Guidelines and Performance Measures for the Prevention and Treatment of Venous Thromboembolism

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ABSTRACT

BACKGROUND: Venous thromboembolism (VTE) is a common and often preventable cause of morbidity and mortality in the United States, with a widespread economic impact.

OBJECTIVE: To describe the prevalence, morbidity, mortality, and risk factors associated with VTE; adherence rates to evidence-based guidelines for VTE prophylaxis and treatment; efforts to raise awareness to address the VTE problem, including strategies to promote VTE prophylaxis; and the optimal treatment of VTE.

SUMMARY: An increased risk for VTE may be present in the early post-discharge period after brief hospitalization for medical and surgical patients. Adequate prophylaxis is the key to preventing VTE, recurrent VTE, post-thrombotic syndrome, and VTE-related death. Evaluation of clinical results indicates that there is considerable room for improvement in VTE prophylaxis use in hospitalized surgical and medical patients and in adherence to guidelines for VTE treatment. The heterogeneity of the patient population at risk for VTE is among the possible reasons for failure to institute pharmacologic or mechanical prophylaxis. National consensus standards for VTE prevention and treatment are applicable from hospitals to home care. Combinations of strategies are more effective than a single strategy in reducing VTE rates. In patients with VTE, the use of low-molecular-weight heparin facilitates early hospital discharge and outpatient treatment. Opportunities to minimize the hospital length of stay and costs by discharging patients with VTE while they are receiving overlapping parenteral and oral anticoagulation therapy are often missed.

CONCLUSIONS: Pharmacists' efforts to increase VTE awareness, ensure VTE prophylaxis, and recommend appropriate VTE treatment can have a favorable clinical and economic impact.

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Deep vein thrombosis (DVT) develops in approximately 2 million Americans each year.¹ Most cases are asymptomatic; however, in approximately 600,000 cases, the thrombus embolizes and travels to the right atrium, through the right ventricle, and into the pulmonary arterial tree, lodging in the pulmonary vasculature. The mortality rate in patients with pulmonary embolism (PE) is high (approximately 10%), with nearly 60,000 deaths attributed to PE annually in the United States. Patients who survive PE may develop chronic pulmonary hypertension due to damage to the pulmonary vasculature. DVT can cause permanent damage to the valves of the venous system and may also result in post-thrombotic syndrome; chronic inflammation, edema, and pain; and, in severe cases, venous stasis ulcers of the lower extremities.

Prevalence

Venous thromboembolism (VTE) risk factors are common among hospitalized patients. Using criteria established by the American College of Chest Physicians (ACCP) in their evidence-based guidelines for the prevention of VTE, review of a U.S. database containing more than 38 million inpatient discharge records showed that more than 12 million (31%) patients met the ACCP criteria for prophylaxis: 4.3 million surgical and 7.7 million medical patients.^{2,3} The larger number of medical patients at risk for VTE is significant because, although VTE risk is well recognized in surgical patients, the danger for medical patients is frequently underappreciated.

While VTE is often considered to be a condition that develops primarily in elderly, bedridden hospital patients, recent medical record analysis provides a different picture.⁴ A review of 1,897 VTE sufferers from Worcester, Massachusetts, showed that 74% of these patients developed VTE signs and symptoms as outpatients. The mean age of those 1,399 outpatients who developed VTE was 63 years, and 33% were aged <55 years. In contrast, the mean age of the 498 inpatients who developed VTE was 67 years, with only 21% aged <55 years. The presence of 5 VTE risk factors (recent hospitalization, recent surgery, active malignant neoplasm, recent infection, history of VTE) was ascertained in outpatients who developed VTE: 30% had no risk factors, 32% had 1, and 34% had 2-3. For patients who experienced VTE within 3 months after hospitalization (with or without surgery), two thirds experienced VTE within 1 month. The median and mean length of stay for this initial hospitalization was 4.0 and 7.4 days, respectively. It appears that an increased risk for VTE is present in the early post-discharge period after brief hospital stays for both medical and surgical patients.

The risk of DVT without prophylaxis is 10%-20% in medical patients, 10%-80% for critical care patients, 20%-50% in patients

with stroke, and 40%-80% in patients with major trauma.² These rates are comparable with those in patients undergoing general or major urologic or gynecologic surgery or neurosurgery (15%-40%) or orthopedic surgery (40%-60%) who do not receive prophylaxis. The wide range in values depicts the asymptomatic nature of the disease and the low sensitivity of detection modalities.

■ VTE Awareness

Despite its prevalence and danger, VTE is a condition that frequently goes unrecognized by the general public. In 2002, the American Public Health Association sponsored a telephone survey of 1,003 American adults.⁵ The study population comprised 48% women, 52% men, 73% Caucasians, 12% African-Americans, 10% Hispanics, and 5% other races and ethnicities. Fifty percent had an education level consisting of a high school diploma or less. The survey demonstrated that 74% of respondents had little or no awareness of DVT. Of those who were aware of VTE, 57% were unable to name any common risk factors or conditions that predispose a person to DVT.⁵ Since 2002, several cases of VTE in public figures have helped to increase awareness. In 2003, David Bloom, an NBC journalist traveling with the U.S. Army 3rd Infantry Division in Iraq, died suddenly at the age of 39 from VTE. His widow, Melanie Bloom, has become active in educating the public about the dangers of DVT through media public service announcements as well as the Coalition to Prevent Deep-Vein Thrombosis (www.preventdvt.org). The latter is a group committed to educating the public, health care community, and policymakers about DVT and includes several pharmacy organizations, managed care providers, and physician groups. In addition, Bonnie Bernstein, a television sports journalist who survived DVT, will also appear in public service announcements as part of a DVT awareness campaign by the Coalition. Finally, Vice President Dick Cheney's travel-associated DVT in 2007 has also raised awareness of the seriousness of this condition.

■ Outreach Efforts

Recognition of VTE as a preventable event has led to various governmental outreach efforts. March was designated as DVT Awareness Month by the U.S. Senate in 2005, and the U.S. Surgeon General's Office is considering a Call to Action to address the problem. The Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention initiated the Surgical Care Improvement Project (SCIP) in 2007 to improve surgical outcomes through reduction of post-operative complications.⁶ The goal of the SCIP is to reduce the incidence of surgical complications by 25% before the year 2010 by targeting adverse cardiac events, surgical site infections, post-operative pneumonia, and VTE.⁷ Specifically, the use of appropriate VTE prophylaxis within 24 hours before or after surgery and the diagnosis of DVT and PE within 30 days after surgery are used as SCIP measures of quality patient care.⁸

The National Quality Forum is collaborating with The Joint Commission to develop national consensus standards for VTE prevention and treatment.⁹ These standards provide a framework by which to identify preferred practices to ensure quality care for patients with or at risk for VTE. Performance measures are being developed to evaluate the quality of care provided to patients in screening for VTE risk, the institution of appropriate prophylaxis, and effective VTE treatment. These standards will be applicable from hospitals to home care. Draft candidate measures require appropriate overlap of parenteral and oral anticoagulation therapy, platelet count monitoring to detect heparin-induced thrombocytopenia (HIT), and justification for use of inferior vena cava filters instead of anticoagulation therapy, among various other aspects of VTE prevention, treatment, and outcomes.¹⁰ Public comments have been solicited, and the measures remain to be finalized.

Anticoagulation therapy is the cornerstone of VTE prophylaxis. The Joint Commission has recognized that anticoagulation therapy is a common cause of adverse drug events.¹¹ A Joint Commission National Patient Safety Goal for 2008 is to reduce the likelihood of patient harm associated with the use of anticoagulation therapy (warfarin, unfractionated, and low-molecular-weight heparin [LMWH], other anticoagulants).¹¹

■ VTE Risk

VTE risk factors (Table 1) involve stasis of the blood or changes in blood components or the endothelium that predispose patients to clot formation. A history of VTE is a particularly important risk factor.²

A retrospective review of the medical records of 1,000 randomly selected patients in 16 acute care hospitals in central Massachusetts evaluated the presence of 10 common risk factors (Table 1) among hospitalized patients. In this population, 78% of patients had 1 or more VTE risk factors, 48% had 2 or more VTE risk factors, 19% had 3 or more risk factors, 6% had 4 or more risk factors, and 1% had 5 or more risk factors.¹² The most common VTE risk factors were aged ≥ 40 years (59%), obesity (28%), and major surgery (23%).

The ACCP has defined 4 levels of risk for VTE in surgical patients based on age, type of surgery, presence of additional VTE risk factors, and incidence of DVT (especially proximal DVT involving clots found above the knee, which is particularly dangerous because of the high propensity to embolize), clinical PE, and fatal PE in untreated patients (Table 2).²

■ VTE Prophylaxis

The acute and long-term effects of VTE are largely preventable. Adequate prophylaxis is the key to preventing VTE, VTE recurrence, post-thrombotic syndrome, and VTE-related death. Various pharmacologic and mechanical interventions (graduated compression stockings [GCS], intermittent pneumatic compression [IPC]) may be used to reduce the risk of VTE.

TABLE 1 Risk Factors for VTE^a

Blood Stasis	Blood Component Changes	Endothelium Changes
Aged ≥40 years	Malignancy	Major surgery
Obesity	Estrogen use	Trauma
Cardiac dysfunction	Cancer therapy	Previous VTE
Cardiac dysfunction	Hypercoagulable conditions	Central venous catheter use
Stroke or paralysis	Nephrotic syndrome	Varicose veins
Prolonged immobility	Inflammatory bowel disease	Smoking
Respiratory failure		
Pregnancy		

^aCommon risk factors are in bold.^{2,12}

VTE=venous thromboembolism.

Anticoagulant therapy may be contraindicated due to a condition or surgery associated with a high risk of bleeding, a history of bleeding events (e.g., intracranial hemorrhage), or an allergy or adverse reaction to anticoagulant therapy. Mechanical prophylaxis is an option for these patients, and there is no risk of bleeding when these modalities are used. The weight of evidence is much greater with use of pharmacologic prophylaxis than with that supporting the efficacy of VTE prophylaxis with GCS and IPC. Mechanical prophylaxis is hindered by poor patient compliance, improper use, patient intolerance, and physical constraints from injuries (e.g., fractures, casts, dressings). The cost of IPC is high, and it is often not available after discharge.¹³ Despite these limitations, clinical trials in a variety of high-risk settings have shown that mechanical prophylaxis reduces the incidence of VTE.¹³ More importantly, when mechanical and pharmacologic strategies are combined, they may have synergistic effects.¹⁴⁻¹⁶ High-risk patients should be considered for combination methods.

Surgical Patients

ACCP-recommended prophylactic strategies for each level of VTE risk in surgical patients are listed in Table 2, with use of progressively more aggressive therapies as the degree of risk increases.² Use of LMWH is recommended instead of low-dose unfractionated heparin (LDUH) for patients undergoing orthopedic surgery or with trauma or spinal cord injury because LMWH is more effective than LDUH in preventing VTE.² However, patients undergoing general, gynecologic, or urologic surgery or neurosurgery may receive either LMWH or LDUH; both therapies are considered equally effective for prevention of VTE in these at-risk patient populations.²

A meta-analysis of 52 randomized controlled trials of VTE prophylaxis in 33,813 general surgery patients found that only

2% of patients discontinued prophylaxis because of bleeding complications.¹⁷ The percentage of patients receiving prophylaxis who required surgical intervention to control bleeding (0.7%) was no different from the percentage of control patients who required surgical intervention to control post-operative bleeding. Hence, concerns about bleeding should not deter clinicians from using low-dose anticoagulant prophylaxis in patients at risk for VTE.

Although aspirin is effective in reducing myocardial infarction, stroke, and thrombotic events on the arterial side of the circulatory system, it is not recommended for VTE prophylaxis.² The reduction in relative risk for DVT after general surgery that is associated with the use of aspirin is only 20%.¹⁸

Medical Patients

ACCP guidelines recommend the use of LDUH or LMWH in acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease or who have been confined to bed with 1 or more additional VTE risk factor.² A meta-analysis of 12 randomized controlled trials comparing the efficacy of subcutaneous LDUH (5,000 units) twice daily versus 3 times daily for VTE prophylaxis in 7,978 acutely ill medical patients found a significant risk reduction for proximal DVT and PE with 3 rather than 2 daily doses (0.9 vs. 2.3 events per 1,000 patient days, $P=0.05$). However, the use of LDUH 3 times daily was accompanied by a small but significant increase in risk for major bleeding (0.96 vs. 0.35 events per 1,000 patient days, $P<0.001$).¹⁹

Few studies have compared the efficacy of LDUH with LMWH for preventing VTE in medical patients. Most involved small numbers of patients and were conducted long ago using currently outmoded technologies to detect VTE. The PREVAIL study of VTE prevention in patients with hemiplegia after acute ischemic stroke is a contemporary trial. This patient population was studied because approximately 780,000 Americans experience stroke each year, and the incidence of DVT is approximately 50% within 2 weeks after hemiplegic stroke.^{20,21} The study examined 1,762 adults with acute ischemic stroke who were randomly assigned within 48 hours after symptom onset to receive LDUH (i.e., 5,000 units) subcutaneously every 12 hours or enoxaparin 40 mg subcutaneously every 24 hours for 10 days.²² Modern methods were used to detect DVT (bilateral contrast venography or ultrasonography) and PE (ventilation perfusion, helical computed tomographic scanning, or pulmonary angiography). The incidence of both VTE and DVT after 14 days was 18% with LDUH and 10% with enoxaparin, representing a significant 43% reduction in the relative risk for VTE and DVT with the use of enoxaparin versus LDUH ($P<0.001$ for both comparisons).²² The incidence of proximal DVT after 14 days was also significantly lower in the enoxaparin group (5%) compared with the LDUH group (10%, $P<0.001$), as well as the incidence of distal DVT after 14 days in the enoxaparin group (7%) compared with the LDUH group (13%, $P=0.001$). The 14-day incidence of PE was lower

TABLE 2 Risk of VTE and Prophylactic Strategies in Surgical Patients^a

Degree of Risk and Patient Characteristics	Calf DVT (%)	Proximal DVT (%)	Clinical PE (%)	Fatal PE (%)	Prophylactic Strategy
<i>Low</i> Minor surgery in patients aged <40 years with no additional risk factors	2	0.4	0.2	<0.01	Early and aggressive ambulation; no specific prophylaxis
<i>Moderate</i> Minor surgery in patients with additional risk factors, or surgery in patients aged 40-60 years with no additional risk factors	10-20	2-4	1-2	0.1-0.4	LDUH (5,000 units subcutaneously every 12 hours), LMWH, GCS, or IPC
<i>High</i> Surgery in patients aged 40-60 years with additional risk factors, or patients aged >60 years	20-40	4-8	2-4	0.4-1.0	LDUH (5,000 units subcutaneously every 8 hours), LMWH, or IPC
<i>Highest</i> Hip/knee arthroplasty, hip fracture surgery, major trauma, spinal cord injury, or surgery in patients aged ≥40 years with additional risk factors	40-80	10-20	4-10	0.2-5	LMWH, fondaparinux, warfarin (target INR 2.0-3.0), IPC or GCS + LDUH (5,000 units subcutaneously every 8 hours), or LMWH

^aFigures are the incidence of DVT or PE when prophylaxis is not used.²

DVT=deep vein thrombosis; GCS=graduated compression stockings; INR=international normalized ratio; IPC=intermittent pneumatic compression; LDUH=low-dose unfractionated heparin; LMWH=low-molecular-weight heparin; PE=pulmonary embolism; VTE=venous thromboembolism.

in the enoxaparin group (<1%) than in the LDUH group (1%), although the difference was not significant ($P=0.059$).

The incidence of bleeding at the end of treatment or within 48 hours after the end of treatment was identical (8%), and both groups had the same incidence of symptomatic intracranial hemorrhage (1%). The incidence of major extracranial hemorrhage was significantly higher in the enoxaparin group (1%) than in the LDUH group (0%, $P=0.015$), although the incidence of minor extracranial hemorrhage did not differ (5% enoxaparin, 6% LDUH; $P=0.50$). All-cause mortality at day 14 was 6% with enoxaparin and 5% with LDUH, constituting a difference that was not significant ($P=0.580$).

Thus, greater efficacy in preventing VTE can be achieved by using enoxaparin instead of LDUH. A post-hoc subgroup analysis revealed that the risk of VTE is reduced to a greater extent by enoxaparin than with LDUH in both men and women; in patients who began therapy 24-48 hours after symptom onset as well as in patients who began therapy less than 24 hours after symptom onset; in patients with and without diabetes, obesity, and a history of stroke; in patients with severe stroke as well as patients with less severe stroke; and in patients aged more than 75 years, aged 65-75 years, and aged less than 65 years. However, it is unclear whether the benefits of enoxaparin would be maintained if it had been compared with LDUH 5,000 units dosed every 8 hours rather than every 12 hours.

In the PRINCE trial, a randomized, open-label, parallel-group, noninferiority study of 451 patients with severe respiratory disease or heart failure, the incidence of thromboembolic events was 10.4% with LDUH subcutaneously 3 times daily and 8.4% with enoxaparin 40 mg subcutaneously once daily, a

difference that was not significant for the hypothesis, which indicated that enoxaparin is at least as effective as LDUH.²³ In the subset of 245 patients with severe respiratory disease, the incidence of thromboembolic events was similar with enoxaparin treatment (7.1%) and LDUH treatment (5.9%). In the subset of 206 patients with heart failure, the incidence of thromboembolic events was lower with enoxaparin (9.7%) than with LDUH (16.1%). However, no statistical difference was seen between the treatment groups. Enoxaparin was associated with significantly fewer injection site hematomas (7.2% vs. 12.6% with LDUH, $P=0.027$) and adverse events (46% vs. 54% with LDUH, $P=0.044$).¹⁸ No significant difference between treatment groups was found in the incidence of bleeding complications (1.5% with enoxaparin vs. 3.6% with LDUH). Once-daily administration of enoxaparin instead of 3-times-daily administration of LDUH contributed to the difference in the incidence of injection site hematomas, which could result in improved patient satisfaction.

Another noninferiority study of 148 patients with acute ischemic stroke found that the incidence of VTE was 19.7% with enoxaparin and 34.7% with LDUH 3 times daily, a difference that was significant ($P=0.044$).²⁴ The findings of these noninferiority studies suggest that the greater efficacy of enoxaparin compared with LDUH is evident primarily in patients at the highest risk for VTE (i.e., patients with heart failure or ischemic stroke), which supports the ACCP guidelines calling for LMWH but not LDUH in surgical patients at the highest risk for VTE based on a difference in efficacy.²

A meta-analysis of 36 randomized controlled trials of LDUH, LMWH, or both for VTE prevention in approximately 23,000

hospitalized medical patients found that LDUH 3 times daily is more effective in preventing DVT than LDUH twice daily.²⁵ Use of LMWH was associated with a significant 32% reduction in risk for DVT compared with LDUH ($P=0.004$).

The efficacy of extended-duration enoxaparin therapy for preventing VTE in medical patients was evaluated in the EXCLAIM trial, a randomized, double-blind, placebo-controlled study of 5,105 high-risk patients with acute medical illness and recent immobilization for up to 3 days.²⁶ Patients received enoxaparin 40 mg subcutaneously once daily for 10 ± 4 days followed by placebo or enoxaparin for an additional 28 ± 4 days. VTE incidence was 2.8% with extended-duration enoxaparin and 4.9% with placebo, representing a significant 44% reduction ($P=0.001$). The incidence of symptomatic VTE was also significantly reduced from 1.1% in the placebo group to 0.3% in the extended-duration enoxaparin group ($P=0.004$). Twelve (0.6%) patients receiving extended-duration enoxaparin and 3 (0.1%) patients receiving placebo experienced major bleeding ($P=0.019$), including 1 patient receiving extended-duration enoxaparin who died from a major bleeding event. There was no significant difference between treatment groups in 6-month all-cause mortality (10.1% with enoxaparin vs. 8.9% with placebo, $P=0.179$). These findings suggest a benefit from continuing enoxaparin after hospital discharge in at-risk, acutely ill medical patients; however, additional research is warranted to evaluate the risk for major bleeding.

HIT is an immune-mediated reaction to unfractionated heparin (UFH) or LMWH that leads to a precipitous drop in the platelet count and a hypercoagulable state, with an increased risk for thrombosis that can manifest as gangrene of the extremities. In 10,121 hospitalized medical patients who received LDUH 3 times daily or enoxaparin 40 mg once daily for VTE prophylaxis, the incidence of HIT was 0.51% and 0.08%, respectively ($P=0.037$).²⁷ The cost for hospitalization was significantly higher in patients with HIT (\$56,364) than in patients without HIT (\$15,231, $P<0.001$). When compared with UFH, LMWH prophylaxis incurs an incremental expense of approximately \$25 per day. When the costs of treating adverse events are included, LMWH prophylaxis in hospitalized medical patients is associated with a cost savings of \$13.88 per patient.

Several considerations might enter into the choice between LDUH and LMWH for an acutely ill medical patient at risk for VTE. The lower acquisition cost and reduced major bleeding risk support LDUH use.²³ The lower risk of minor bleeding and HIT, greater patient acceptance, and savings in nursing time for drug administration support the use of LMWH.^{23,27}

Guideline Adherence

A variety of reasons may contribute to failure to use VTE prophylaxis or improper prophylaxis, including the heterogeneity of the patient population at risk and the fact that prevention and treatment of VTE does not fall under the purview of any one

specialty practitioner. Some practitioners appear to underappreciate the risk of VTE and its dangers, and assessing VTE risk may be perceived as an unnecessary burden.

Data from U.S. and international registries reveal that only a minority of hospital patients with acute medical illness receive VTE prophylaxis, and differences exist in the strategies employed.²⁸⁻³¹ The IMPROVE Registry found IPC to be the most common VTE prophylaxis strategy used in the United States. For pharmacologic prophylaxis, UFH was the most commonly employed in the United States, whereas LMWH prophylaxis was more common outside the United States.

The rate of adherence to ACCP guidelines for the prevention of VTE in hospitalized patients with trauma, acute spinal cord injury, or medical conditions that place them at increased risk (e.g., acute myocardial infarction, ischemic stroke, cancer, heart failure, severe lung disease) as well as in patients undergoing major orthopedic, general, gynecologic, or urologic surgery or neurosurgery was assessed in a retrospective study.³² The overall guidance adherence rate was 13%: 7% in gynecologic surgery, 10% in urologic surgery, 13% in general surgery, 52% in orthopedic surgery, and 5% in patients with medical conditions that place them at risk. Failure to use prophylaxis of any kind when warranted was a common cause for nonadherence to ACCP guidelines, affecting more than one half of the patients regardless of the type of surgery or medical condition. In some patients, nonadherence was also attributed to inadequate duration of prophylaxis due to therapy starting late, ending early, or both. These findings suggest considerable room for improvement in the use of VTE prophylaxis in hospitalized surgical and medical patients. They also suggest a role for pharmacists to devote efforts to ensuring that prophylaxis is used when warranted and that therapy starting and ending times are appropriate.

In a separate analysis of data from nearly 200,000 hospitalized medical patients at risk for VTE, the rate of VTE prophylaxis was 62%, and the rate of appropriate prophylaxis in accordance with ACCP guidelines was 34%.³³ Results were similar when patients were stratified by disease or condition (myocardial infarction, heart failure, stroke, trauma, cancer, lung disease, spinal cord injury). These findings are consistent with the observations of other investigators.^{34,35}

In a study of 227 hospitalized medical patients, 153 patients had at least 1 VTE risk factor.³⁶ Prophylaxis was not provided to 52 (34%) of these at-risk patients. In the other 101 at-risk patients, prophylaxis was continued until hospital discharge in only 33 (22%) at-risk patients.

In an historical cohort study of 253 cases of VTE diagnosed at a large teaching hospital, 179 (71%) were spontaneous, 44 (17%) were preventable, 21 (8%) were nonpreventable, and 9 (4%) were ineligible for prophylaxis.³⁷ In the 44 preventable cases, prophylaxis was omitted in 21 (48%), the duration of prophylaxis was inadequate in 10 (23%), and the remainder involved the wrong type of prophylaxis, delay in initiation of prophylaxis, or

inadequate dose or dosing frequency. These findings suggest that opportunities to prevent VTE often are missed in hospitalized medical patients.

In a subgroup analysis of data from a prospective registry of 5,451 patients with DVT at 183 American hospitals, the incidence of PE was significantly higher in medical patients with DVT (22.2%) than in surgical patients with DVT (15.5%, $P < 0.001$).³⁸ The use of VTE prophylaxis was significantly lower in medical (25%) than in surgical patients with DVT (54%, $P < 0.001$). These findings underscore the need for efforts to ensure the use of VTE prophylaxis in medical patients.

The presence of some VTE risk factors is not always immediately apparent. The complexity of dosing and therapeutic monitoring for anticoagulants may be daunting. A clinician's concerns about anticoagulant-related hemorrhagic complications may pose a barrier to prophylaxis use. A survey of surgeons found that, although 73% stated that they perform risk stratification, a detailed analysis of prescribing practices failed to confirm this. Furthermore, more than one half of these surgeons recalled a complication of their preferred prophylaxis strategy.³⁹ A survey of hospital pharmacists showed that only 59.8% of hospitals had programs that encouraged VTE prophylaxis.⁴⁰ Opportunities exist for pharmacists to improve the bedside delivery of VTE prophylaxis as well as implement performance improvement programs.

Strategies to Improve VTE Prophylaxis

Various approaches have been used to promote VTE prophylaxis including risk assessment scoring systems, risk recognition systems, and prophylaxis default systems. Risk assessment scoring systems provide a tool not only to identify patients in whom prophylaxis is warranted, but also to determine the type of prophylaxis to use. Many such scoring systems are incorporated into order forms or computerized physician order-entry systems. A weighted point value is assigned to VTE risk factors, a total score is calculated manually or automatically, and a prophylactic intervention is recommended based on the total score, usually in accordance with ACCP guidelines.^{41,42} Risk recognition systems involve the identification of comorbid conditions and other factors that increase the risk for VTE without determining a score to quantify the risk for VTE. One such system involves the use of a flow diagram to identify patients at risk for VTE because of acute medical illness or other risk factors and to determine whether pharmacologic or nonpharmacologic prophylaxis is indicated.⁴³ Prophylaxis default systems involve the use of automatic orders for VTE prophylaxis. Orders are discontinued by the physician for patients who are not at risk for VTE.

The efficacy of an intervention to improve VTE prophylaxis rates in 5,500 medical patients was evaluated in a tertiary care university teaching hospital.⁴⁴ The intervention involved the use of a patient history form containing a scheme for assessing and documenting risk for VTE at the time of admission, an admission

order set with recommendations for optimal VTE prophylactic regimens, and educational sessions for house staff and clinical pharmacists. In high-risk patients, the prophylaxis rate was 43% before the intervention and 72% after the intervention. In lower-risk patients, prophylaxis improved from 31% to 64%.

At a community teaching hospital, clinical pharmacists developed an education program focused on the importance of providing VTE prophylaxis to medically ill patients.⁴⁵ The program involved in-service education, newsletters, and quality assurance presentations. Retrospective data from 344 patients before the intervention were compared with data from 297 patients after the intervention. The use of VTE prophylaxis increased significantly from 43% before the intervention to 58% after the intervention ($P < 0.001$). Significant increases also were observed in the use of suitable prophylaxis (LDUH 2-3 times daily or LMWH) from 38% before the intervention to 49% after the intervention ($P = 0.006$) as well as the use of optimal prophylaxis (LDUH 3 times daily or LMWH) from 11% to 44% ($P < 0.001$).

In 13 tertiary care teaching hospital medical wards, a practice guideline defining patients at risk for VTE and appropriate prophylaxis was implemented in conjunction with the use of educational presentations, printed educational materials, and feedback to providers.⁴⁶ In the pre-intervention period, 18% of clinicians required recommendations to prescribe appropriate prophylaxis, whereas in the post-intervention period, only 7% required similar directives. The incidence of DVT decreased from 9.5% in the pre-intervention period to 3.2% in the post-intervention period ($P < 0.01$).

The impact of a computer-alert program designed to encourage VTE prophylaxis on the incidence of DVT was evaluated in a randomized controlled trial of 2,506 high-risk patients at a tertiary care teaching hospital.⁴⁷ The computer-alert program calculated a VTE risk score and sent an electronic alert to physicians if a patient's score exceeded an established threshold of 4 or more risk-score points. The alert provided the score as well as an electronic link to VTE prevention guidelines and facilitated computerized entry of prophylaxis orders. Alerts were not sent to physicians of patients randomly assigned to the control group. The use of VTE prophylaxis was significantly higher in the intervention group (34%) than in the control group (15%, $P < 0.001$). The incidence of VTE after 90 days was significantly lower in the intervention group (4.9%) than in the control group (8.2%, $P < 0.001$). There was no significant difference between the 2 groups in the incidence of major hemorrhage after 30 days (1.5% in both groups, $P = 0.87$).

A systematic review of 30 intervention studies designed to improve VTE prophylaxis rates revealed that combinations of strategies were more effective than a single strategy.⁴⁸ Systems for reminding clinicians to assess patients for VTE risk, electronic decision-support systems or paper-based reminders, and audit and feedback were the most effective strategies.

■ VTE Treatment

According to ACCP guidelines, VTE may be treated using weight-based dosing of intravenous UFH to achieve an activated partial thromboplastin time (aPTT) within the therapeutic range established by the laboratory performing the assay, with dosage adjustments made using a standardized nomogram.⁴⁹ The use of subcutaneous LMWH once or twice daily is an alternative that facilitates early hospital discharge and subsequent outpatient treatment.⁴⁹

Triage of VTE patients from the emergency department and primary care provider offices has further facilitated care in the ambulatory care setting without compromising therapy effectiveness or patient safety.⁵⁰ Reduction in LMWH dosage is recommended if LMWH is used in patients with severe renal impairment;⁵¹ however, intravenous UFH is preferred over LMWH therapy for such patients.⁴⁹ Warfarin therapy should be initiated at the same time as UFH or LMWH in patients with VTE;⁴⁹ the therapies should overlap by at least 5 days. UFH or LMWH should be discontinued when the international normalized ratio (INR) is stable and exceeds 2.0.⁴⁹

In a randomized study of 500 patients with acute proximal DVT who were randomly assigned to receive standard intravenous UFH or enoxaparin 1 mg per kg subcutaneously twice daily, there was no significant difference in the rate of recurrent VTE (6.7% vs. 5.3%, respectively; $P=0.570$) or major bleeding (1.2% vs. 2.0%, respectively; $P=0.500$).⁵² The mean duration of hospital stay was 6.5 days in the UFH group and 1.1 days in the enoxaparin group.

Fixed-dose, weight-adjusted subcutaneous UFH therapy without dose adjustment based on aPTT values may be used for VTE treatment, with the potential for substantial cost savings. This therapy was compared with LMWH in the FIDO study, a randomized, open-label, noninferiority trial of 708 patients with acute VTE.⁵³ Patients assigned to the UFH group received a 333-units-per-kg subcutaneous dose followed by 250 units per kg subcutaneously every 12 hours. Patients assigned to the LMWH group received enoxaparin or dalteparin 100 units per kg subcutaneously every 12 hours (the choice of LMWH depended on local availability). Both treatments were given for at least 5 days on an inpatient or outpatient basis. Warfarin was initiated on the same day as UFH and LMWH in most cases, and warfarin was continued for at least 3 months, with doses adjusted to achieve an INR of 2.0-3.0.

In the FIDO study, treatment was administered on an outpatient basis in 72% of patients in the UFH group and 68% of patients in the LMWH group.⁵³ No significant difference between treatment groups was found in the incidence of recurrent VTE after 3 months (3.8% with UFH, 3.4% with LMWH; $P=0.002$). Incidence of major bleeding within 10 days was similar in the UFH (1.1%) and LMWH groups (1.4%). Blinded aPTT values were obtained on the third day of UFH therapy due to concerns that low values might be associated with recurrent VTE and high

values might be associated with bleeding during fixed-dose UFH therapy, but no such associations were found in the UFH group. Although the number of patients enrolled in this study was small, fixed-dose, weight-adjusted subcutaneous UFH, without routine aPTT monitoring, appears as safe and effective as LMWH for the treatment of acute VTE.

Fondaparinux, a subcutaneously delivered antithrombotic agent that inhibits activated coagulation factor X, was not approved by the U.S. Food and Drug Administration (FDA) at the time that the ACCP guidelines for VTE treatment were released. The FDA has since approved the drug for treatment of acute DVT and PE.⁵⁴ Fondaparinux was compared with intravenous UFH and enoxaparin in randomized, controlled, noninferiority studies of patients with acute symptomatic DVT or PE.⁵⁵⁻⁵⁶ In an open-label trial, 2,213 patients with acute symptomatic PE were randomly assigned to receive UFH by continuous intravenous infusion, with the aPTT at 1.5-2.5 times a control value, or by single daily subcutaneous doses of fondaparinux 5.0 mg, 7.5 mg, or 10.0 mg for patients weighing less than 50 kg, 50 kg-100 kg, or more than 100 kg, respectively.⁵⁵ Both treatments were continued for at least 5 days until an INR >2.0 was achieved with warfarin therapy. No significant difference between treatment groups was found in the incidence of recurrent VTE (5.0% with UFH, 3.8% with fondaparinux). Incidence of major bleeding was also similar in the 2 treatment groups (1.1% with UFH, 1.3% with fondaparinux). Fondaparinux was at least as safe and effective as adjusted-dose intravenous UFH for the treatment of acute symptomatic PE.

In a randomized, double-blind study, 2,205 patients with acute symptomatic DVT were randomly assigned to receive enoxaparin 1 mg per kg subcutaneously twice daily or single daily subcutaneous doses of fondaparinux, as described in the previous paragraph.⁵⁶ Both treatments were continued for at least 5 days until an INR >2.0 was achieved with warfarin therapy. No significant difference between treatment groups was found in the incidence of recurrent VTE (4.1% with enoxaparin, 3.9% with fondaparinux). Incidence of major bleeding was also similar in the 2 treatment groups (1.2% with enoxaparin, 1.1% with fondaparinux). Fondaparinux was at least as safe and effective as weight-based enoxaparin for the treatment of acute symptomatic DVT.

Most outpatient VTE treatment protocols call for daily monitoring of the INR with a target value of 2.5 and a therapeutic range of 2.0-3.0.⁴⁹ In patients receiving UFH or LMWH, platelet counts typically are measured on days 3-7 of treatment to detect HIT. At Brigham and Women's Hospital in Boston, outpatients receiving treatment for VTE are monitored using daily telephone calls by nurses and pharmacists. Physician follow-up is conducted through clinic visits scheduled 1 week after hospital discharge and then as needed to ensure thrombus resolution and appropriate patient outcomes.

The appropriateness of anticoagulant therapy for VTE was evaluated in a retrospective review of data from medical records

of 939 inpatients at 38 U.S. hospitals.³⁵ Overlap of parenteral and oral anticoagulant therapies was appropriate in 246 (51%) of the 486 patients who received overlapping therapies. Most patients were not discharged from the hospital until after parenteral therapy was discontinued. A total of 241 (27%) patients were discharged receiving bridge (both parenteral and oral) anticoagulation therapy. The mean length of stay was significantly shorter in patients discharged receiving bridge therapy compared with patients discharged receiving warfarin alone after discontinuation of parenteral anticoagulation therapy in the hospital (4.0 vs. 8.1 days, $P < 0.001$). These findings suggest that there is room for improvement in adherence to ACCP recommendations for overlap of anticoagulation therapy, and opportunities to minimize the hospital length of stay and costs by discharging patients while they are receiving bridge therapy often are missed.

ACCP guidelines address the duration of warfarin therapy in patients with VTE.⁴⁹ In patients with VTE caused by a risk factor that is reversible or transient (e.g., associated with surgery), 3 months of warfarin therapy are recommended. At least 6-12 months of warfarin therapy are recommended for patients with a first episode of idiopathic VTE, and indefinite therapy should be considered for such patients. Anticoagulation treatment for an indefinite period is recommended for patients with 2 or more VTE episodes and for patients with a first episode of VTE and cancer or certain inherited causes of thrombophilia.

On the other hand, there are potential alternatives to long-term warfarin treatment. Long-term LMWH (tinzaparin) therapy was compared with usual care involving intravenous or subcutaneous UFH and warfarin therapy in a randomized, open-label study of 737 patients with proximal DVT.⁵⁷ No significant difference between treatment groups was found in the incidence of VTE recurrence after 3 months (4.9% with LMWH, 5.7% with usual care) or at 12 months (8.9% with LMWH, 9.8% with usual care). Incidence of bleeding was significantly lower with LMWH (13.0%) than with usual care (19.8%, $P = 0.011$), which was largely due to less minor bleeding. These findings suggest that LMWH may be used as safely and effectively as warfarin on a long-term basis.

In summary, LMWH, fondaparinux, and subcutaneous UFH represent effective alternatives to intravenous UFH for acute VTE treatment and can be administered safely either in the hospital or on an outpatient basis. In addition, these agents represent alternatives to oral warfarin for long-term prevention of recurrent VTE events.

Conclusions

VTE is a major clinical problem with significant financial implications, yet awareness is limited both in the general public and also, to some extent, in the medical profession. Despite the existence of considerable research evidence and the publication of specific guidelines for VTE prophylaxis, these measures are often not implemented. When VTE strikes, treatment options now extend

beyond the hospital walls and should be considered to avoid or abbreviate hospital stays. Pharmacists can play an important role in increasing awareness of the morbidity and mortality associated with VTE, improving the identification of patients at risk for VTE, increasing adherence to evidence-based guidelines for VTE prevention, and enhancing treatment to optimize outcomes. Efforts to improve VTE prophylaxis and treatment should not focus on hospitals alone, but should also be applied to patients in long-term care facilities, to home care patients, and to outpatients.

DISCLOSURES

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