELINES

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 prophylaxis³ 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 vitamin K antagonist (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;



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- Thromboprophylaxis with LMWH, LDUH, or fondaparinux is recommended for patients admitted to the 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.⁷ These guidelines address 5 critical questions:

1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?
2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?
3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?
4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?
5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

Both sets of guidelines emphasize the necessity of weighing the benefit of thromboprophylaxis and thrombolytic therapy 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. In general, thrombolytic therapy increases the risk of major bleeding 1.5-fold to 3-fold in patients with acute VTE.¹⁸

The National Comprehensive Cancer Network (NCCN) has developed practice guidelines for VTE in patients with cancer.¹⁹ The guidelines recognize the increased risk of VTE in patients with cancer and recommend VTE thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications. High-risk individuals, such as cancer surgery patients, should receive prophylaxis for up to 4 weeks after the operation. The guideline panel identified areas for prospective clinical trials to expand evidence-based recommendations for this special group of high-risk patients.

VTE PROPHYLAXIS

Several random-controlled trials (RCTs) of anticoagulants for VTE prophylaxis in acutely ill hospitalized medical patients report significant reduction in VTE with pharmacologic prophylaxis.⁷ The results summarized in **Table 5** 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 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, $P = 0.09$).²⁰ The results also support the use of asymptomatic DVT as a surrogate marker for clinical outcome.

The vitamin K antagonist (VKA) warfarin is one of the most widely used anticoagulants. It is orally available, inexpensive, and effective. However, its small therapeutic window limits its usefulness.

Table 5. Trials of anticoagulants for VTE prophylaxis in acutely ill hospitalized medical patients.⁷

	Total Patients, #	Cancer Patients, %	Placebo Events, %	Treatment Events, %	Relative Risk	Variable P-value	95% CI
MEDENOX	579	12.4	14.9	5.5	0.37	< 0.001	0.22 to 0.63
PREVENT	3706	5.1	4.96	2.77	0.55	0.0015	0.38 to 0.8
ARTEMIS	849	15.4	10.5	5.6	0.47	0.029	0.08 to 0.69

MEDENOX, Prophylaxis in Medical Patients with Enoxaparin; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; ARTEMIS, ARixtra for ThromboEmbolism Prevention in a Medical Indications Study.



Several multicenter, randomized, double-blind trials compared the synthetic pentasaccharide fondaparinux to enoxaparin in patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture. A meta-analysis of 4 studies²¹ found that fondaparinux significantly reduced the incidence of VTE by day 11 (6.8%) compared with enoxaparin (13.7%), with a common odds reduction of 55.2% (95% confidence interval, 45.8% to 63.1%; $P < 0.001$); this beneficial effect was consistent across all types of surgery and all subgroups. Although major bleeding occurred more frequently in the fondaparinux-treated group ($P = 0.008$), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups.

The ARTEMIS study²² assessed the efficacy and safety of fondaparinux in older acute medical inpatients at moderate to high risk of VTE. Subjects were 849 medical patients aged ≥ 60 hospitalized for congestive heart failure, acute respiratory illness in the presence of chronic lung disease, or acute infectious or inflammatory disease and expected to remain in bed for at least four days. Fondaparinux or placebo was administered once daily for 6 to 14 days. The primary efficacy outcome was VTE detected by venography or symptomatic VTE up to day 15. VTE was detected in 5.6% of patients treated with fondaparinux and 10.5% of patients given placebo, a relative risk reduction of 46.7% (95% CI, 7.7% to 69.3%). Major bleeding occurred in one patient (0.2%) in each group. After 1 month, 14 patients in the fondaparinux group (3.3%) and 25 in the placebo group (6.0%) had died. ARTEMIS showed that fondaparinux is effective in the prevention of VTE in older acute medical patients, without increased risk of major bleeding.

According to the ACCP guidelines, mechanical methods of thromboprophylaxis should be used primarily in patients at high risk for bleeding, or possibly as an adjunct to anticoagulant-based thromboprophylaxis.³ Since poor fitting of devices and poor patient compliance are common, careful attention should be directed toward the proper use of these methods. A meta-analysis examined effectiveness of intermittent pneumatic compression (IPC)

devices in postsurgical patients.²³ In comparison to no prophylaxis, IPC devices reduced the risk of DVT by 60% (RR = 0.40, 95% CI 0.29–0.56; $P < 0.001$).

In a study of 2518 immobilized hospital patients admitted within 1 week of a stroke, graduated compression stockings (GCS) provided no more protection for popliteal or femoral vein DVT than routine care alone (10.0% versus 10.5%).²⁴ However, skin breaks, ulcers, blisters, and skin necrosis were significantly more common with GCS (OR = 4.2). Thus, the CLOTS 1 study does not support the use of thigh-length GCS in patients admitted to the hospital with acute stroke.

Since the VTE 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 6).³

Table 6: Levels of thromboembolism risk and recommended thromboprophylaxis in hospital patients.³

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. ³ LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; INR, international normalized ratio



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EMERGING THERAPIES

Dabigatran is an oral direct thrombin inhibitor under investigation for a variety of VTE prevention and treatment indications. Several phase 3 studies compared dabigatran to enoxaparin. The RE-NOVATE trial²⁵ in 3494 patients undergoing total hip replacement (THR) and the RE-MODEL trial²⁶ in 2076 patients undergoing total knee replacement (TKR) showed that dabigatran initiated 1-4 hours after surgery was non-inferior to enoxaparin (40 mg OD) in the primary endpoint of total VTE plus any-cause death. In the TKR RE-MOBILIZE trial,²⁷ the dabigatran dose was delayed until 8-12 hours after surgery and the enoxaparin dose was increased to 30 mg bid. With this protocol, dabigatran was inferior to enoxaparin ($P < 0.05$). The rate of VTE with dabigatran was significantly higher in the RE-MOBILIZE study than in the RE-MODEL study ($P = 0.003$), where the major difference was the delay of dabigatran initiation after surgery. Dabigatran is approved for use in Europe and Canada for VTE prophylaxis after total hip or knee replacement.

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. RECORD3²⁸ 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. In RECORD4,²⁹ enoxaparin was dosed at 30 mg bid beginning 12 to 24 hours after surgery. Patients treated with rivaroxaban had a 3.2% lower absolute risk of the composite endpoint of any deep-vein thrombosis,

non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery ($P = 0.01$). 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. [Table 7](#) compares the features of recent and established anticoagulants. Rivaroxaban is approved for use in Europe and Canada for VTE prophylaxis after total hip or knee replacement.

Several factor Xa inhibitors are in clinical development.³⁰ Apixaban is an oral drug in phase 3 clinical evaluation. The indirect Xa inhibitor idrabiotaparinux (biotinylated idraparinux) is a synthetic analog of the core heparin pentasaccharide.^{31,32} Two ultra-low molecular weight heparins (ULMWH), AVE5026 (sanofi-aventis, phase 3) and RO-14 (Rovi, phase 1) preferentially inhibit factor Xa. They will probably have once-daily dosing schedules and may be useful for the management of cancer-associated thrombosis.

BARRIERS

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 several studies supporting the use of VTE prophylaxis, alert systems that increase the rate of prophylaxis, and resources that can help with implementation of prophylaxis initiatives.

Thromboprophylaxis is underutilized.³ One barrier is fear of bleeding. Underestimation of the risk of VTE and caution about heparin-induced thrombocytopenia (HIT) also contribute. Renal insufficiency requires dose adjustment for some drugs. 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.

SUCCESSFUL STRATEGIES

A meta-analysis by Toohet et al³³ 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

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Table 7. Features of newer and established anticoagulants.³⁰

Feature	Dabigatran	Rivaroxaban	LMWH	Fondaparinux	VKA
Oral administration	X	X	-	-	X
Fixed once-daily dosing	X	X	X	X	-
Rapid onset and offset of action	X	X	X	X	-
Predictable PK/PD	X	X	X	X	-
Few drug and food interactions	X	X	X	X	-
No need for routine anticoagulation monitoring	X	X	X	X	-
Available anticoagulation monitoring	-	-	X	-	X
Antidote readily available	-	-	X [†]	-	X
No potential/very low risk of severe thrombocytopenia	X	X	-	X	X
No potential risk of DTH at injection site	X	X	-	-	X
Easy management with neuraxial analgesia	-	-	X	-	-
VTE prevention in THR/TKR surgery	X	X	X	X	X
VTE prevention in HFS surgery	-	-	X	X	X
VTE prevention in abdominal surgery	-	-	X	X	-
VTE prevention in acutely ill medical patients	-	X [‡]	X	X	-
Initial acute VTE treatment [§]	-	X [‡]	X	X	-
Long-term VTE treatment	X [‡]	X [‡]	X	-	X
Coronary syndromes	X [‡]	X [‡]	X	X	X
Stroke prevention in atrial fibrillation	X [‡]	X [‡]	-	-	X
Prevention of clotting in hemodialysis	-	-	X	-	-
Not contraindicated in severe renal failure	-	-	X	-	X
Recommended during pregnancy [¶]	-	-	X	-	-

LMWH, fondaparinux, and the VKA warfarin are FDA approved.
 LMWH: low molecular-weight heparin; VKA: vitamin K antagonist; PK/PD: pharmacokinetics/pharmacodynamics; DHT: delayed-type hypersensitivity; VTE: venous thromboembolism; THR: total hip replacement; HFS: hip fracture surgery. [†]Partial neutralization by protamine sulphate; [‡]Currently in phase III clinical trials; [§]With no need for overlapping with a parenteral anticoagulant; [¶]Referred to the whole period (1st, 2nd, and 3rd trimester).

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 study³⁴ 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.³⁵ Consecutive patients were evaluated for VTE risk according to a system assigning 1 point for each characteristic: age > 70, obesity (body mass index > 29), bed rest, HRT, or combined oral contraceptives; 2 points for each major surgery; and 3 points each for cancer, prior VTE, or hypercoagulability. Patients with a score of at least 4 points were considered at increased risk.



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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 endpoint 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; $P = 0.001$).

Not all institutions are able to institute a computerized alert system, so a similar study asked whether an alert delivered by a hospital staff member to the attending physician can reduce the rate of symptomatic VTE among high-risk patients not already receiving prophylaxis.³⁶ Patients ($n = 2493$) at multiple sites were randomized to 2 groups. Physicians in one group received alerts, while those in the other did not. The primary endpoint was symptomatic VTE within 90 days. The system increased the rate of prophylaxis; patients whose physicians were alerted were more than twice as likely to receive VTE prophylaxis as control subjects (46.0% versus 20.6%; $P < 0.0001$). The group receiving alerts had a lower rate of symptomatic VTE (2.7% versus 3.4%; hazard ratio, 0.79; 95% CI, 0.50 to 1.25), but the difference was not significant. The rate of major bleeding at 30 days in the 2 groups was similar (2.1% and 2.3%; $P = 0.68$). The human alert protocol resulted in a higher rate of prophylaxis than the computer alert system in the previous trial (46% versus 33%), though the interpretation of the difference is not clear.

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,³⁷ 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.³⁸ In 2008, the US Centers for Medicare & Medicaid Services (CMS) included

VTE after THR or TKR surgery on the list of “never events.” This restricts reimbursement for treatment of patients and thus creates a financial motivation for VTE prophylaxis. In a recent commentary, Streiff and Haut highlight several shortcomings of the policy in its current form.

1. The rate of VTE is not reduced to zero with prophylaxis, so evidence-based treatment will not be reimbursed sometimes
2. The rate of postsurgical VTE may be higher in “real world” settings than in clinical trials
3. The policy creates a disincentive to treat high-risk patients
4. The policy creates a disincentive to accurately diagnose VTE after THR and TKR surgery
5. The policy might encourage overly aggressive prophylaxis.

The authors propose a more global approach to VTE prophylaxis and a more subtle evaluation of which cases should be reimbursed.

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 in this activity has increased my confidence regarding the appropriate prophylaxis of venous thromboembolism (VTE) in my patients
- b) _____ What I learned in this activity has improved my ability to assess the risk of venous thromboembolism in my patients
- c) _____ What I learned in this activity will result in an improvement in my patients' health
- 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



*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

- Use a standardized tool for evaluating patients for VTE risk
(Specify) _____
- Use ACCP VTE Guidelines to help evaluate and manage patients at risk for VTE
- Work within my institution to improve mechanisms for reducing thromboembolic risk
(Specify) _____
- 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.VTEducation.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 have VTE? 1% 1-5% 6-20% > 20%

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) _____ List the risk factors for VTE and assess overall risk in each hospitalized patient
- b) _____ Demonstrate awareness of the most recent guidelines for risk assessment and prophylaxis in VTE and identify potential gaps in relation to current practice
- c) _____ Develop a strategy for improving guideline adherence and reducing thromboembolic risk within the hospital setting

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. Early ambulation after surgery
 - D. Congestive heart failure
 - E. Trauma
2. Which of the following increases the odds ratio of postsurgical VTE?
 - A. Malignant disease
 - B. Pre-op hospitalization \geq 6 days
 - C. Pre-op transfusion > 1 unit
 - D. Leg ulcers
 - E. All of the above
3. Among cancer patients, those with pancreatic and brain cancer are at highest risk for VTE.
 - A. True
 - B. False
4. TV is a 75 y/o man, admitted for symptoms consistent with influenza. He will be discharged after 3 days and instructed to observe bed rest for another week. What is his level of VTE risk, according to the 2008 ACCP guidelines?
 - A. Low (DVT risk < 10% w/o prophylaxis)
 - B. Moderate (DVT risk 10% to 40% w/o prophylaxis)
 - C. High (DVT risk 40% to 80% w/o prophylaxis)
5. Which statement is NOT true about E-alerts and VTE prophylaxis?
 - A. The decrease of VTE incidence lasts for at least 2 years
 - B. Prophylaxis rates increase for mechanical (6-fold) and pharmacologic (2-fold) methods
 - C. The incidence of VTE decreased 40% with E-alerts at 90 days (Kucher et al. *NEJM*. 2005)
 - D. They are inexpensive to set up and do not require a lot of information technology infrastructure and assistance
6. The 2008 ACCP guidelines recommend aspirin as a low-cost effective anticoagulant for thromboprophylaxis.
 - A. True
 - B. False
7. Which of the following is NOT a barrier to effective VTE prophylaxis?
 - A. Fear of bleeding
 - B. Underestimation of thrombotic risk
 - C. Lack of time to think about VTE risk
 - D. Lack of familiarity with guidelines
 - E. Lack of effective agents
8. Since 2008, the US Centers for Medicare & Medicaid Services (CMS) considers VTE after total hip replacement or total knee replacement surgery a “never event.”
 - A. True
 - B. False
9. After participating in this activity, which of the following will you use to improve adherence to thromboprophylaxis guidelines in patients at risk for VTE? (May circle more than one)
 - A. Oral reminders
 - B. Computer reminders
 - C. Public displays of results for different services
 - D. Standard order sets
 - E. Other: Please list _____

