

# Deep Venous Thrombosis: An Overview

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**D**eep venous thrombosis (DVT) is the third most common cardiovascular disease in the United States, surpassed only by acute myocardial infarction (MI) and stroke. It accounts for more than 250,000 hospital admissions and between 50,000 and 200,000 deaths each year.<sup>1,2</sup> Two-thirds of cases of DVT are first episodes, and the remainder are recurrences.<sup>3</sup> DVT and pulmonary embolism are, in fact, considered 2 spectra of the same disease, namely venous thromboembolism.

With regard to DVT, morbidity and mortality are correlated with the location of the clot. Approximately 25% to 50% of proximal (ie, located at the popliteal vein or above) DVTs cause pulmonary emboli. A distal (ie, located below the popliteal vein) DVT will propagate upward to a proximal location in 20% to 30% of cases. Compared with distal DVTs, proximal DVTs are more likely to be associated with pulmonary embolism, a higher death rate, and a higher rate of postthrombotic syndrome.<sup>4,5</sup>

This article reviews the physiologic mechanisms leading to DVT, as well as the standard ways of diagnosing and treating the disorder. The differential diagnosis of DVT will also be examined.

## **MECHANISMS OF DEEP VENOUS THROMBOSIS**

Virchow's triad of stasis, hypercoagulability, and endothelial damage comprises the major mechanisms leading to formation of DVT.<sup>6</sup> Disorders of stasis occur in patients in the postoperative or perioperative state, especially when orthopaedic procedures are involved, and in patients with debilitating illnesses, such as acute MI, congestive heart failure, or cerebral vascular accident. Hypercoagulability (**Table 1**) can occur secondary to malignancy, nephrotic syndrome, estrogen therapy, pregnancy, or antiphospholipid antibody syndrome. In addition, hypercoagulability can be hereditary, as in primary hypercoagulable states (eg, thrombophilic disorders); the latter may involve factor V Leiden gene mutation (ie, activated protein C resistance), prothrombin gene 20210A mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, and hyperhomocystinemia (a condition that also can be acquired).<sup>7</sup> Leg trauma causing endothelial

damage is the third mechanism predisposing patients to thrombosis. When combined, these mechanisms can greatly enhance the risk for DVT. Examples would include a woman taking oral contraceptives who has the factor V Leiden gene or a patient with a congenital thrombophilic disorder who undergoes a surgical procedure.<sup>8</sup>

Testing for a primary hypercoagulable state should be performed in patients with idiopathic DVT, DVT at an unusual site, or recurrent DVT. Such testing is also appropriate for patients who have a family history of DVT, patients who develop DVT at a young age (< 45 years), and female patients who have experienced recurrent pregnancy loss (in whom antiphospholipid antibody syndrome is a possibility). Results of this testing, however, rarely affect the management of acute thrombosis. Because heparin therapy can lower protein C and S levels, measurement of these levels should be performed after treatment ceases; assessment for factor V Leiden gene mutation, prothrombin gene 20210A mutation, antiphospholipid antibody, and homocystine can be performed during the acute treatment phase.

## **DIAGNOSIS OF DEEP VENOUS THROMBOSIS**

### **Assessment and Differential Diagnosis**

Patients with acute DVT usually present with a red, swollen, painful leg. However, results of physical examination by themselves can be unreliable in diagnosing DVT.

Often, acute DVT is confused with cellulitis; in cases of cellulitis, however, areas of the leg are spared, whereas in cases of acute DVT, the erythema is confluent and no skip areas exist. Moreover, with cellulitis, there is evidence of a port of bacterial entry, as in cases of tinea pedis. Rupture of the medial head of the gastrocnemius muscle, which causes blood to dissect down the fascial plane and collect around the gastrocnemius tendon, also can mimic DVT. A ruptured Baker's cyst

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(causing pseudothrombophlebitis) rounds out the differential diagnosis list for patients with suspected DVT.<sup>9</sup>

### Imaging Studies

**Ultrasonography.** Because clinical findings are not always reliable, objective testing is needed to diagnose acute DVT. Compression ultrasonography has become the diagnostic test of choice. The most accurate diagnostic criterion from ultrasonography is the presence of a noncompressible segment of the common femoral or midpopliteal vein when pressure is applied by the probe.<sup>10,11</sup> Echogenic thrombi may also be detected by compression ultrasonography, but they have a lower sensitivity for diagnosing DVT than does noncompressibility of the veins.

By combining ultrasonography with Doppler techniques (as in a duplex scan), one can detect changes in the venous blood flow pattern; for example, the absence or augmentation of flow after compression suggests DVT. The accuracy of a venous duplex scan for diagnosing acute DVT in symptomatic patients in the iliofemoral to popliteal region is impressive, with an approximately 97% sensitivity and 95% specificity. In contrast, in patients with infrapopliteal (ie, calf) DVT, duplex scan sensitivity is lower (approximately 73%), and as many as 40% of calf studies are inadequate<sup>12</sup>; imaging the calf is also very time consuming. Another advantage of the duplex scan is its ability to identify other causes of swelling (eg, a Baker's cyst, a popliteal artery aneurysm).

Some patients in whom there is a strong suspicion of DVT have negative results on venous duplex scans. Classically, these patients receive serial leg duplex or ultrasound scans. However, Wells and colleagues have proposed a way to eliminate the need for serial testing by using a model of clinical probability (**Table 2**), which assigns points to risk factors for DVT.<sup>13</sup> A score of 0 implies a low probability, a score of 1 to 2 points suggests a moderate probability, and a score of 3 or more indicates a high probability of DVT. If there is a clinical suspicion of DVT but normal results on ultrasonography and a low clinical probability, DVT can be excluded without further testing. However, if the clinical probability is moderate or high, ultrasonography should be repeated in a week.<sup>14</sup>

**D-dimer assay.** D-dimer is released in the blood when clots are formed. Not surprisingly, the D-dimer level is typically elevated in patients with acute DVT. However, this level also is elevated in patients in the postoperative state or with clinical conditions such as disseminated intravascular coagulation, trauma, and malignancy. Consequently, negative results on a D-dimer assay are more significant than positive ones. Negative results on

**Table 1.** Hypercoagulable States Leading to Deep Venous Thrombosis

#### Primary

Factor V Leiden gene mutation  
Prothrombin gene 20210A mutation  
Protein C deficiency  
Protein S deficiency  
Antithrombin III deficiency

#### Secondary

Disorders of stasis (in the postoperative period, from immobilization)  
Malignancy  
Nephrotic syndrome  
Estrogen use or pregnancy

#### Primary or secondary

Antiphospholipid antibody syndrome  
Hyperhomocystinemia

D-dimer testing combined with negative results on leg ultrasonography can eliminate the need for serial leg ultrasonography. There are different assays for measuring the D-dimer level; enzyme-linked immunosorbent assays are generally more sensitive than are latex agglutination assays.

A randomized controlled trial compared the D-dimer assay combined with use of a pretest probability strategy with use of pretest probability alone.<sup>15</sup> In this trial, the pretest probability score was changed to either unlikely (a score  $\leq 1$ ) or likely (a score  $\geq 2$ ). If the DVT pretest probability was unlikely and results of the D-dimer assay were negative, then no leg ultrasonography was considered necessary; however, if the pretest probability was unlikely but results of the D-dimer assay were positive, then leg ultrasonography was obtained. This algorithm eliminated a large number of patients from the total of those actually needing an imaging test. Of course, if the pretest probability score was likely, negative results on a D-dimer assay were not considered sufficient to stop the work-up, and ultrasonography was considered necessary.

**Nuclear imaging with technetium Tc 99m apcitide.** Technetium Tc 99m apcitide is a small, synthetic, 13-amino acid peptide that binds to the glycoprotein 11b/111a receptor. This receptor is expressed only on platelets and is key in mediating the binding of fibrinogen to platelets when platelets are activated during clotting. If technetium Tc 99m apcitide binds to these

**Table 2.** Risk Factors for Determining Pretest Probability of Deep Venous Thrombosis\*

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|--|
| Active cancer  |
| Cast immobilization  |
| Swelling of leg  |
| Pitting edema that is greater in the affected leg                |
| Paralysis  |
| Leg tenderness   |
| Calf swelling (> 3 cm) located 10 cm below the tibial tuberosity |
| Dilated veins  |

Data from Wells et al.<sup>13</sup>

\*The presence of each risk factor equals 1 point; if there is a diagnosis as likely as deep venous thrombosis (eg, muscle tear, hematoma), subtract 2 points.

receptor sites on nuclear scanning, then acute DVT is present.<sup>16</sup> This type of imaging can be used in patients with obesity, in whom ultrasonography is often difficult to perform, and in patients wearing orthopaedic leg casts; it may also have a role in differentiating acute from nonacute DVT in patients with equivocal results on ultrasonography.

## TREATMENT OF DEEP VENOUS THROMBOSIS

### Heparin

When a patient receives a diagnosis of acute DVT or if there is a high clinical suspicion of DVT but a delay in diagnosis, the patient should receive anticoagulation therapy. Classic treatment involves intravenous administration of unfractionated heparin (a bolus followed by an infusion). Although there are various ways of implementing this therapy, an effective method is to use a weight-based regimen, with a bolus of 80 units/kg body weight followed by an infusion of 18 units/kg per hour.<sup>17</sup> The goal is to achieve a therapeutic partial thromboplastin time (ie, 60–85 seconds) within 24 hours.

Since the early 1990s, low-molecular-weight heparin (LMWH) has been used to treat acute DVT. Three early meta-analyses have shown that LMWH decreased symptomatic DVT recurrence, decreased major bleeding, and had a mortality advantage compared with unfractionated heparin.<sup>18–20</sup> More recent meta-analyses have not shown as much superiority of LMWH, but they have shown that LMWH is at least as effective as unfractionated heparin.<sup>21</sup> Moreover, 2 key studies published in late 1995 showed that it was safe to treat acute DVT with LMWH in an outpatient setting.<sup>22,23</sup> This finding had an obvious potential impact on cost, and so on December 31, 1998, the US Food and Drug Administration

approved LMWH for outpatient treatment of DVT.

Advantages of LMWH include its better bioavailability after a subcutaneous injection, its dose-independent clearance, its longer half-life, and its fewer adverse effects (eg, less associated bleeding, less heparin-induced thrombocytopenia). Unlike unfractionated heparin, LMWH does not bind to plasma proteins or vascular endothelium. The more predictable anticoagulant response obviates the frequent laboratory monitoring and subsequent dosage adjustment that are necessary with standard heparin.<sup>24</sup> All patients, however, are not candidates for home therapy; a patient's overall medical and psychosocial condition must be carefully considered when deciding on home treatment.

The LMWH specifically approved for acute DVT treatment is enoxaparin, but there are no clearcut differences between various LMWH preparations. Dosing can be either 1 mg/kg twice daily or 1.5 mg/kg daily; only the former dosage is approved for outpatient treatment.<sup>25</sup> The dosing can, however, be uncertain in very obese patients. Moreover, patients with renal insufficiency and obese patients need to be monitored by obtaining a midinterval anti-factor Xa level (ie, a heparin level), which monitors if the LMWH is in the therapeutic range; such monitoring is not routinely performed in other patients receiving LMWH. Finally, LMWH appears to be safe to use in pregnant patients.

Although LMWH is usually more expensive than is unfractionated heparin, the cost is usually offset by the fewer necessary laboratory tests and lower infusion costs, as well as by a significantly decreased length of hospitalization.

### Thrombolytic Therapy

Catheter-directed thrombolytic therapy can clear thrombi more quickly than can anticoagulant drugs and can decrease the frequency of postthrombotic syndrome.<sup>26,27</sup> However, it is labor intensive. This type of therapy is sometimes used to treat iliofemoral DVT. It can also be used to treat phlegmasia cerulea dolens. The latter condition, also known as *venous gangrene*, occurs when there is iliofemoral thrombosis of all outflow veins and collateral veins in a leg.<sup>28</sup> Blood can be pumped into the leg but cannot be removed from it. Eventually, venous and tissue pressures become greater than arterial pressure, and the patient can develop arterial insufficiency and gangrene. This condition most often occurs in DVT that is secondary to malignancy.

### Inferior Vena Cava Filters

Inferior vena cava (IVC) filters have a role in the treatment of acute DVT. They are primarily used for

patients in whom anticoagulation is contraindicated, complications of anticoagulation occur, or adequate anticoagulation is not achieved. Although IVC filters have been shown to acutely decrease episodes of pulmonary embolism, their overall benefit is lost over the long term because of a higher incidence of recurrent DVT.<sup>29</sup> If an IVC filter is inserted but later it is determined that the patient can be anticoagulated, anticoagulation should proceed.

### Warfarin

Oral anticoagulation with warfarin should be initiated at the same time as therapy with unfractionated heparin or LMWH, provided the patient is hemodynamically stable and there are no contraindications to the drug. Warfarin should be started with a maintenance dose of 5 to 7.5 mg. This dose avoids excessive prolongation of the international normalized ratio (INR) and also avoids a transient hypercoagulable state caused by decreased levels of protein C, a vitamin K-dependent factor with a short half-life.<sup>30,31</sup> There should be an overlap of 5 days between parenteral and oral anticoagulation, even if the INR reaches therapeutic levels earlier; the desired INR is 2 to 3.

Adverse effects of warfarin administration include bleeding, alopecia, and skin necrosis. Concomitant use of acetaminophen while taking warfarin can increase a patient's INR.<sup>32</sup> Moreover, 2% to 3% of persons metabolize warfarin slowly because of a genetic mutation and thus require a very low dose of the drug (< 1.5 mg daily).<sup>33</sup>

### Duration of Anticoagulation

The duration of anticoagulation necessary to treat acute DVT is subject to debate. If the DVT is caused by a transient risk factor (eg, recent surgery, temporary immobilization), then 3 months is adequate. The duration of anticoagulation after idiopathic DVT is less well defined but clearly should be at least 6 months.<sup>34,35</sup> Recently, the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial showed that patients with idiopathic DVT had a lower incidence of recurrence when treated indefinitely with long-term, low-intensity warfarin, aiming for an INR of 1.5 to 2, after their 3 to 12 months of treatment with full-intensity warfarin.<sup>36</sup> Issues determining the length of treatment in such circumstances include the patient's risk for recurrent DVT, the patient's risk for bleeding while taking warfarin, patient preference, quality-of-life issues, and cost.

Certain patients with thrombophilic disorders (eg, antiphospholipid antibody syndrome, protein C deficiency, protein S deficiency, antithrombin III deficiency)

cy) should probably receive life-long anticoagulation. It is unclear how long to anticoagulate patients with more common thrombophilic states, such as presence of the factor V Leiden gene mutation or the prothrombin gene mutation.<sup>37</sup> However, a subgroup of patients with these genetic abnormalities in the PREVENT trial had a low risk for recurrent thromboembolism when treated with long-term, low-intensity anticoagulation with warfarin.<sup>36</sup>

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