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Introduction

Venous thromboembolism (VTE), clinically manifest as deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common group of disorders that can lead to substantial morbidity and mortality. The long-term consequences of postthrombotic syndrome (PTS), related to residual venous obstruction and valvular incompetence, are significant. The clinician faces the challenge not only of accurate diagnosis of the disorder but also of providing patients with the most appropriate, cost-effective treatment options.

This supplement to The American Journal of Medicine was derived from presentations by experts in the field during a 2-day symposium “Vascular Medicine for the Primary Care Physician,” held October 15 to 16, 2003, in Las Vegas, Nevada, in conjunction with Vascular Interventional Advances (VIVA), a national educational course for peripheral vascular interventions. The articles presented herein offer a general overview of the current issues facing primary care clinicians who treat patients at risk for or with established venous thromboembolic disease.

Although rapid diagnosis and treatment of VTE are critical to prevent serious complications, including significant morbidity due to PTS or mortality due to massive PE, the differential diagnosis remains complex for the practicing clinician. This is due in part to the fact that clinical symptoms are often neither sensitive nor specific for the disease. In the first article, Dr. Geno Merli presents a clinical perspective on the accurate diagnosis of VTE and takes a detailed look at the strengths and weaknesses of currently available diagnostic strategies, including such new additions as magnetic resonance direct thrombus imaging, D-dimer assays, and spiral computed tomography scanning.

Once a diagnosis of DVT has been confirmed, an effective therapeutic regimen with rapid and predictable onset of action is critical to the prevention of thrombus extension or embolization and (ideally) maintenance of venous valvular function. These strategies reduce the risk of PE and long-term complications caused by PTS. In the second article, Dr. Merli discusses the 2 available therapeutic options—unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs)—as well as new oral products on the horizon. Clinical evidence indicates that outpatient treatment with subcutaneously administered LMWH is an appropriate option for a majority of patients. It is important for clinicians to assess their patients individually based on detailed history and evaluation in order to stratify risk and identify appropriate candidates for outpatient treatment. Additionally, novel oral agents that provide their effects through direct inhibition of thrombin are currently in clinical development. However, until such treatments are approved for clinical use, LMWHs offer the most convenient and cost-effective option.

In the third article, Dr. L. Bernardo Menajovsky provides a perspective on the clinical syndrome of heparin-induced thrombocytopenia (HIT) and the unique strategies required for its early diagnosis and treatment. Dr. Menajovsky’s review of the pathophysiology, diagnostic criteria, clinical presentations, and currently available management strategies for HIT are illustrated in the context of 2 case studies. Although anticoagulation therapy with UFH or LMWH is safe and effective in many patients, some patients produce platelet antibodies through an immune-mediated reaction after exposure to heparin, leading to the development of HIT. This syndrome results in paradoxical thrombosis, resulting in serious clinical consequences, including exacerbation of VTE, arterial thromboembolic disease, limb loss, and mortality. The routine assessment of platelet counts is therefore necessary with any heparin therapy, as decreasing platelet levels are potentially indicative of HIT. This syndrome must be suspected in patients experiencing progressive or new thrombotic events despite adequate heparin therapy, because early identification and treatment can prevent the more serious complications associated with this disorder.

Anticoagulation with UFH and, more recently, LMWH, followed by long-term maintenance therapy with warfarin, are the established standards of therapy for acute DVT. As discussed by Dr. Andrew Blum and Erin Roche in the fourth article in this supplement, treatment with LMWH has many clinical advantages over treatment with intravenous UFH, including less-frequent dosing, elimination of anticoagula-
tion intensity monitoring, and the attractive option of outpatient therapy. Although anticoagulation can be effective in the prevention of recurrent VTE, it sometimes results in insufficient protection against thrombus extension, embolization, or the development of PTS. The restoration of venous patency and early lysis of thrombi through the use of catheter-directed thrombolytic therapy has been effective in appropriate patient subsets. When used in conjunction with anticoagulation, catheter-directed thrombolysis may potentially lead to improved long-term outcomes in some patients with DVT. Several device manufacturers have developed novel percutaneous devices that may rapidly and safely remove the majority of acute proximal venous thrombi, thereby offering rapid decompression of an acutely edematous limb, and hopefully preventing long-term venous valvular dysfunction and PTS. Clinical trials are in the planning stages in the United States.

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Diagnostic assessment of deep vein thrombosis and pulmonary embolism

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KEYWORDS: Contrast venography; D-dimer assay; Magnetic resonance direct thrombus imaging; Pulmonary angiography; Venous thromboembolism

Venous thromboembolism (VTE) is a common disorder that can lead to substantial morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Although rapid diagnosis and treatment are critical in preventing PE, mortality and major morbidity due to conditions such as postthrombotic syndrome may complicate the differential diagnosis of VTE. The clinical symptoms associated with DVT are neither sensitive nor specific and can be indicative of a wide range of diagnoses. Because imaging studies can be expensive and are sometimes inconclusive, they should be used judiciously in patients with highly suspected VTE. This review offers a clinical perspective on the accurate, routine diagnosis of VTE, including an overview of common clinical signs and symptoms, as well as the advantages and drawbacks of available diagnostic strategies.

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provides an overview of the clinical models and diagnostic strategies available to assess for thromboembolic disease.

**Etiology of venous thromboembolism and relative risk**

VTE can occur as an idiopathic syndrome or may be caused by an underlying condition that predisposes a patient to thrombosis. In a retrospective study of 366 validated cases of VTE, approximately 48% were idiopathic and 52% were secondary to an underlying condition. Rudolf Ludwig Karl Virchow was the first to identify 3 primary clinical factors associated with a substantial risk of thrombosis. Together, these factors are known as the Virchow triad and include (1) vessel wall damage due to inflammation or trauma; (2) changes in blood flow or volume due to immobility, ischemia, and other conditions; and (3) hypercoagulable factors present in the blood, including inherited and acquired coagulation disorders.

The consideration of risk factors in the assessment and diagnostic evaluation of patients with potential DVT is important; however, it is also important to consider the relative risk for each factor independently. Some reports suggest that hospitalized medical patients subjected to an extended period of immobility may be at risk for VTE, especially if presenting with additional risk factors, including acute infectious disease, previous history of VTE, or advanced age (>75 years).

Although immobilization is commonly cited in the literature as a predisposing risk factor for VTE, results from some studies suggest that the associated risk may not be as significant. In a retrospective cohort analysis, Gatt and colleagues evaluated 18 mobile and 8 immobile patients with a mean age of 85 for a duration of 10 years. The immobile patients were bedridden for a prolonged period (>3 months). No difference in baseline characteristics, which included the assessment of risk factors, was observed between the 2 groups. The incidence of VTE was similar between the immobile and mobile patient groups (13.9 and 15.8, respectively; \( P = 0.77 \)). Although these results are not consistent with previous studies—an inconsistency that is due, in part, to a relatively small study population—they do highlight the importance of considering the added threat conferred by each risk factor both independently and in combination with other risk factors.

Similarly, an analysis that was conducted using data from the American College of Surgeons National Trauma Data Bank evaluated the frequency of VTE following trauma. The results demonstrated that incidence of VTE in these patients is also relatively low. Data was collected from 131 trauma centers. The following 6 risk factors were found to be associated with VTE: age \( \geq 40 \) years, lower extremity fracture with Abbreviated Injury Score (AIS) \( \geq 3 \), head injury with AIS \( \geq 3 \), ventilator delays \( >3 \), venous injury, and history of a major operative procedure. Of the 450,375 patients who experienced trauma from 1994 to 2001, a total of 1,602 experienced DVT, resulting in an incidence of 0.36%.

In contrast to the lower relative risk conferred by immobilization and trauma, a much stronger association exists between VTE and cancer. In a recent study, 26% of patients presenting with bilateral DVT were diagnosed with cancer after the occurrence of DVT, and metastasis had occurred in 70% of these patients. Other reports cite as much as a 2-fold increase in DVT risk among patients with cancer and suggest that the risk of recurrent thromboembolism is as much as 3.5 times higher in patients with malignancy compared with cancer-free patients. Therefore, patients presenting with unprovoked VTE should be further assessed for potential malignancy by means of physical examination, laboratory tests, and appropriate imaging studies as indicated by physical findings.

Finally, hypercoagulability—especially hypercoagulability due to a genetic predisposition, acquired syndromes, and certain medications, such as oral contraceptives—can increase the risk of thrombosis. Hereditary risk factors include factor V Leiden mutation; prothrombin G20210A gene mutation; and deficiencies of protein C, protein S, and antithrombin III. Hyperhomocysteinemia and elevated levels of factors XIII and V, which may be hereditary and/or acquired, are also risk factors. Additionally, ABO blood type is another VTE risk factor that was recently noted in cancer patients and is believed to be associated with hypercoagulability resulting from influence on the levels of von Willebrand factor and factor VIII.

**Diagnosis of venous thromboembolism**

It is important to note that 50% of patients who have VTE do not present with any symptoms. Classic symptoms associated with DVT include leg swelling, pain upon palpation in the calf or thigh, and the Homans sign (calf pain with dorsiflexion of the foot). However, these signs have been proved to occur at the same frequency in those without DVT. The second diagnostic step in the identification of DVT is the stratification of patients through the assessment of risk factors. Such stratification increases the accuracy of diagnosis and reduces the unnecessary use of expensive imaging tests in patients with low risk.

Anderson and associates, Ruiz-Giménez and coworkers, and Wells and colleagues developed the first clinical model for the diagnosis of patients presenting with suspected DVT. This model includes a thorough clinical examination and identification of any risk factors that predispose patients to have increased risk of thrombosis. In accordance with this model, patients are first divided into 3 risk categories (low, moderate, or high) and are further assessed through ultrasonography (Table 1). Patients who are stratified to the high-risk category, or who have abnormal ultrasound results, are further assessed through venog-
Clinical model for predicting pretest probability for deep vein thrombosis

<table>
<thead>
<tr>
<th>Risk factor category</th>
<th>Stratification (clinical probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
</tr>
<tr>
<td>● Active cancer*</td>
<td>High</td>
</tr>
<tr>
<td>● Paralysis, paresis, or recent immobilization of lower extremities</td>
<td>Moderate</td>
</tr>
<tr>
<td>● Bedridden ≥3 days and/or major surgery within previous 4 wk</td>
<td>Low</td>
</tr>
<tr>
<td>● Localized tenderness of deep venous system†</td>
<td>● No alternative diagnosis plus</td>
</tr>
<tr>
<td>● Swelling of thigh and calf confirmed by measurement</td>
<td>— ≥3 major risk factors or</td>
</tr>
<tr>
<td>● Calf swelling showing ≥3 cm difference vs. nonsymptomatic calf‡</td>
<td>— ≥2 major and ≥2 minor risk factors</td>
</tr>
<tr>
<td>● Strong family history of DVT (≥2 first-degree relatives with history of DVT)</td>
<td>● Alternative diagnosis plus</td>
</tr>
<tr>
<td>● History of trauma to affected leg (within ≥60 days)</td>
<td>— 1 major and ≥1 minor risk factor or</td>
</tr>
<tr>
<td>● Pitting edema in symptomatic leg</td>
<td>— ≥2 minor risk factors</td>
</tr>
<tr>
<td>● Dilated nonvaricose veins in symptomatic leg</td>
<td>● Alternative diagnosis plus</td>
</tr>
<tr>
<td>● Hospitalization within previous 6 mo</td>
<td>— 1 major and ≥2 minor risk factors or</td>
</tr>
<tr>
<td>● Paralysis, paresis, or recent immobilization of lower extremities</td>
<td>— ≥3 minor risk factors</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.
Adapted with permission from Lancet.24
*Patient receiving ongoing treatment, treatment within previous 6 months, or palliative therapy.
†Elicited in the anatomic distribution of the deep venous system of either the thigh or calf.
‡Measured 10 cm below tibial tuberosity.

Clinical practice guidelines for the diagnosis of DVT from the American Thoracic Society (ATS) concur with this strategy, recommending the use of venography as a follow-up to inconclusive compression ultrasound results, and the use of serial ultrasound or impedance plethysmography in patients with normal compression ultrasound results.28

For patients presenting with PE, shortness of breath, with or without leg pain, may be the first symptom; however, a number of specific criteria allow for a more accurate diagnosis. Similar to the clinical model for diagnosis of DVT, Wells and colleagues27 also defined a clinical algorithm for the diagnosis of PE (Figure 2). When used in conjunction with D-dimer testing, this algorithm safely reduces the need for expensive imaging diagnostics. It uses a point system for calculating the low, moderate, or high pretest probability of PE. Points are assigned based on clinical symptoms of DVT, including heart rate of >100 beats per minute, immobilization for ≥3 days or recent surgery in the past 4 weeks, a clinical history of VTE, hemoptysis, malignancy, or clinician determination that PE is as likely or more likely than another diagnosis (Table 2).27

The patient history and physical examination findings reported in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial illustrate the difficulty in quickly identifying or ruling out a diagnosis of PE. In PIOPED, the most common past and current physical findings included dyspnea, pleuritic chest pain, cough, tachycardia, and tachypnea (Table 3).29 These symptoms also can be indicative of heart failure, interstitial lung disease, or pneumonia. For this reason it is especially important to conduct thorough examinations and risk stratification when examining patients for potential VTE.

Objective testing for venous thromboembolism

Diagnostic evaluation of suspected VTE includes a clear correlation between clinical probability, test selection, and test interpretation.30 However, a variety of diagnostic approaches are feasible, and availability and familiarity with particular technology may influence the choice of approach. Additionally, the sensitivity of certain diagnostic tests is affected by the location of the thrombus.28 In addition to traditional tests, such as contrast venography for DVT and pulmonary angiography for PE, newer modalities such as D-dimer assays and magnetic resonance direct thrombus imaging (MRDTI) offer promise for better detection with less invasiveness and have the potential for use in detection of both DVT and PE.

Imaging modalities for deep vein thrombosis

Contrast venography imaging

Contrast venography is no longer appropriate as the initial diagnostic test in patients exhibiting DVT symptoms, although it remains the “gold standard” for confirmatory diagnosis of DVT. Venography is nearly 100% specific and sensitive, and it provides the ability to investigate the distal and proximal venous system for thrombosis. Its use is no longer widespread owing to the need for administration of a contrast medium and the increased availability of noninvasive diagnostic strategies. However, venography is still warranted when noninvasive testing is inconclusive or impossible to perform.28 Additional drawbacks of venography include contraindication in patients with renal insufficiency and lack of accuracy in recurring cases of suspected DVT owing to the difficulty of visualizing an intraluminal defect in veins that have been thrombosed previously.28
Compression ultrasound

Doppler compression ultrasound with real-time, B-mode imaging is used at most institutions because of its safety, availability, reliability, and noninvasive nature. Benefits include detection of acute symptomatic proximal DVT, as well as DVT of the upper extremities, and it is also capable of identifying other pathologies. It is also useful in combination with venous flow detection (duplex ultrasonography). The demonstration of venous noncompressibility is the major diagnostic criterion for venous thrombosis. However, compression ultrasound is not specific or sensitive for the detection of DVT in patients with asymptomatic proximal DVT or in patients with symptomatic or asymptomatic DVT of the calf, and it demonstrates limited accuracy in cases of chronic DVT. Its use is also limited in patients who are obese or who have edema. Currently, a number of ongoing large trials are in progress for the assessment of magnetic resonance venography and computed tomographic (CT) venography in the diagnosis of DVT.

Diagnostic tests for pulmonary embolism

Blood gas analysis and electrocardiogram

Arterial blood gas analysis and electrocardiogram (ECG) are routinely used to diagnose PE with varying rates of success. Hypoxemia is a common feature of acute PE but is not present in all cases. Thus, although arterial blood gas levels reveal the blood oxygen saturation level, they are not specific or sensitive for the definitive diagnosis of PE. The use of transcutaneous oximetry will provide information regarding hypoxemia without the need for an arterial puncture, but it is not sensitive or specific for the diagnosis of PE.

Hemodynamically significant PE induces transient ECG abnormalities reflecting right ventricular overload and/or strain; however, these abnormalities are neither sensitive nor specific for VTE, although a classic S1Q3T3 pattern might warrant consideration of PE in the presence of other signs and symptoms. ECG can also be used to suggest an alternative cardiac diagnosis. Additionally, recent investigators have suggested that a simple scoring system based on ECG might be useful in predicting individuals with the greatest percentage of perfusion defect. Because neither of these methods is suggested as a proven diagnostic tool for the initial screening or exclusion of VTE, they should not be routinely used for definitive diagnosis. Instead, they should be used in conjunction with clinical examinations and other diagnostic studies to reinforce the clinical suspicion of PE.

Imaging techniques

Chest X-ray

Chest X-ray is often used in combination with ECG to reinforce suspicion of PE. Although chest X-ray is com-
Figure 2  Clinical algorithm for initial evaluation of patients with suspected pulmonary embolism (PE). DVT = deep vein thrombosis; PTP = pretest probability; spiral CT = spiral computerized tomographic pulmonary arteriography; V/Q = ventilation–perfusion. (Reprinted with permission from Ann Intern Med.27)

Table 2  Suspected pulmonary embolism (PE): a simple clinical model and d-dimer to assess pretest probability*

<table>
<thead>
<tr>
<th>Specific factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical DVT (objective leg swelling, tenderness)</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization ≥3 days or surgery in previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
<tr>
<td>PE as likely or more likely than alternative diagnosis</td>
<td>3.0</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis. Adapted with permission from Ann Intern Med.27

*Interpretation of point total: <2 points = low risk (mean probability, 3.6); 2–6 points = moderate risk (mean probability, 20.5); > 6 points = high risk (mean probability, 66.7).

Table 3  Common patient symptoms with a positive pulmonary embolism diagnosis in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study

<table>
<thead>
<tr>
<th>Patient history</th>
<th>Percentage of patients (N = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>73%</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>66%</td>
</tr>
<tr>
<td>Cough</td>
<td>37%</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>28%</td>
</tr>
<tr>
<td>Leg pain</td>
<td>26%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>13%</td>
</tr>
</tbody>
</table>

Adapted with permission from Chest.29
monly ordered during the process of differential diagnosis of pulmonary conditions, PE patients most commonly have normal chest X-ray results. However, they sometimes present with nonspecific radiographic findings. A normal chest X-ray in the presence of severe dyspnea or hypoxemia without evidence of bronchospasm or cardiac shunt is strongly suggestive of but not diagnostic for PE.28

The Hampton hump, which is visible in some X-rays, is a classic finding caused by a pleural-based abnormality due to pulmonary infarction; its presence, however, is not common and cannot be used to confirm or exclude PE (Figure 4). Chest X-ray is most useful to rule out other conditions that may mimic PE, such as pneumothorax or pneumomediastinum.28,36

Figure 3 The S1Q3T3 pattern with concomitant symptoms and signs of pulmonary embolism warrants further investigation.

Figure 4 The Hampton hump (arrow), which is visible in some X-rays, is a classic finding caused by a pleural-based abnormality due to pulmonary infarction. Its presence is not common and should not be used to confirm or exclude pulmonary embolism.
Ventilation–perfusion scan

The ventilation–perfusion (V/Q) scan is used to detect areas of abnormal perfusion due to PE. It has long been considered a preferred diagnostic modality in suspected PE (Figure 5). The ventilation component of the test excludes a diagnosis of pneumonia and other respiratory conditions. However, the V/Q scan is only diagnostic of PE in a minority of cases. Moreover, PE frequently occurs in combination with other lung diseases, such as pneumonia or chronic obstructive pulmonary disease. Because most lung diseases affect pulmonary blood flow as well as ventilation, their presence may decrease the scan’s specificity. The PIOPED study investigators at the National Heart, Lung, and Blood Institute (NHLBI) reported that a high-probability V/Q scan was sensitive for the diagnosis of PE and that a low-probability scan was sensitive for the absence of PE. The V/Q scan was not useful in patients with previous VTE. Indeterminate scans require further diagnostic studies to assess disease accurately, and 33% of PIOPED participants with indeterminate scans were later found through angiography to have thromboemboli.

Spiral CT pulmonary arteriography

Spiral (also known as helical) CT has demonstrated a higher degree of sensitivity and interobserver agreement than V/Q scan, making this strategy a less-invasive, alternative diagnostic tool in patients with suspected PE (Figure 6). Spiral CT has demonstrated a high rate of sensitivity and specificity in detecting PE to segmental levels, but it cannot accurately detect subsegmental emboli. Although the clinical significance of these subsegmental emboli has not been established, a negative spiral CT cannot safely rule out thrombosis and must be confirmed with pulmonary angiography. In addition, a low sensitivity rate of 70% has been reported in a previous study, providing additional evidence that confirmatory pulmonary angiography is required in patients with negative spiral CT findings. A 1-year follow-up study in patients with a normal spiral CT scan demonstrated a low 2% rate of clinical PE, suggesting that additional data will be required to characterize the safety of a negative spiral CT without other confirmatory diagnostics.

Pulmonary angiography

Pulmonary angiography has been considered a gold standard test for PE. It is an invasive test that is used in some settings to detect PE in patients with indeterminate V/Q scans. However, it is not necessary for a diagnosis of PE in the acute setting when the perfusion scan is normal. One study of pulmonary angiography demonstrated sensitivity of 85% for the detection of lobar and segmental emboli, with less reliability in detecting peripheral subsegmental emboli (1 in 5). These results are consistent with those of the PIOPED study, in which interobserver agreement was 98% for lobar PE, 90% for segmental PE, and only 66% for subsegmental emboli. However, there has been some debate surrounding the true clinical importance of these peripheral emboli. Some investigators posit that they are caused by isolated calf vein thrombi and do not require treatment, whereas others believe that they are a precursor to larger emboli.
Newer diagnostic techniques

Indirect CT venography

Indirect CT venography has been investigated as an adjunct to the pulmonary angiography conducted during the differential diagnosis of PE. This technique results in a high rate of detection of DVT—the underlying cause of many subsequent PE events—and requires no additional contrast material.

MRDTI

MRDTI is a novel technique that has demonstrated accuracy and reproducibility for DVT diagnosis in limited studies. It detects the presence of methemoglobin in clots, allowing visualization of thrombi without using IV contrast material; the technique is thus useful for detecting subacute thrombosis.

MRDTI has several major advantages over conventional modalities. Because data suggest that it is highly accurate in detecting both DVT and PE, MRDTI provides a single imaging modality for detecting VTE. This technique provides direct visualization of thrombi, avoiding the pitfalls of conventional techniques that have identified thrombi either as filling defects or in terms of surrogates. MRDTI also allows simultaneous imaging of the legs and chest, permitting a comprehensive assessment of thrombus load, minimizing the importance of overlooked subsegmental PE, and potentially facilitating more titrated treatment. The safety of withholding treatment in suspected DVT and PE on the basis of negative MRDTI alone is being evaluated in ongoing outcome studies. Additionally, because it has proved useful in identifying complicated plaque in the carotid arteries in the setting of transient and permanent cerebral ischemia, MRDTI offers promise as a technique that is capable of detecting high-risk vessel wall disease before significant or permanent end-organ damage. As costs for this type of imaging decrease and institutions gain wider access to the technology, it should offer an attractive alternative to the invasive use of contrast venography with application in a wide range of vascular disease settings.

Bedside D-dimer assays

A number of D-dimer assays have been evaluated as diagnostic markers for VTE and are considered to be inexpensive as well as timely. The predictive value of the assay depends on several attributes, including the prevalence of VTE in the population being tested. Ruiz-Giménez and colleagues found that the VIDAS (bioMérieux, Marcy L’Etoile, France) and enzyme-linked immunosorbent assay (ELISA) D-dimers are suitable approaches as a first diagnostic tool for the exclusion of DVT. However, some data suggest that D-dimer testing offers limited specificity and cannot be solely used to exclude a diagnosis of DVT; this has been demonstrated in patients who are elderly, in the emergency department, or hospitalized for ≥3 days. Another important issue is that some institutions do not have

Figure 6  Spiral computed tomographic pulmonary arteriography has demonstrated a high rate of sensitivity and specificity in detecting pulmonary embolism (arrow).
access to immediate D-dimer results. Nevertheless, D-dimer testing, especially the most-specific ELISA, offers an attractive bedside assay that is sensitive for DVT diagnosis, if not specific under certain circumstances. D-dimer testing will still result in a reduction in the need for imaging diagnostics when DVT can be diagnosed and treated earlier. A positive D-dimer result is not necessarily useful for definitively diagnosing VTE, but a negative result, when it coincides with ultrasound results, can rule out the diagnosis.

Although D-dimer testing is a recent addition to the strategy for diagnosing PE and has been shown to be a valuable tool with excellent sensitivity, there have been rare reports of patients with PE but negative D-dimer tests. One investigation at an academic health center indicated that D-dimer measurement was of limited utility in patients with suspected PE and nondiagnostic lung scans or negative spiral (helical) CT results. Another study of 150 patients admitted to the hospital for PE who underwent D-dimer measurement compared results in patients with negative D-dimers versus patients with raised D-dimers. The sensitivity of raised D-dimers for PE was high (96%), but the finding of chest pain was statistically greater in the group with negative D-dimers ($P = 0.01$). In these negative D-dimer cases, the emboli were all distal ($P = 0.0003$) and the diagnostic value of ultrasound investigations (echocardiography, ultrasonography of lower limb veins) was less than in patients with higher D-dimers ($P < 0.0001$). The authors suggested that measurement of D-dimers by the ELISA method may be nondiagnostic in distal PE, perhaps because of the less-extensive thromboembolic process. They concluded that in cases with negative D-dimers, a strong clinical suspicion of PE should signal a need for further investigation.

Summary

Clinical evidence indicates that patients who are at moderate-to-high risk for developing VTE include those with a history of cancer, prior thrombosis, and acquired syndromes or genetic disorders that predispose them to a hypercoagulative state. Among these patients, VTE should be highly suspected with the presentation of classic symptoms. Such cases require rapid assessment and accurate diagnosis to prevent the progression of DVT, long-term morbidity due to postthrombotic syndrome, or the occurrence of potentially fatal PE.

Clinical presentation for 50% of patients with VTE is often nonspecific, and can be confused with a variety of other conditions, including heart failure, cellulitis, hematomatoma, or edema due to an unrelated condition. Although contrast venography remains the gold standard for diagnosis of DVT, the availability of less-invasive diagnostic techniques has limited the use of this test as a first-line diagnostic. Rather, it is used when the less-invasive tests, such as duplex ultrasonography, are inconclusive or impossible to perform.

When clinical symptoms warrant consideration of PE, objective testing should begin with less-invasive techniques such as D-dimer, V/Q scan, or spiral CT scan, followed by gold-standard pulmonary angiography when the scans are nondiagnostic. New additions to the diagnostic battery and increased awareness of risk stratification paradigms have the potential to allow more accurate identification of VTE in some patients, thereby greatly reducing the incidence of morbidity and mortality.

References


Anticoagulants in the treatment of deep vein thrombosis

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Intravenous (IV) infusion of unfractionated heparin (UFH) followed by oral administration of warfarin remains the cornerstone of clinical treatment of deep vein thrombosis (DVT). Results from numerous clinical trials demonstrate that subcutaneously administered low-molecular-weight heparin (LMWH) is at least as effective and as safe as IV UFH. Treatment with LMWH has several clinical advantages over treatment with UFH, including less-frequent dosing and elimination of the need for monitoring. The introduction of LMWHs has made it possible for physicians to offer outpatient treatment of DVT, with the associated advantage of reduced costs due to shortened hospital stays. However, the optimal duration of anticoagulant therapy after DVT is still debated, as it depends on an individual patient’s potential risk for recurrence or treatment-associated complications. Patients are usually risk stratified on the basis of multiple clinical characteristics, including the location of thromboemboli, the presence or absence of cancer, the assumed etiology or cause of DVT (idiopathic vs. due to a transient risk factor), and the presence of certain thrombophilic conditions. High-risk patients often receive inpatient treatment with UFH or LMWH and are candidates for long-term (≥6 months) oral anticoagulation, whereas short-term anticoagulation (3 to 6 months) is usually indicated for patients who are at lower risk of recurrence or therapeutic complications and who can be treated with LMWH on an outpatient basis. The introduction of LMWHs has resulted in significant clinical progress for the treatment of DVT.

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KEYWORDS:
Deep vein thrombosis; Direct thrombin inhibitors; Low-molecular-weight heparin; Unfractionated heparin; Venous thromboembolism; Warfarin

Despite the recognition of risk factors for venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as the evolution of more accurate diagnostic technologies and the availability of effective preventive treatments, this syndrome continues to carry a high burden of morbidity and mortality. It is estimated that in North America approximately 600,000 patients per year are hospitalized for DVT alone. The purpose of this article is to provide an overview of the evolving landscape for the outpatient treatment of DVT and to review recent changes in the duration of anticoagulant treatment.

Low-molecular-weight versus unfractionated heparin

Until recently, treatment with unfractionated heparin (UFH) and warfarin was considered to be the standard treatment for DVT. The advent of low-molecular-weight heparins (LMWHs) and other newer anticoagulants has led to rapid evolution of the treatment landscape for DVT. Before the introduction of LMWH, the use of UFH required continuous intravenous (IV) application and frequent monitoring, thus precluding the possibility of outpatient therapy or early discharge. Clinical use of LMWH has revolutionized the treatment of DVT by offering many treatment advantages over UFH, including less-frequent dosing, fixed dosages, and the opportunity to initiate outpatient or short-stay inpatient programs for DVT treatment, with a consequent reduction in costs to patients and the healthcare system due to decreased resource utilization.
Clinical trial data

The most important studies affecting current approaches to anticoagulant therapy are those that have compared UFH with LMWH in the treatment of DVT. These trials have provided extensive evidence supporting the safety, efficacy, and feasibility of LMWH for use as an outpatient treatment for DVT. In 1996, Leizorovicz and colleagues\(^3\) published the results of a meta-analysis of 20 randomized controlled clinical studies comparing multiple clinical outcomes of LMWH and UFH. Treatment with LMWHs was shown to have a higher benefit-to-risk ratio than treatment with UFH. More recently, Dolovich and associates\(^4\) published a pooled analysis of relative risk in patients with acute VTE, demonstrating that LMWH is at least as effective as UFH in terms of risk of major bleeding, PE, and recurrent VTE; LMWH fared significantly better in risk of mortality. Minor bleeding was the only effect measured that reflected slightly reduced relative risk among patients treated with UFH.\(^4\) Two published meta-analyses report similar findings with regard to major bleeding and mortality, demonstrating that LMWHs have equivalent or better safety and efficacy than UFH (Figure 1).\(^5,6\)

Levine and colleagues\(^7\) were the first researchers to report on the results of a controlled trial that evaluated safety and efficacy of LMWH as an outpatient treatment for DVT. Patients (N = 500) were randomized to receive either outpatient treatment with enoxaparin (an LMWH administered subcutaneously twice daily in 1 mg/kg injections) or inpatient treatment with IV infusions of UFH. Patients who received treatment with enoxaparin spent an average of only 1.1 days in the hospital compared with 6.5 days for UFH-treated patients. In fact, of the 247 patients who received enoxaparin, 120 did not undergo hospitalization at all and the remaining 127 spent an average of 2.2 days in the hospital after randomization. The incidence of major bleeding was similar between the 2 groups and occurred in 5 patients from the enoxaparin treatment group compared with 3 patients from the standard heparin group (\(P = 0.50\)). Examining recurrent thromboembolisms, patients assigned to LMWH treatment experienced 1.4% fewer embolic events than their UFH-treated counterparts. Factoring in these data, the study concluded that enoxaparin was safe and effective in many patients with acute DVT.

Similarly, a large study by Koopman and colleagues\(^8\) randomized 400 patients to receive treatment with nadroparin (an LMWH) or UFH, resulting in a significant reduction in hospital stay for those treated with LMWH. In fact, 75% of patients in the LMWH group either were not admitted to the hospital at all or were discharged early, translating to an overall mean reduction in length of hospitalization of 67% among the LMWH treatment group compared with the UFH treatment group. Rates of recurrent VTE between the 2 groups were not significantly different; however, LMWH-treated patients had less impairment of physical activity and social functioning.

Inpatient treatment with unfractionated heparin and warfarin

Although patients must be assessed individually to determine whether they are appropriate candidates for outpatient
treatment, certain general observations can be made. For example, patients with proximal or symptomatic distal DVT are customarily hospitalized and are usually dosed with UFH and warfarin using standard dosing or weight-based dosing regimens. For most patients, whether they are treated on an inpatient basis with UFH or on an outpatient basis with LMWH, warfarin can be initiated in conjunction with heparin initiation. Treatment with heparin is usually discontinued after 5 to 6 days, provided that the last 2 consecutive days of treatment reach therapeutic International Normalized Ratio (INR) levels.\(^8\)

**Standard unfractionated heparin dosing (Hull method)**

A standardized UFH dosing regimen was established by Hull and coworkers\(^8\) after the results of their study demonstrated that subtherapeutic dosing in the first 24 hours resulted in a significantly greater risk of subsequent VTE. These investigators reported that a failure to achieve a therapeutic level within 24 hours resulted in a 23.3% frequency of VTE compared with 4% to 6% for those whose levels exceeded the therapeutic threshold within 24 hours (\(P = 0.02\)). The standard treatment regimen, or Hull method, consists of administration of an IV bolus of 5,000 U with subsequent continuous IV infusion of UFH 30,000 U/24 hr for 5 to 7 days or until target therapeutic levels are reached.\(^10\) Platelet counts are monitored between days 3 and 5 for the development of heparin-induced thrombocytopenia (HIT).\(^11\) Initiation of warfarin (5 mg) in conjunction with UFH initiation on day 1 of hospitalization reduces length of stay and therefore also reduces overall treatment cost.

Dosing of UFH requires the monitoring of activated partial thromboplastin time (aPTT) every 6 hours for the first 24 hours, and then daily as needed thereafter.\(^11\) Dosing for UFH should be adjusted upward or downward by increments of 200 U to achieve an aPTT ratio of 1.5 to 2.5 times baseline; this correlates with a therapeutic level of 0.2 to 0.4 IU/mL by protamine titration or an anti-Xa level of 0.3 to 0.6 IU/mL by an amidolytic assay. For warfarin, the therapeutic level is defined as maintenance of an INR of 2.0 to 3.0 for 2 consecutive days.\(^11\)

**Weight-based unfractionated heparin dosing (Raschke method)**

The weight-based method was developed by Raschke and colleagues,\(^12\) who found that the use of a weight-based UFH nomogram resulted in significantly faster titration to target levels than standard therapy. Indeed, 97% of patients who were dosed using the weight-based method reached target aPTT levels within the first 24 hours of treatment compared with 77% of patients who received standard dosing (\(P < 0.002\)).\(^12\) Also known as the Raschke method, the weight-based method calls for the delivery of an initial bolus of UFH 80 IU/kg, followed by a continuous infusion of UFH 18 IU/kg per hour. As with standard dosing, warfarin treatment (5 mg) is initiated on day 1 and platelet counts are measured on days 3 and 5.\(^11,13\) Target aPTT and INR are the same for weight-based dosing as they are for standard dosing (aPTT target, 1.5 to 2.5 times baseline; INR target, 2.0 to 3.0 for 2 consecutive days). As with standard dosing, aPTT is also monitored every 6 hours. Appropriate incremental dosing for the weight-based nomogram method is shown in Table 1.\(^11\)

**Outpatient treatment for deep vein thrombosis with low-molecular-weight heparins**

Outpatient therapy offers reduced economic costs to patients and the healthcare system as a result of decreased resource utilization. Once- or twice-daily dosing and fixed dosages combined with a well-planned program of patient education and professional support offer convenience to patients while enhancing successful adherence to home treatment.\(^14\)

Treatment guidelines for LMWH are similar to guidelines for UFH, except that treatment is self-administered and does not require continuous monitoring (Table 2).\(^11,13\) The safety and efficacy profiles of LMWHs, such as dalteparin, enoxaparin, nadroparin, logiparin, and tinzaparin, are well established.\(^7,8,15,16\)

The first clinical trials for LMWHs were conducted to show therapeutic equivalence to UFH. As observed through the course of these trials, LMWHs offer many potential advantages over UFH, including predictable dose-dependent linear clearance,\(^17-20\) a longer plasma half-life,\(^20-22\) high bioavailability (\(~\text{96\%}\)) when administered subcutaneously,\(^17,19\) and no need for aPTT monitoring.\(^13\) Higher benefit-risk ratios have also been observed, with subcutaneous LMWH reported to be at least equal to IV UFH in terms of safety and efficacy.\(^18\) Additionally, treatment with LMWH shows reduced variation and increased sustainability of plasma anti-factor activity,\(^19\) with reported ranges of 88% to 97% for anti-factor Xa and 62% to 64% for anti-factor IIa.\(^23\)

Absolute contraindications for outpatient treatment of DVT/PE include active bleeding, cardiopulmonary instability, hereditary bleeding disorders, history of HIT, or allergy to heparin or LMWH. On the other hand, there are a number of relative contraindications for the outpatient treatment of DVT/PE that require clinical judgment: inability to support the cost of the drug; potential for medication nonadherence; residue from a unit dosage; gastrointestinal or genitourinary bleeding <6 months; renal insufficiency (CrCl <30 mL/min); or geographic inaccessibility for follow-up care (Figure 2).

From a pharmacoeconomic perspective, the study by Levine’s group\(^7\) established the safety and efficacy of treating acute proximal DVT with enoxaparin, an LMWH ad-
ministered primarily at home (n = 247) versus UFH administered in the hospital (n = 253). Economic analysis of a subset of trial subjects (n = 300) who presented as outpatients and were followed up for 3 months demonstrated a substantially lower average cost of treatment for the enoxaparin/outpatient group relative to the UFH inpatient group (Can$2,278 vs. $5,323).24

The authors of the Canadian study 24 attempted to generalize their economic findings to the United States by substituting a US national average hospital per diem for the Canadian rate, and applying a US–Canadian exchange-rate conversion to other costs. On this basis, average savings of US$2,750 were predicted for the enoxaparin/outpatient approach relative to UFH inpatient care. Several observational studies have evaluated the economic impact of outpatient DVT management with enoxaparin in the United States, and have reported estimated cost savings ranging from $547 to $2,471 per patient.25-27

A study in a group-model HMO estimated $2,828 in cost savings from the program based on estimated hospital costs.28 Spyropoulos and colleagues,29 who completed a retrospective replication of the Levine group study in a managed care setting, found similar clinical and economic outcomes. These studies provide useful evidence for US healthcare policy de-
cision makers and third-party payers that the use of LMWHs may provide cost savings in the care of patients with DVT.

### Duration of warfarin therapy

Although there is some debate regarding the recommended length of warfarin therapy after intervention with UFH or LMWH, the minimum recommended duration is 3 months. Study results indicate that treatment beyond 3 months is beneficial in patients who have a higher risk of recurrence. In a prospective cohort study, patients (N = 355) given standard therapy with UFH followed by ≥3 months of warfarin treatment and were observed for up to 8 years; the majority (69%) completed at least 5 years of observation. The risk of recurrence was significantly higher among patients with nontransient risk factors, such as cancer or impaired coagulation, than it was in patients who had transient risk factors, such as trauma or surgery.

Other studies have also demonstrated that anticoagulant treatment beyond 3 months may be beneficial. In a multicenter, randomized trial, Schulman and associates compared warfarin treatment durations of 6 weeks and 6 months, following patients for 2 years; a striking difference in the recurrence of thromboembolic events in favor of extended treatment was observed (Figure 3). Results from this study demonstrated that patients who were treated with anticoagulants for 6 weeks were more than twice as likely to experience recurrence of VTE as patients who received 6 months of treatment (odds ratio, 2.1; 95% confidence interval, 6.8–12.2). The incidence of recurrent thromboembolism was significantly lower in patients with permanent risk factors who were treated for 6 months (12.1%) versus 6 weeks (24.2%)(P < 0.001). Although this trend was also observed for patients with temporary risk factors (4.8% incidence in the 6-month group vs. 8.6% in the 6-week group), the difference was not statistically significant (P < 0.24). Interestingly, there was no increase in the rate of major bleeding between the 2 groups despite the vast difference in treatment duration; however, this may have been due, in part, to a relatively low dosing regimen, as indicated by a lower INR target range of 2.0 to 2.85. Considered together, the results of this study and the previous study by Prandoni and colleagues provide strong support for 6-month warfarin treatment in patients with permanent risk factors.

Kearon and colleagues and Agnelli and associates further explored the utility of extended anticoagulant therapy in patients with idiopathic VTE who are therefore at a high risk for recurrence. The results for both studies favored extending anticoagulant treatment beyond 3 months in patients with idiopathic DVT. In fact, a later double-blinded study conducted by Kearon and colleagues was stopped early so that patients in the placebo group could be given the opportunity to receive extended anticoagulant treatment. Initially designed as a 2-year trial, the trial was ended after 10 months when results showed that 27.4% of patients in the placebo group could already experienced recurrence, compared with 1.3% of patients in the anticoagulant treatment group (P <0.001).

Unfortunately, as Agnelli and associates observed, the protective effects conferred by an extended 1-year course of anticoagulant treatment are not maintained after discontinuation of treatment. In a study on low-dose anticoagulant treatment, Ridker and coworkers demonstrated that continuation

### Table 2 Guidelines for inpatient unfractionated heparin (UFH) treatment and outpatient low-molecular-weight heparin (LMWH) treatment

<table>
<thead>
<tr>
<th>VTE Suspected</th>
<th>UFH*</th>
<th>VTE Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UFH</strong> or LMWH</td>
<td><strong>UFH</strong></td>
<td><strong>LMWH</strong></td>
</tr>
<tr>
<td>Obtain baseline aPTT, PT, CBC, PLTs</td>
<td>Rebolus with heparin 80 IU/kg IV and start maintenance infusion at 18 IU/kg</td>
<td>Give LMWH (dalteparin†, enoxaparin‡, nadroparin§, tinzaparin)</td>
</tr>
<tr>
<td>Check for contraindication to heparin therapy</td>
<td>Check aPTT at 6 hr to keep aPTT in a range that corresponds to a therapeutic blood heparin level</td>
<td>Start warfarin therapy on day 1 at 5 mg and adjust the subsequent daily dose according to INR</td>
</tr>
<tr>
<td>Order imaging study</td>
<td>Anticoagulant with warfarin for ≥3 mo at an INR of 2.5; range 2.0–3.0</td>
<td>Stop heparin therapy for at least 4–5 days of combined therapy when INR is &gt;2.0; check PLT count between day 3 and day 5</td>
</tr>
<tr>
<td>Consider giving heparin 5,000 U IV or LMWH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aPTT = activation partial thromboplastin time; CBC = complete blood cell count; INR = International Normalized Ratio; IV = intravenous; PLT = platelet; PT = prothrombin time; VTE = venous thromboembolism.

Adapted with permission from Chest:11,13

*For subcutaneous treatment with UFH, give 250 IU/kg q12h to obtain a therapeutic aPTT at 6 hours and adjust dose up or down.
†Dalteparin sodium 200 anti-Xa IU/kg per day subcutaneously. Single dose should not exceed 18,000 IU (approved in the United States and Canada).
‡Enoxaparin sodium 1 mg/kg q12h subcutaneously or enoxaparin sodium 1.5 mg/kg per day subcutaneously. Single dose should not exceed 180 mg (approved in the United States and Canada).
§Nadroparin calcium 86 anti-Xa IU/kg bid subcutaneously for 10 days (approved in Canada) or nadroparin calcium 171 anti-Xa IU/kg. Single dose should not exceed 17,100 IU.
⁴Tinzaparin sodium 175 anti-Xa IU kg/day subcutaneously daily (approved in the United States and Canada).
of low-dose anticoagulant treatment beyond 6 months significantly reduces the risk of recurrent events compared with placebo. However, Kearon and colleagues further determined that although extended low-dose anticoagulant treatment may be more effective than placebo, it is not as effective as conventionally dosed therapy, nor does it reduce the risk of bleeding.

Results from these studies indicate that although 3-month anticoagulant treatment after DVT may be sufficient for patients with transient risk factors, it is not sufficient for patients who have permanent risk factors or idiopathic DVT. In accordance with recommendations from the Seventh American College of Chest Physicians Consensus Conference on Antithrombotic Therapy, patients with idiopathic DVT should receive at least 6 to 12 months of anticoagulant therapy after an acute thromboembolic episode. The panel also recommends indefinite anticoagulant treatment for patients who experience recurrent events and for those who exhibit permanent or long-term risk factors.

Contraindications and other treatment considerations

The first step in treating DVT is to establish an accurate diagnosis, thereby avoiding the unnecessary risk and ex-
pense that might result from a false-positive diagnosis. Recent advances in diagnostic technologies have improved the accuracy of such methods and are described in greater detail elsewhere in this supplement.36

Risk stratification is also important and helps physicians determine which patients should be hospitalized and treated with UFH as inpatients or with LMWH as outpatients. It is estimated that as many as 75% of patients are eligible for outpatient treatment with LMWH.8 Risk stratification should be based on a detailed history and evaluation through which the following factors are assessed: (1) presence of underlying comorbid conditions; (2) hemodynamic stability of the patient and likelihood for hemorrhage; (3) presence or absence of PE; and (4) location of thrombosis. Additionally, the ability of a patient to self-administer subcutaneous injections of LMWH at home and the likelihood of therapeutic adherence should also be addressed.

Patients who are at risk for hypercoagulability or increased clotting include those with a family history of VTE, those who develop DVT in the upper extremities, and those who experience DVT in the absence of transient risk factors such as immobility, trauma, or surgery. Consultation with a hematologist or vascular medicine specialist may be helpful in determining the scope and appropriate timing of any necessary tests for patients with such risk factors.

Cancer is a common cause of hypercoagulability. Therefore, patients presenting with unprovoked VTE should be further examined for potential malignancy by means of physical examination and/or additional screening, such as mammography or fecal occult blood testing. Results from 2 recent studies suggest that prolonged treatment (3 to 6 months) with LMWH in cancer patients in lieu of warfarin therapy may result in reductions in the number of recurrent events and in the incidence of major bleeding.37,38

New oral anticoagulants

Anticoagulants work by directly or indirectly inhibiting enzymes involved in the coagulation pathway. Heparins and warfarin provide their effects through the indirect inhibition of thrombin, whereas a number of new agents in development for the treatment of thromboembolic disease provide their effects through the direct inhibition of thrombin; these agents are known as direct thrombin inhibitors (DTIs). Lepirudin, bivalirudin, and argatroban are examples of parenterally dosed DTIs. All of these drugs have relatively short half-lives and, in contrast to LMWH, require monitoring.39

Ximelagatran is the first orally available DTI to reach phase 3 clinical trials, and it does not require monitoring.40 Ximelagatran is the inactive prodrug of the active drug, melagatran, which has been demonstrated to have a relatively wide therapeutic window. Clinical studies have shown that ximelagatran is comparable in efficacy to standard therapy with dalteparin (an LMWH) and warfarin in the treatment of DVT.41 Additional data on the benefit–risk ratio and clinical equivalence of ximelagatran to other LMWHs are awaited from future clinical trials involving patients with DVT. Recently, the US Food and Drug Administration did not grant approval for the use of ximelagatran based on elevations of lower enzymes associated with continuous use.42 Further studies are in progress to evaluate the mechanism of this side effect. Fondaparinux is a synthetic and selective inhibitor of factor Xa.43 This new agent has been shown to be as effective as enoxaparin and UFH for the treatment of DVT and PE.43,44 Multiple subcutaneous doses of fondaparinux were based on patient weights (5 mg, <50 kg; 7.5 mg, 50–100 kg; 10 mg, >100 kg).43

Summary

Until recently, there were few therapeutic options available for the treatment of patients with DVT. Inpatient treatment with UFH and warfarin has remained the mainstay of treatment for nearly 30 years. Now, with the introduction of LMWHs, new, more convenient and cost-effective treatment options are emerging. Clinical evidence suggests that the majority of patients are eligible for outpatient treatment with LMWHs; however, not all patients are appropriate candidates for such treatment. For some patients, the use of LMWHs is contraindicated or the risk of PE is too great to allow for outpatient treatment. It is therefore important for physicians to familiarize themselves with risk-stratification strategies to effectively identify patients who would be appropriate candidates for treatment with LMWHs. For patients who are treated on an inpatient basis, it is crucial that therapeutic levels of heparin be achieved as quickly and as safely as possible to minimize the risk of long-term recurrence. This can best be accomplished through frequent monitoring and titration using the standard or weight-based dosing regimens.

LMWHs represent a significant clinical advance in the treatment of DVT. Eventually, the use of subcutaneously administered LMWHs may be superseded by newer oral agents. Until new, safer oral agents appear, however, LMWHs offer a less expensive and more convenient alternative to standard inpatient UFH therapy for DVT.

References

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Heparin-induced thrombocytopenia: clinical manifestations and management strategies

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Thrombocytopenia is a relatively frequent and usually benign clinical complication of heparin therapy. However, some patients receiving heparin and heparin-based products experience an immune-mediated reaction due to the development of heparin-induced antibodies. This reaction leads to a highly specific and paradoxical form of thrombocytopenia, known as type II heparin-induced thrombocytopenia (HIT). Unlike other types of drug-induced thrombocytopenia, HIT promotes thrombosis rather than bleeding; therefore HIT should be suspected in patients who experience thrombotic events despite adequate anticoagulation therapy. Early identification and treatment of HIT can prevent more serious complications associated with this disorder (e.g., exacerbation of venous thromboembolism, limb gangrene, and skin necrosis). Both arterial and venous thrombosis can arise from a single episode of HIT. Routine assessment of platelet counts is necessary with heparin therapy, as a decreased platelet level is usually the only indication of HIT. Although compared with unfractionated heparin, low-molecular-weight heparin therapy is less likely to result in HIT, the use of these agents is contraindicated in HIT patients. Concomitant warfarin therapy is not contraindicated in such patients but must be carefully monitored. Treatment with a direct thrombin inhibitor, such as lepirudin or argatroban, is an effective strategy in reversing the thrombocytopenia associated with HIT and reducing its complications. This article discusses the clinical syndrome of HIT, including pathophysiology, diagnostic criteria, clinical presentations, and current available management strategies in the context of 2 case studies.

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Heparin is a widely used anticoagulant drug for the prevention and treatment of venous and arterial thromboembolic diseases. Thrombocytopenia, a frequently occurring complication of heparin therapy and known as heparin-induced thrombocytopenia (HIT), may occur in 2 distinct types. The more common, type I (sometimes called heparin-associated thrombocytopenia), occurs in approximately 10% to 20% of patients receiving heparin, and is a nonimmunogenic response to therapy. This mild thrombocytopenia is not progressive, nor is it associated with bleeding or thrombosis. No special treatment is required; the platelet count is usually >100 × 10^9/L and gradually rises to pretreatment levels within a few days even if heparin therapy is not discontinued.

The less-frequent but more severe form, HIT type II, is the subject of this article and henceforth will be referred to as “HIT.” This is an immune response caused by the idioopathic presence of drug-related antibodies. It occurs in 1% to 3% of all patients exposed to unfractionated heparin (UFH) and in 0% to 0.8% of patients receiving low-molecular-weight heparin (LMWH). There is greater risk in those patients receiving heparin of bovine compared with porcine origin. Although the main risk of thrombocytopenia...
HIT is a paradoxical primary risk for thrombosis. HIT can lead to a systemic thrombotic response that can span both venous and arterial vascular beds, although venous events are 4 times more common. The most frequent complications are deep venous thrombosis (DVT) and pulmonary embolism (PE). In rare cases, patients with HIT may develop life-threatening thromboses such as thromboembolic occlusions of limb arteries, acute myocardial infarction (MI), and stroke. Other possible complications include warfarin-induced skin necrosis, acute systemic reactions, and transient global amnesia.

**Pathophysiology of heparin-induced thrombocytopenia**

Given the severe sequelae associated with HIT, immediate recognition and efficient treatment are of the utmost importance. Typical presentation begins after ≥5 days of therapy (the minimum period required for pathogenic antibodies to reach clinically significant levels) but may clinically manifest much sooner if the patient has had previous exposure to heparin. Recognition and diagnosis are complicated; however, because HIT has been reported up to 3 weeks after exposure to heparin, there also exists a phenomenon known as delayed-onset HIT. In order to fulfill this particular diagnosis, heparin treatment must have stopped for ≥5 days prior to the onset of symptoms, assuring that all heparin given intravenously or subcutaneously would have cleared the system at that time.

The cellular interactions that lead to HIT begin with the formation of antibodies. Following heparin administration, platelet factor-4 (PF-4)—which is normally found on endothelial cells and the α-granules of platelets—and heparin bind together, forming a PF-4—heparin complex. Patients develop antibodies to this complex, usually in the form of immunoglobulin G, which results in platelet activation, the release of microparticles with procoagulant properties. These microparticles initiate thrombin generation and have been theorized to play a significant role in subsequent thrombotic events (Figure 1).

**Risk factors**

Patients who have had recent major surgery represent 1 of the highest risk groups for development of HIT. The syndrome is more prevalent in patients receiving antithrombotic prophylaxis after peripheral vascular, coronary artery bypass graft, and orthopedic surgery. The observed thrombotic complications are consistent with the baseline thrombotic risks that are more prevalent in each respective surgical population. A lower incidence of HIT is seen in medical patients and general surgery patients receiving prophylactic doses of UFH or LMWH. Medical and obstetric patients treated with prophylactic doses of LMWH represent the lowest-risk groups.

However, because HIT is an immunologic reaction, it can potentially develop from exposure to any dose of heparin. Incidental exposure through heparin-coated catheters and heparin flushes to maintain an intravenous (IV) line can also provide an independent stimulus for HIT. In a study of 12 patients, Laster and colleagues found that the
thrombocytopenia resulting from heparin-coated catheters continued as long as the catheters were in place, regardless of whether other sources of the drug were discontinued. Thrombosis and skin necrosis that occur during heparin therapy should also be linked to a high degree of suspicion for HIT. Warfarin treatment in patients with active HIT can cause DVT to progress to venous limb gangrene and can also induce skin necrosis.14

Unfractionated versus low-molecular-weight heparin

The reduced binding to plasma proteins and endothelial cells with LMWH compared with UFH is associated with greater bioavailability and a more predictable dose response.19 However, switching from UFH to LMWH therapy should be avoided in patients with HIT because of the potential for cross-reactivity with these drugs (approaching 100% with sensitive assays).6,20 Although HIT is generally less common with the use of LMWH,4,21 recent data suggest that patients who do develop LMWH-induced HIT may experience severe thrombocytopenia and frequent thrombotic events, similar to the population that develops HIT due to UFH.5,22 Moreover, delayed-onset HIT can occur in patients exposed to UFH alone or in combination with LMWH even after an apparently benign hospital discharge23; individuals with LMWH-induced HIT exhibit a longer delay in the onset of symptoms compared with patients who have UFH-induced HIT.22

Clinical manifestations and diagnosis

In HIT, the relative decrease in platelet counts is key to diagnosis34; clinical criteria include a decrease in platelet count of ≥50% or to levels <100 × 10⁹/L, current use of heparin, and a new thrombotic or thromboembolic event.5,23 Thrombocytopenia caused by drugs other than heparin commonly presents with bleeding, whereas HIT is recognized as a markedly thrombotic syndrome with bleeding complications occurring less frequently. Between 30% and 75% of patients develop thrombosis,5 which is counterintuitive to a decrease in platelet count.4,9,25 Figure 2 illustrates a normal distribution of thrombotic events based on platelet count nadir and emphasizes the presence of thrombosis across the clinical spectrum of the syndrome.9

The most common complications of HIT are presented in Table 1. Some 50% of patients presenting with isolated thrombocytopenia eventually experience a thrombotic event, and approximately 20% of these patients experience

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Thrombotic complications of heparin-induced thrombocytopenia</th>
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<tbody>
<tr>
<td>Venous</td>
<td>Arterial</td>
</tr>
<tr>
<td>● Deep vein thrombosis</td>
<td>● Aortic occlusion</td>
</tr>
<tr>
<td>● Pulmonary embolism</td>
<td>● Acute thrombotic stroke</td>
</tr>
<tr>
<td>● Cerebral dural sinus thrombosis</td>
<td>● Myocardial infarction</td>
</tr>
<tr>
<td>● Adrenal hemorrhagic infarction</td>
<td>● Cardiac intraventricular thrombosis</td>
</tr>
<tr>
<td></td>
<td>● Thrombosis in upper limb, lower limb, mesenteric, renal, and spinal arteries</td>
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venous thrombosis, with DVT and PE identified as the most common events.26

Whereas previous retrospective studies often focused on specific patient populations at high risk for arterial thrombosis, a 14-year study of patients with HIT conducted by Warkentin and colleagues found that the syndrome is mainly associated with venous thrombosis.25 Life-threatening venous thrombosis, especially PE, is an important presentation of HIT, and may be consistent with the fact that many patients with HIT receive heparin prophylaxis due to their high baseline risk for thrombotic events.25

Despite venous thrombosis being the primary clinical presentation of HIT, a variety of exceptions to this classic description of HIT have been reported and should be considered during the process of differential diagnosis in suspect patients. A high index of suspicion, as well as acute awareness and vigilance, are required when diagnosing and treating patients vulnerable to HIT. Specifically, clinicians should be cognizant of several key points:

● Platelet count does not have to decrease below 150 × 10^9/L initially (100,000 platelets is clinically acceptable; 150,000 platelets lowers the suspicion threshold) for HIT to be present.9 This is particularly true in patients with HIT-induced skin lesions. Skin lesions tend to develop at heparin injection sites and can range from painful red plaques (Figure 3) to overt skin necrosis.

● Thrombosis may present as late as 40 days after heparin exposure.

● Early onset of thrombocytopenia may occur in cases of HIT. This is true in patients with recent exposure to heparin (usually within 3 months).

Laboratory diagnosis of heparin-induced thrombocytopenia

The diagnosis of HIT is based primarily on clinical grounds. Laboratory finding of the heparin antibodies is useful to corroborate the diagnosis and to monitor its presence in cases when there is a clinical need to rechallenge a specific patient with heparin or heparin products (i.e., on-pump open heart surgery).10 Among the different assays available for the diagnosis of HIT, the PF-4—heparin enzyme linked immunosorbent assay (ELISA) and the 14C-serotonin release assay (SRA) are the most widely used. The main differences between the 2 assays with regard to clinical applicability are explained in Table 2.27–30

As is true for every diagnostic test or screening, it is paramount to establish the clinical pretest probability in order to help decide which test needs to be ordered and, more importantly, how to interpret the results. In other words, estimating the pretest probability and knowing the likelihood ratios will allow the clinician to truly quantify the reliability of either a positive or a negative test. Although yet to be validated, the “4 Ts” (thrombocytopenia, timing, thrombosis, and the absence of other explanations) clinical scoring system has been proposed by Warkentin.31 Clinicians can use the guidelines in Table 3 to calculate the pretest probability of having the disease.

Assuming a linear correlation between the individual score obtained from Table 3 and the pretest probability (expressed in percentage), and knowing the likelihood ratios calculated in Table 2, the clinician can estimate the posttest probability of either a positive or a negative test (Table 4).32,33 Practically speaking, for a patient with very low (<10%) or high (>60%) pretest probability for HIT, a negative or positive, respectively, PF-4—heparin ELISA test should suffice to either rule in or rule out the diagnosis. In other patient groups (moderate risk), the SRA should be the test of choice; however, in no circumstances will it help to rule out the disease.

Atypical clinical presentation

Several clinical syndromes are caused by HIT but do not present with classic symptoms. These include acute sys-
Table 2  Clinical differences between platelet factor–4 (PF-4)–heparin enzyme-linked immunosorbent assay (ELISA) and \(^{14}\)C-serotonin release assay (SRA)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Readily Available</th>
<th>Labor Intensity</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR(+) (*)</th>
<th>LR(−) (†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-4–heparin ELISA</td>
<td>Yes</td>
<td>+</td>
<td>(\geq 90%)</td>
<td>(~80%)</td>
<td>4.5</td>
<td>0.13</td>
</tr>
<tr>
<td>SRA</td>
<td>No</td>
<td>++++</td>
<td>(\geq 90%)</td>
<td>98%</td>
<td>4.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

\(LR = \) likelihood ratio.

 Adapted with permission from Thromb Haemost,\(^{27}\) Am J Clin Pathol,\(^{28}\) Thromb Haemost,\(^{29}\) and N Engl J Med.\(^{30}\)

*Positive result is the sensitivity divided by 1 minus the specificity.

†Negative result is 1 minus the sensitivity divided by the specificity.

Table 3  Estimating the pretest probability of heparin-induced thrombocytopenia (HIT): the “4 Ts”

<table>
<thead>
<tr>
<th>Points*</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>(&gt;50%) platelet decrease to nadir (\geq 20)</td>
<td>(30%-50%) platelet decrease, or nadir 10–19</td>
<td>(&lt;30%) platelet decrease, or nadir &lt;10</td>
</tr>
<tr>
<td>Timing(^1) of onset of platelet fall (or other sequelae of HIT)</td>
<td>Days 5–10, or (\leq) day 1 with recent heparin (past 30 days)</td>
<td>(&gt;) Day 10 or timing unclear, or (&lt;) day 1 with recent heparin (past 31–100 days)</td>
<td>(&lt;) Day 4 (no recent heparin)</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Proven new thrombosis, skin necrosis, or acute systemic reaction after IV UFH bolus</td>
<td>Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)</td>
<td>None</td>
</tr>
<tr>
<td>Other causes of platelet fall</td>
<td>None evident</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

\(IV = \) intravenous; UFH = unfractionated heparin.

Reproduced with permission from Circulation.\(^{31}\)

*0, 1, or 2 points for each of 4 categories; maximum possible score = 8. Pretest probability scores: 6–8 indicates high; 4–5, intermediate; and 0–3, low.

\(^1\)First day of immunizing heparin exposure considered day 0.

Table 4  Posttest probability: enzyme-linked immunosorbent assay (ELISA) and \(^{14}\)C-serotonin release assay (SRA)

<table>
<thead>
<tr>
<th>Pretest Probability,(\ast) 4 Ts score (%)</th>
<th>Posttest Probability, Positive ELISA (%)</th>
<th>Posttest Probability, Negative ELISA (%)</th>
<th>Posttest Probability, Positive SRA (%)</th>
<th>Posttest Probability, Negative SRA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 (10%)</td>
<td>33</td>
<td>1.4</td>
<td>83</td>
<td>1</td>
</tr>
<tr>
<td>2 (20%)</td>
<td>53</td>
<td>3</td>
<td>92</td>
<td>2.5</td>
</tr>
<tr>
<td>3 (30%)</td>
<td>66</td>
<td>5</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>4 (40%)</td>
<td>75</td>
<td>8</td>
<td>97</td>
<td>6</td>
</tr>
<tr>
<td>5 (50%)</td>
<td>82</td>
<td>12</td>
<td>98</td>
<td>9</td>
</tr>
<tr>
<td>6 (60%)</td>
<td>87</td>
<td>16</td>
<td>98.5</td>
<td>13</td>
</tr>
<tr>
<td>7 (70%)</td>
<td>91</td>
<td>23</td>
<td>99</td>
<td>19</td>
</tr>
<tr>
<td>8 (80%)</td>
<td>95</td>
<td>34</td>
<td>99.5</td>
<td>29</td>
</tr>
</tbody>
</table>

\(HIT = \) heparin-induced thrombocytopenia.

Adapted with permission from N Engl J Med\(^{35}\) and JAMA.\(^{33}\)

\(\ast\)Pretest probability = likelihood of having HIT before test results.

\(\ast\)Posttest probability = likelihood of having HIT after test results.
Hepatic reactions after IV bolus, disseminated intravascular coagulation, and warfarin-associated venous limb gangrene or skin necrosis. Recent reports also suggest that HIT could explain approximately 5% of cases of acute adrenal failure caused by bilateral adrenal hemorrhagic infarction.3,9,34,35

Originally diagnosis of postoperative HIT was based on immune-related manifestations; however, the standard baseline measurement of preoperative platelet counts was inappropriate for patients who often develop variations in postoperative thrombosis. Warkentin and associates21 have recommended that postoperative rather than preoperative peak in platelet count may be a more appropriate baseline on which to calculate decreases in platelet count with heparin therapy, and thus may be a more accurate alternative for identifying patients affected by HIT.21

Case studies

Case 1

Background

A 68-year-old woman receiving long-term anticoagulation with warfarin for nonvalvular atrial fibrillation was admitted to the hospital with chest pain and was subsequently diagnosed with a non-ST-segment elevation MI. The patient underwent cardiac catheterization followed by placement of 2-vessel coronary artery stents; the recovery period was complicated by a nosocomial pneumonia for which she was treated with antibiotics. The patient received anticoagulation therapy for her atrial fibrillation with heparin.

Seven days after admission, warfarin therapy was reinitiated. The following day, the patient experienced right lower extremity pain with signs of distal gangrene, requiring a right leg below-the-knee amputation. No differential diagnosis of the etiology of these thrombotic events was conducted at the time of procedure.

Assessment

Four weeks after initial hospital discharge, the patient presented to the referring hospital with left lower extremity pain, swelling, and distal gangrenous changes. The diagnosis of arterial thromboembolic event secondary to atrial fibrillation was made and subcutaneous enoxaparin, an LMWH, was initiated at a dosage of 1 mg/kg every 12 hours. Within 30 minutes of receiving enoxaparin, the patient developed dyspnea, tachycardia, and flushing; immediate transfer to a reference tertiary care medical center was arranged.

The patient presented with a swollen left leg, shortness of breath, tachycardia, a blood pressure of 140/92 mm Hg, pulse of 125 beats per minute, and a room air pulse oxygen level of 90%. Examination of the leg revealed edema, tenderness, erythema, and gangrenous changes distally with adequate peripheral pulses (Figure 4). Noninvasive studies revealed right superficial femoral vein thrombosis and left iliofemoral vein thrombosis. Furthermore, laboratory studies revealed a platelet count of 75/L, normal prothrombin time and activated partial thromboplastin time, and a creatinine level of 3.2 mg/dL. A laboratory assessment for the presence of heparin-induced antibody SRA tests led to a positive result.

Treatment

Treatment with the direct thrombin inhibitor (DTI) argatroban was initiated, leading to a rapid and dramatic resolution of the thrombosis. A left transmetatarsal amputation was eventually required, but further amputation was found to be unnecessary. Warfarin therapy was reinitiated in overlap with the DTI until the platelet count increased to >120/L.

Key points

An accurate diagnosis of the initial thrombotic event could have prevented a second thrombotic event, and the adverse outcomes associated with the first incident may have been avoided. Multiple thrombotic events are common in patients presenting with HIT. The venous gangrene and skin necrosis

Figure 4 Depiction of the gross morphologic consequences of warfarin-associated gangrene of the left foot. This 68-year-old woman admitted for myocardial infarction and treated subsequently with warfarin for atrial fibrillation developed warfarin-associated gangrenous skin necrosis of the right foot. This unanticipated complication necessitated a right-side below-the-knee amputation.
demonstrated in this case should lead to consideration of HIT diagnosis in patients receiving therapy with warfarin or other heparin therapies. Although LMWH therapy is less likely than heparin therapy to cause an initial case of HIT,4,21 these agents are contraindicated for the treatment of HIT; treatment with an LMWH in this case resulted in a rapid clinical deterioration consistent with an exacerbation of HIT.

Case 2

Background

A 72-year-old woman was admitted for an elective left hip replacement. Unfractionated heparin therapy at a sub-

Figure 5 Phlegmasia cerulea dolens. This total hip replacement patient was treated with postsurgical prophylactic unfractionated heparin (UFH) followed by full-dose UFH after the discovery of a diagnosis of superficial femoral and popliteal vein thrombosis. The patient presented 8 days postsurgery with increasing leg pain. A clinical examination and arteriogram determined a thrombotic occlusion of the right superficial femoral artery. Unsuccessful lytic therapy and surgical intervention led to a left above-the-knee amputation.

cutaneous dosage of 5,000 U tid was initiated after surgery for DVT prophylaxis. Five days after surgery, the patient complained of pain and swelling in her left leg. A compression ultrasound reading demonstrated superficial femoral and popliteal vein thrombosis. Intravenous UFH was initiated at a dose of 15 U/kg per hour without bolus, but no baseline platelet count was recorded before UFH therapy.

Assessment

Eight days postsurgery the patient reported worsening leg pain. Clinical examination revealed a blue, discolored lower extremity with decreased sensation and movement. Popliteal and pedal pulses were absent in the affected limb. A hematology consultation was obtained, which led to the recommendation for transfer to a tertiary care medical center.

Treatment

The patient was transferred with the diagnosis of phlegmasia cerulea dolens (venous gangrene) and possible arterial occlusion (Figure 5). The platelet count at time of transfer was 52/L. A laboratory evaluation for HIT (SRA) was ordered and yielded a positive result. A subsequent arteriogram determined a thrombotic occlusion of the right superficial femoral artery. Unsuccessful lytic therapy and surgical intervention led to a left leg above-the-knee amputation.

Key Points

The development of femoral and popliteal vein thromboses, as well as an arterial occlusion, demonstrates that both arterial and venous thromboses are possible during a single HIT event. The low platelet count assessed on the ninth postoperative day was consistent with HIT. Platelet counts should be routinely assessed during heparin therapy. Recent data do suggest that patients without previous heparin exposure or without exposure within the previous 3 months can be safely assessed for platelet counts on the fifth postoperative day, as this period should be sufficient for detecting HIT in time.11 Acute-onset HIT, however, has been described up to 165 days after previous heparin exposure.10 Patients who have had heparin exposure within the past 3 months are more vulnerable to HIT and should have platelet counts measured consistently from the first postoperative day.11

Current management strategies

The current management of HIT begins with the immediate removal of all sources of heparin. However, cessation of heparin therapy alone is insufficient to reverse the process
of HIT. Platelet activation and the coagulation cascade may continue because heparin cessation also eliminates the classic heparin-antithrombin–mediated inhibition of coagulation. Indeed, the incidence of HIT-related complications remains high, particularly in the first week after stopping heparin. Figure 6 demonstrates the lack of difference in thrombosis rates in a population of patients presenting with isolated thrombocytopenia. Although half of the patients were treated with heparin cessation alone and half were treated with heparin cessation combined with the addition of warfarin, cumulative thrombosis rates remained at 52.8%. Additional pharmacologic therapies must be used in these patients, due to both the lack of efficacy of heparin cessation alone and the prevalence of underlying thrombosis in patients diagnosed with HIT.

Conservative treatment of isolated HIT has been associated with a high rate of subsequent thrombosis; patients presenting with HIT should be treated with early, aggressive therapy. Despite the risks for skin necrosis and DVT progression, warfarin therapy, in some cases, can be safely administered in patients who have, or are at risk of developing, HIT. Srinivasan and coworkers caution, however, that adequate systemic coagulation with a thrombin inhibitor is essential before administering warfarin in any thrombotic process and recommend initiation of therapy at a low dosage (≤5 mg/day) in warfarin-naive patients with HIT.

**Direct thrombin inhibitors**

Appropriate pharmacologic therapy with a DTI such as lepirudin or argatroban is generally safe and effective in reversing the process of HIT and reducing the risk of thrombotic events. Use of lepirudin, however, requires careful monitoring to avoid potential bleeding complications, as approximately 50% of patients with HIT who receive this drug generate antibodies that may enhance its anticoagulant activity. Furthermore, in patients with renal insufficiency, argatroban might be a better therapeutic choice because lepirudin is renally metabolized, whereas argatroban is metabolized by the liver.

Bivalirudin possesses high specificity and potency for thrombin inhibition, antithrombin-independent activity, inhibition of both free and clot-bound thrombin, and lack of platelet activation. Additionally, it is not associated with immune-mediated thrombocytopenia and thrombosis and exhibits no cross-reactivity with HIT antibodies. In a report of a prospective, open-label, single-arm study on the use of percutaneous coronary intervention (PCI) in patients with HIT, Mahaffey and associates found that bivalirudin demonstrated safety and efficacy in patients enrolled at 24 centers in the United States and Germany. Patients were divided into 2 groups and given bivalirudin 5 minutes before PCI. The high-dose group received the drug as a 1 mg/kg bolus, followed by a 2.5 mg/kg per hour infusion for 4 hours; the low-dose group was given a 0.75 mg/kg bolus, followed by a 1.75 mg/kg per hour infusion for 4 hours. There was a 98% rate of procedural success and a 96% rate of clinical success, and no patient had significant thrombocytopenia after treatment. Only 1 major bleeding event was reported; this occurred in a patient receiving high-dose therapy who underwent elective bypass surgery.
The heparinoid danaperoid sodium is also generally safe in patients with HIT, but limitations have been reported. These include in vitro cross-reactivity with HIT antibodies in 10% to 20% of cases; a relatively long half-life (24 hours for anti–factor Xa activity), making monitoring essential during high-dose treatment; and no available antidote. This drug is no longer available in the United States.

Summary

HIT is a serious complication of heparin therapy that can result in significant clinical consequences and possible mortality. Compared with LMWH, UFH is associated with more cases of HIT; however, the onset of the disease due to use of either heparin may cause severe, frequent thrombotic events. The case studies presented illustrate the difficulty in identifying the syndrome and the need for early therapy to prevent limb amputation, skin necrosis, and thrombotic events. DTI therapy can effectively reverse the HIT process and should be initiated early in the identification of the syndrome to prevent significant complications, including the risk of additional thromboses and the possible need for limb amputation due to warfarin-induced skin necrosis and gangrene. DTI therapy should also be used in patients with a history of HIT who require anticoagulation. Prophylactic heparin therapy to reduce the risk of thrombotic events needs to be carefully monitored, and initial patient assessment is important before the initiation of any therapy in order to reduce the risk of HIT and subsequent complications.

References


Endovascular management of acute deep vein thrombosis

Andrew Blum, MD, Erin Roche, MS

Division of Vascular Interventional Radiology, Midwest Heart Specialists, Elmhurst, Illinois, USA; and Riverside, California, USA.

The goals of successful management of deep vein thrombosis (DVT) include relief of acute symptoms with restoration of venous patency, prevention of clot propagation and subsequent pulmonary embolism, and maintenance of venous valvular function. Valvular incompetence is the leading cause of postthrombotic syndrome (PTS), which is characterized by chronic leg heaviness and aching, lower extremity edema, and impaired viability of subcutaneous tissues, which may lead to chronic trophic skin changes and venous ulceration.

Anticoagulation with unfractionated or low-molecular-weight heparin followed by warfarin is recognized as the standard therapy for acute DVT. Although this approach may effectively prevent recurrent thrombosis, it often fails to meet the other treatment goals. Recent studies have demonstrated that early clot lysis through the use of catheter-directed thrombolytic therapy and other adjunctive endovascular techniques rapidly restores venous patency, more effectively preserves valvular function, and improves quality of life. When used in conjunction with anticoagulation, these minimally invasive endovascular techniques have the potential to lead to improved long-term outcomes in patients with DVT.

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KEYWORDS:
Deep vein thrombosis; Low-molecular-weight heparin; Postthrombotic syndrome; Unfractionated heparin

Deep vein thrombosis (DVT) is a common condition, with >250,000 new cases reported annually in the United States. When inadequately treated, DVT may be complicated acutely by the development of pulmonary embolism (PE) and in the long-term by chronic venous insufficiency, also known as postthrombotic syndrome (PTS). As many as 7 million individuals experience complications of severe chronic venous disease, many cases of which are the direct result of previous DVT. The economic impact of complications related to PTS have been estimated to account for as much as 75% of the total care cost of DVT.

Current treatment of deep vein thrombosis

Historically, the standard treatment for DVT has been the administration of anticoagulant drugs to prevent thrombus propagation and embolization. Anticoagulation typically consists of a short course of treatment with intravenous (IV) unfractionated heparin (UFH) followed by a period of 3 to 6 months of oral warfarin. Results from several recent randomized clinical trials demonstrate that outpatient anticoagulant treatment with subcutaneous low-molecular-weight heparin (LMWH) is feasible, and may confer several advantages over inpatient treatment with IV UFH. The potential advantages of LMWH include once- or twice-daily dosing due to its longer half-life and fixed dosages due to a more predictable antithrombotic effect. The use of LMWH therefore eliminates the need for laboratory monitoring, reducing the costs associated with hospital stays in these patients and promoting earlier discharge.

Although anticoagulation is useful in the reduction of recurrent thrombotic events and the prevention of PE, used alone it is rarely able to facilitate clot lysis adequately. Preservation of valve function and prevention of PTS has not been established with UFH use. Anticoagulation regimens, along with their strengths and weaknesses, are further explored by Merli elsewhere in this supplement.
The objective of this article is to review the utility of thrombolytic therapy and other adjunctive endovascular techniques in the setting of more extensive iliofemoral DVT.

Goals of deep vein thrombosis treatment

Without adequate treatment, many patients with DVT experience persistent venous outflow obstruction and valvular incompetence, both of which are known to contribute to the development of PTS. It is estimated that 6 million to 7 million patients in the United States have chronic venous insufficiency as a result of PTS, including about 500,000 who may eventually progress to ulceration. Patients with more extensive DVT involving the proximal segments, including the iliac veins and inferior vena cava (IVC), are more likely to develop PTS.

Successful treatment of DVT and prevention of post-thrombotic complications require realization of the following 5 goals: (1) prevention of clot propagation; (2) prevention of PE and recurrent thrombosis; (3) restoration of venous patency and flow; (4) preservation of valvular function; and (5) elimination of clinical symptoms associated with PTS.

Although studies of new anticoagulation regimens focus on short-term goals, such as prevention of PE, few consider the long-term aim of preservation of valvular function as a significant therapeutic end point. It has been demonstrated that early recanalization of thrombi correlates with prevention of valvular reflux and preservation of valve function. These factors are considered to be highly important in the prevention of PTS and its associated complications, and thrombolytic agents are better able than standard anticoagulation alone to achieve this end point (Table 1).

Catheter-directed thrombolysis and adjunctive endovascular treatment options

Practitioners who manage patients with DVT should be familiar with the various interventional and surgical treatment strategies, which include pharmacologic thrombolysis, percutaneous mechanical thrombectomy, adjunctive stenting, and surgical thrombectomy. The endovascular strategies are often used in combination, allowing for better resolution of venous clot burden than when a single modality is used alone. Results with surgical thrombectomy have improved with the advent of the Fogarty balloon and other refined techniques, yet the procedure has generally fallen out of favor because of the associated operative morbidity. Surgery remains a valid option, however, in the event of impending venous gangrene or failure of endovascular techniques.

Streptokinase, urokinase, and tissue plasminogen activator (t-PA) are the primary thrombolytic agents used in the treatment of DVT. These agents dissolve thrombi by catalyzing the conversion of plasminogen into its active form, plasmin, which in turn breaks down fibrin into soluble byproducts. In a randomized trial that compared thrombolysis and anticoagulation with anticoagulation alone in patients with iliofemoral DVT, thrombolysis was associated with improved patency (72% vs. 12%; *P* < 0.001) and venous valvular competence (89% vs. 59%; *P* = 0.04) at 6 months. Although most studies of venous thrombolysis have used urokinase, more recent data suggest that treatment with tissue t-PA also may be effective.

Although systemic thrombolysis (via a peripheral IV infusion) is more effective than treatment with anticoagulation alone, this method results in significantly less thrombus dissolution in obstructed segments than in partially thrombosed segments (10% vs. 52%). This is likely due to reduced diffusion of these agents into larger venous thrombi under conditions of little or no flow. There is also a greater risk of bleeding associated with systemic thrombolysis than with standard anticoagulation alone. The limitations of systemic thrombolytic therapy have prompted studies of catheter-directed, “local” infusions of thrombolytic agents in order to enhance clot dissolution and minimize bleeding. These interventional techniques offer the advantages of more concentrated delivery of the thrombolytic agent into the clot, with less risk of systemic bleeding. These methods also allow for imaging of the affected veins with the option of adjunctive endovascular techniques such as stent placement to ensure optimal patency and flow.

In 1994, Semb and colleagues reported their initial experience with catheter-directed thrombolysis in 21 patients with iliofemoral DVT. These authors reported a technical and clinical success rate of 85%. Based on these results, the National Venous Thrombosis Registry was initiated, through which 287 patients with large obstructed venous segments (71% with iliofemoral DVT) were recruited from 63 participating centers and observed over a period of 1 year after treatment with catheter-directed urokinase. Complete resolution of thrombus was achieved in 31% of cases, and partial (50%–99%) thrombus resolution was reported in 52%. At 1 year, primary patency was 60%. The study enrolled patients with both acute and chronic forms of DVT, and success rates were considerably higher in the population with acute DVT. Only 6 patients in the study developed PE, and, of those cases, 2 resulted in

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**Table 1** Outcome of anticoagulation versus systemic thrombolytic infusion for acute deep vein thrombosis: results of 13 studies

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>None/Worse (%)</th>
<th>Partial (%)</th>
<th>Significant/Complete (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (254)</td>
<td>82</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Thrombolysis (337)</td>
<td>37</td>
<td>18</td>
<td>45</td>
</tr>
</tbody>
</table>

Adapted with permission from *Semin Vasc Surg*.13

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death. Major bleeding complications were primarily related to catheter-insertion site bleeding, and were noted in 11% of patients.18

In a subsequent study involving a subset of this registry’s patients, Comerota and coworkers19 demonstrated better physical functioning and health-related quality of life (HRQOL) in patients with iliofemoral DVT treated by catheter-directed thrombolysis than in those patients treated with anticoagulation alone. Patients successfully treated with urokinase reported better overall physical functioning (P = 0.046), less health distress (P = 0.022), and fewer incidents of PTS (P = 0.006), compared with patients treated with heparin alone. Patients in the urokinase group who failed to achieve adequate lysis had HRQOL scores similar to those of patients treated with heparin.

Data from the National Venous Thrombosis Registry have established the optimal catheter-directed treatment approach and patient population.18 An antegrade catheter-directed approach using urokinase in patients with acute iliofemoral DVT duration of <10 days and no prior history of DVT leads to the best result, with complete lysis in 65% of those patients.

Analysis of long-term clinical outcome is pending, but early results suggest improved valve function and fewer symptoms at 1 year in patients with complete thrombolysis. These promising data should serve as the basis for future randomized trials of catheter-directed thrombolysis for the treatment of acute DVT.

Recently, the development of percutaneous mechanical thrombectomy devices has added to the interventional armamentarium in the management of DVT. These devices are a natural extension of traditional open surgical techniques. A variety of low-profile mechanical devices are currently in investigational use in this setting. Early results with these devices are promising, with dramatically reduced infusion times and bleeding complications, and may obviate the need for thrombolysis in some circumstances.

Table 2: Contraindications for thrombolytic therapy

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Active or recent internal bleeding</td>
<td>● Recent major surgery/organ biopsy</td>
</tr>
<tr>
<td>● Recent cerebrovascular accident</td>
<td>● CPR</td>
</tr>
<tr>
<td>● Known intracranial neoplasm</td>
<td>● Trauma</td>
</tr>
<tr>
<td>● Recent craniotomy or spinal surgery</td>
<td>● Pregnancy</td>
</tr>
<tr>
<td></td>
<td>● Diabetic hemorrhagic retinopathy</td>
</tr>
<tr>
<td></td>
<td>● Uncontrolled hypertension</td>
</tr>
<tr>
<td></td>
<td>● Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>● Hepatic failure</td>
</tr>
<tr>
<td></td>
<td>● Renal failure</td>
</tr>
</tbody>
</table>

Contraindications for thrombolytic therapy and risk of pulmonary embolism

Primary contraindications for thrombolytic therapy include concomitant medical conditions that increase the risk of bleeding complications, such as recent surgery, stroke, or gastrointestinal bleeding (Table 2). In addition to hemorrhage, potential complications of catheter-directed thrombolysis include migration of the thrombus and subsequent PE. In published thrombolytic series, these complications are rare, and routine prophylactic IVC filter placement has not been necessary during these infusions. The recent introduction of temporary retrievable filters, however, may lower the threshold for placement, as they may be removed following clot dissolution.

In general, patients who might benefit from IVC filters include those for whom anticoagulation therapy is contraindicated, has resulted in complications, or has failed to prevent embolic events. This includes patients at high risk for bleeding, e.g., those with extensive trauma or malignancy and those undergoing certain surgical procedures.4 Under certain circumstances, IVC filter placement and anticoagulation may be used in conjunction. This approach is often used for patients with severe cardiopulmonary disease in whom a recurrent embolic event may otherwise prove to be fatal.

May-Thurner syndrome

Some patients develop DVT for anatomic rather than physiologic reasons. May-Thurner syndrome, most commonly found in young women with DVT, is a condition in which the left common iliac vein is narrowed by extrinsic compression by the overlying right common iliac artery. Intraluminal venous webs may develop as a result. Before the more widespread use of imaging studies, this anomaly often went undetected. Venography following thrombolytic infusion may identify such a culprit lesion, allowing for subsequent endovascular stenting or surgical repair (Figure 1).20

Phlegmasia cerulea dolens

Phlegmasia cerulea dolens (PCD) refers to an ischemic condition caused by massive venous thrombosis that often involves the IVC and extends to the collateral veins and small postcapillary venules. The condition is characterized by massive edema with cyanosis due to arterial stasis and compromise, and it may lead rapidly to acute compartment syndrome and venous gangrene (Figure 2). There are multiple triggering factors, including May-Thurner syndrome, malignancy, and surgery.

The initial treatment for mild PCD should be conservative measures, including steep limb elevation, anticoagulation with IV heparin, and fluid resuscitation.21 Strong con-
sideration should be given to thrombolytic therapy in more advanced cases, with surgical thrombectomy an option if there is no immediate response. Thrombectomy alone cannot open the small venules affected in venous gangrene, and some investigators have used thrombolysis via an intra-arterial infusion as an alternative that delivers the thrombolytic agent to the arterial capillaries and subsequently to the venules.\textsuperscript{13,21} Data from the National Venous Thrombosis Registry has shown that this procedure restored venous outflow and arrested tissue ischemia in a number of patients.\textsuperscript{22}

**Case study**

**History and presentation**

A 75-year-old woman with a confirmed history of DVT and several previous recurrences presented with severe bilateral lower extremity edema and impending PCD or venous gangrene 6 months after IVC filter placement. Venography revealed extensive thrombus within bilateral femoral veins (Figure 3). There was a filling defect and no flow within the IVC filter, which is consistent with caval thrombosis and occlusion at that level (Figure 4).

**Intervention**

Infusion catheters were advanced from both popliteal veins across the thrombosed femoral segments and extended into the occluded IVC filter (Figure 5). A thrombolytic infusion of urokinase was administered via these catheters for a period of 18 hours.

**Figure 1** May-Thurner syndrome (iliac vein compression syndrome).

**Figure 2** Phlegmasia cerulea dolens.

**Figure 3** Thrombosed femoral vein (right side shown).
Clinical response

Follow-up venography after thrombolysis demonstrated clearance of the thrombus and restoration of patency and flow within the filter, IVC, and femoral veins (Figure 6). There was rapid resolution of clinical symptoms.

Summary

Anticoagulation remains the standard treatment regimen in patients with acute DVT. With the advent of LMWH, outpatient treatment is initially more cost-effective. However, in more severe cases with extensive clot, or in the younger, more active patient, the risk of PTS and its complications remains high with anticoagulation alone. In these situations, anticoagulation and thrombolysis are complementary. Catheter-directed thrombolysis, aided by adjunctive endovascu-
lar techniques, followed by outpatient management with anticoagulation is highly recommended in such instances. Placement of temporary or permanent IVC filters before catheter-directed thrombolysis may benefit patients at high risk for PE and is a stand-alone option for those with complications from or contraindications for anticoagulation therapy and thrombolysis. Surgical thrombectomy is reserved for patients who have failed therapy with these less-invasive techniques. With continuing development and a growing body of experience with these new and/or refined methods to treat DVT, the goals of successful management are closer to being met.

References