VENOUS THROMBOEMBOLISM AND THE COMMUNITY PHARMACIST

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ABSTRACT

Venous thromboembolism (VTE), which encompasses deep venous thrombosis (DVT) and pulmonary embolism, is a significant cause of morbidity and mortality. DVT can lead to long-term complications that include recurrent VTE and post-thrombotic syndrome. The rationale for the use of primary thromboprophylaxis is based on the high prevalence of VTE, serious complications that can occur even with treatment, and high mortality rates. Identification of patient risk factors for VTE is critical to the appropriate selection and initiation of prophylactic therapy, and the presence of multiple risk factors can cumulatively increase the risk for a thromboembolic event. (Adv Stud Pharm. 2007;4(9):242-246)

Deep venous thrombosis (DVT) and pulmonary embolism (PE) represent different manifestations of the same clinical entity, known as venous thromboembolism (VTE). Venous thrombosis typically develops when red blood cells, fibrin, and (to a lesser extent) platelets and leukocytes form a mass within a deep vein at a site of vascular trauma and in areas of sluggish blood flow. This accumulation of fibrin and platelets causes rapid growth in the direction of the blood flow, potentially reducing venous return. PE occurs when a segment of thrombus within the deep venous system detaches from the vessel, travels to the lungs, and lodges within the pulmonary arteries.1 The pelvic veins and those of the lower extremities are the source of more than 70% of all PE.2

Epidemiology

Venous thromboembolism is estimated to affect approximately 1 to 2 per 1000 people each year and increases exponentially with age. Therefore, the prevalence of VTE throughout the United States can be extrapolated to an annual prevalence of more than 250,000 cases per year.4 More than 33% of these cases are thought to represent recurrent disease.3 Despite initial management of a first DVT or PE, patients remain at high risk for recurrence, with 7% to 14% of patients experiencing a subsequent DVT or PE. The majority of recurrence is typically noted within 3 months following the incident DVT or PE event.6

Approximately 30% of patients with VTE will develop post-thrombotic syndrome (PTS), which consists of chronic pain, edema, and sometimes ulceration of the leg, up to 8 years after the initial event.2,7 This is particularly devastating because the survival rate diminishes with recurrence, from 80% at 2 years to 69% at 8 years.2 It is important to note that although DVT and PE most commonly complicate the course of sick, hospitalized patients, they also may affect ambulatory and otherwise healthy patients.8

Financial Burden of VTE

Few data exist to quantify the overall economic
burden of DVT and PE. However, morbidity and mortality data suggest that VTE creates a substantial economic healthcare system burden—estimated to be somewhere in the area of $1.5 billion (US), excluding physicians’ charges. In a recent retrospective cohort study in 2 large US healthcare plans, the mean total reimbursed costs associated with VTE incidence were $7712 (median: $3131) for a DVT event, rising to $12 200 for a combined DVT and PE event (median: $6678). This study also showed that patients who experienced recurrent DVT, PE, or both incurred an additional mean total healthcare cost of $12 326 per event.

Several studies have attempted to estimate the burden of DVT and PE in specific patient populations. For example, in a study of patients who had undergone orthopedic surgery and subsequently developed DVT or PE, average inpatient costs were twice those for a patient without DVT or PE. The mean total inpatient cost of care was estimated to be $9345 for the postorthopedic patient with no thromboembolic complications compared with $17 114 for a patient with postoperative DVT and $18 521 for a patient with postoperative PE. The long-term complications after occurrence of a DVT and PE are more difficult to quantify, but it is recognized that PTS and its treatment represent a significant portion of the overall economic burden of DVT. After total hip replacement, the lifetime costs of managing the complications of a postoperative DVT (recurrent DVT or PE and PTS) have been estimated be $3069 per patient per year.

**Pathophysiology**

**DVT**

Venous thrombi typically develop within a deep vein at a site of vascular trauma and in areas of sluggish blood flow, such as in the venous sinuses of the calf or within a valve cusp. An accumulation of fibrin and platelets causes rapid growth in the direction of the blood flow, potentially reducing venous return. Endogenous fibrinolysis results in a partial or complete resolution of the thrombus. Residual thrombus will organize and the vein may completely recanalize, which often results in narrowing of the lumen and valvular incompetency, although in some cases an extensive collateral network can develop.

Signs and symptoms of DVT include leg pain, edema, erythema, and warmth in the affected area. Physical examination often reveals distention of the collateral veins and a palpable cord if there is an associated superficial vein thrombosis. Patients presenting for the first time with a suspected DVT may have minimal or atypical symptoms, which could be caused by several disorders. Other common causes of leg swelling and tenderness include a Baker’s cyst, infective cellulitis, superficial thrombophlebitis, or lymphatic obstruction. Imaging techniques are normally required to confirm a diagnosis of DVT because diagnosis is difficult when based on symptoms alone. Whereas only 25% of patients will have a confirmed diagnosis on objective testing or imaging, many patients with DVT will have no symptoms. The presence of risk factors with or without accompanying signs and symptoms should alert the clinician to the increased possibility of a DVT (Table 1).

**PE**

The presence of DVT makes the diagnosis of PE far more likely, with a 10% incidence of symptomatic PE from an untreated DVT; nearly 50% of patients with DVT have an asymptomatic PE at the time of

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for VTE</th>
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<td>Risk Factor</td>
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<td>Age</td>
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<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
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<td>Previous VTE</td>
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<td>Malignancy</td>
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<td>Hormone therapy</td>
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<td>Oral contraceptives</td>
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<td>Tamoxifen</td>
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<td>High-dose progestogens</td>
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<td>Raloxifene</td>
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<td>Pregnancy</td>
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<td>Immobility</td>
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<td>Hospitalization/surgery</td>
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BMI = body mass index; VTE = venous thromboembolism.

their diagnosis. Thrombi that embolize to the lungs will typically lodge either within the lobar arteries or the distal main pulmonary artery, although occasionally they will straddle the pulmonary artery bifurcation. Smaller thrombi can travel more distally. A PE can cause several important physiologic changes that cause the presenting symptoms. These include stimulation of irritant receptors that increase the respiratory rate and impairment of gas exchange, which causes bronchoconstriction and hypoxemia, as well as the loss of alveolar surfactant, which can result in atelectasis and edema—often within hours. The most common findings on physical examination are tachypnea, rales, tachycardia, a fourth heart sound, accentuation of the second heart sound (closure of the pulmonic valve), DVT, and diaphoresis.

DIAGNOSIS

DVT

Initial diagnosis of any patient with a suspected DVT or PE must begin with urgent referral. This is required to confirm or rule out the diagnosis and to begin appropriate anticoagulation strategies to reduce the risk of further events. A clinical model has been designed and prospectively validated whereby patients are classified as having a high, intermediate, or low probability of developing DVT based on history and clinical signs. This clinical model has been used in diagnostic algorithms to reduce the number of diagnostic tests required on patients with suspected DVT (Table 2).20,21 D-dimers are formed when plasmin degrades cross-linked fibrin. Elevated levels of D-dimers are found in nearly all patients with VTE; therefore, D-dimer measurement is most useful in excluding a diagnosis of VTE disease. In patients who are clinically suspected of having DVT, a D-dimer level less than 500 ng/mL on enzyme-linked immunosorbent assay testing has a negative predictive value of 95% and can eliminate the need for ultrasonography.20,21 Duplex ultrasonography is used to detect the presence of intraluminal echoes and to assess blood flow characteristics. In a symptomatic patient, an inability to fully compress a vein and thereby obliterate its lumen is a clear sign (>95% sensitivity and specificity) of proximal DVT.22 This test is less sensitive for the detection of calf vein thrombosis. The advantages of duplex ultrasonography are its wide availability and its noninvasiveness. Its drawbacks include the fact that it is operator-dependent and can be difficult to perform on patients who are obese, patients with significant tenderness or edema, and patients whose limbs are in a cast or other immobilizing device. A third diagnostic option—contrast venography—has been considered the ‘gold standard’ for diagnosing DVT, but it is rarely used as the initial diagnostic test because of patient discomfort, exposure to contrast material, and limitations of availability. Venography is more sensitive than duplex ultrasonography in detecting calf vein thrombosis, and it can be used to demonstrate the presence of reflux.

PE

The assessment for PE begins with a careful clinical examination and a determination of risk factors. The chest X-ray, arterial blood gas measurements, and electrocardiogram also can be used to establish a high, intermediate, or low risk of PE. This algorithm, similar to the one for DVT, incorporates the use of a clinical prediction rule to determine the pretest probability of disease and options for imaging. The value of a laboratory test or imaging study in predicting the presence of PE depends on the likelihood of

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
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<td>Active cancer (treatment ongoing or within previous 6 mos or palliative)</td>
<td>1</td>
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<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the legs</td>
<td>1</td>
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<tr>
<td>Recently bedridden for &gt;3 d or major surgery within 4 wks</td>
<td>1</td>
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<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
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<tr>
<td>Entire leg swollen</td>
<td>1</td>
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<tr>
<td>Calf swelling by &gt;3 cm compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
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<tr>
<td>Pitting edema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or more likely than that of DVT</td>
<td>-2</td>
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RESULTS:

≤0: low probability
1–2: moderate probability
≥3: high probability

DVT = deep venous thromboembolism.

Data from Bergqvist et al.20

244
Manuscript Title

Management of VTE

Given the morbidity, mortality, and cost burden of VTE, there is a clear need for pharmacologic agents that will prevent and treat these thrombotic disorders. In the past, options were limited to aspirin, unfractionated heparin (UFH), and warfarin. However, UFH has an inconsistent pharmacokinetic profile, can be cumbersome to administer, and is associated with heparin-induced thrombocytopenia—an immune-mediated adverse effect that occurs in approximately 1% to 5% of patients receiving UFH.24 Warfarin, which is administered orally, has a narrow therapeutic index and delayed onset of action that result in complicated dosing titration and also interacts with a significant number of medications and common foods. Therefore, novel antithrombotic agents that have more specific activity on the coagulation cascade, more predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements have been developed to overcome limitations associated with some of the nonspecific traditional anticoagulants.

Emerging evidence supports the use of factor Xa inhibitors (eg, fondaparinux, idraparinux, rivaroxaban, and apixaban) and oral direct thrombin inhibitors (eg, dabigatran, which is undergoing phase II trials) for the prevention and treatment of VTE. In recent clinical trials of more than 7000 hospital inpatients undergoing major orthopedic surgery, fondaparinux was comparable in efficacy and safety to the low molecular weight heparin (LMWH) enoxaparin and offered substantial relative risk reduction for VTE.25 In addition, studies comparing fondaparinux to enoxaparin and UFH found that once-daily subcutaneous fondaparinux was at least as effective and safe as twice-daily enoxaparin and as intravenous UFH in the initial treatment of patients with symptomatic DVT and PE.26-27 A recent study of more than 144,000 patients who underwent hip or knee replacement in 500 hospitals across the United States showed that patients receiving fondaparinux experienced fewer VTE events following orthopedic surgeries compared to patients who received enoxaparin, dalteparin, or UFH.28 The benefits of extended anticoagulation for secondary VTE prevention also have been recently demonstrated with both low (international normalized ratio [INR] 1.5–2) and regular intensity (INR 2–3) warfarin therapy.29,30 All of these data suggest a new paradigm for the treatment and prophylaxis of VTE that is based on the use of emerging antithrombotic therapies in the acute treatment period and both traditional and novel agents in the chronic, extended-treatment period.

Recent guidelines from the American College of Chest Physicians17 recommend that acutely medically ill patients admitted with congestive heart failure or severe respiratory disease, or those who are confined to bed and have at least 1 additional risk factor for VTE, should receive primary thromboprophylaxis. Although a complete review of the guidelines is beyond the scope of this article, 2 important points can be made. First, thromboprophylaxis should be continued after discharge for patients at continued risk for VTE because episodes of VTE often develop up to several months later. Second, the use of LMWH is preferred over UFH for prophylaxis and treatment of VTE, and fondaparinux can now be considered a practical alternative to LMWH because of recent efficacy and safety data and also convenience of use.

Conclusions

Venous thromboembolism is generally a disorder of hospitalized patients, with PE being one of the major preventable killers in these individuals. A variety of measures are available to reduce or eliminate the risk of VTE. These include careful risk assessment of individual patients and the use of thromboprophylactic measures in patients at risk of an event. New antithrombotic drug therapies with improved clinical profiles and less complex administration requirements have been developed. Clinical research suggests that these new agents are at least as effective and safe to use for treating acute VTE as the older standard agents.

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Extended duration therapy using older or newer agents has been found to be useful for the secondary prevention of VTE.

REFERENCES