Diagnosis And Management Of Deep Venous Thrombosis In The Emergency Department

Abstract

Although the clinical presentations of deep venous thrombosis are notoriously subtle and nonspecific, risk stratification tools such as the Wells clinical model have improved the efficiency of the diagnostic evaluation. The emergency clinician may be guided down several pathways, including D-dimer assays and/or ultrasonography. New oral anticoagulants offer alternatives to the traditional heparins and vitamin K antagonists in the treatment of deep venous thrombosis. This review examines the current literature, evidence, and guidelines in the diagnosis and management of deep venous thrombosis. It also explores some of the controversies and developments regarding risk stratification, including special populations, age-adjusted D-dimer thresholds, isolated distal deep venous thrombosis, upper extremity deep venous thrombosis, outpatient treatment, and the new oral anticoagulants.

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CME Objectives

Upon completion of this article, you should be able to:
1. Risk stratify a patient with suspected first-time DVT for pretest probability of disease.
2. Choose appropriate diagnostic testing for patients with suspected DVT.
3. Describe the anticoagulant regimens used to treat patients with a confirmed diagnosis of DVT.

Prior to beginning this activity, see "Physician CME Information" on the back page.

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Case Presentations

Your first patient of the shift is a 42-year-old woman who details a family history of protein S deficiency and presents with new-onset atraumatic left calf swelling and pain. The proximal compression ultrasound is normal, but your patient is understandably still nervous, and your own suspicion for DVT remains high as well. You wonder about the next best steps to ensure a safe discharge.

As your shift gets progressively busier, your ultrasound technician informs you that he is backed up with studies and will take “a while” before he is caught up again. Unfortunately, your next patient is a 22-year-old otherwise healthy man sent from a clinic to “rule out DVT,” with a handwritten script requesting an ultrasound. The patient reports unilateral left calf pain after starting a new exercise regimen and has no other risk factors or predispositions for DVT. You wonder if you can safely rule out a DVT in this patient with a D-dimer instead of the ultrasound.

In the meantime, a patient whom your colleague had previously signed out to you as admitted for a straightforward, proximal DVT of the left lower extremity now approaches the nurses’ station expressing his frustration about the extended wait for his inpatient bed upstairs. The patient no longer wants to stay and asks why he cannot just follow up with his primary care doctor tomorrow. You wonder if it would be safe to discharge him with an outpatient treatment plan.

Introduction

Deep venous thrombosis (DVT) is commonly diagnosed and managed in the emergency department (ED), accounting for about 1 in 1000 patients per year.\(^1\) In just the past 2 decades, the evaluation and recognition of DVT have significantly advanced from the days of uncertainty about how to address notoriously vague physical signs and symptoms and performing unwieldy venograms. Clinical judgment is supplemented by the use of standardized risk stratification tools, primarily the Wells clinical score, which has undergone several modifications over time. Uncomfortable venograms have been replaced with noninvasive proximal or whole-leg ultrasound. In addition, the use of D-dimer assays to exclude DVT in appropriately risk-stratified patients has increased rapidly, reducing the need for ultrasound in certain patients.

Evidence-based recommendations, including several clinical practice guidelines, help clinicians navigate the expanding array of available diagnostic tools and therapeutic options. On the diagnostic side, ultrasonography is migrating to the bedside and into the hands of emergency clinicians, while newer evidence challenges the upper-limit thresholds of D-dimer interpretation in select populations. On the therapeutic side, updated guidelines now challenge the emergency clinician to consider outpatient management of proximal DVT as well as initial nontreatment of certain types of DVT. Furthermore, the newest oral formulations of anticoagulants offer an enticing glimpse of a possible future without daily injections, dietary restrictions, and frequent international normalized ratio (INR) checks. In short, there is much new ground to cover.

Critical Appraisal Of The Literature

A literature search of PubMed and the Cochrane Database of Systematic Reviews was carried out using combinations of the following key search terms: DVT, D-dimer, Wells score, Wells criteria, venous thromboembolism, proximal ultrasound, whole-leg ultrasound, distal DVT, calf vein DVT, and anticoagulation. Targeted literature searches were also performed for recurrent DVT, pregnancy and DVT, upper extremity DVT, inferior vena cava filter, thrombolysis and DVT, thrombectomy and DVT, and novel oral anticoagulants.

There are several comprehensive evidence-based guidelines on the diagnosis and therapy of acute DVT, most notably the 2012 American College of Chest Physicians (ACCP) ninth edition recommendations for antithrombotic therapy and prevention of thrombosis.\(^1\)\(^-\)\(^4\) Throughout this review, level of evidence and strength of recommendations are ranked as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.\(^5\)\(^,\)\(^6\) Definitions for strength of recommendation and levels of evidence are available at: http://journal.publications.chestnet.org/article.aspx?articleid=1084215. Other available guidelines to consider include the American College of Emergency Physicians (ACEP) clinical policy recommendations for suspected DVT (which have not been revisited since 2003),\(^7\) the 2013 guidelines provided by the Institute for Clinical Systems Improvement regarding venous thromboembolism (VTE) diagnosis and treatment,\(^8\) and the 2013 fifth edition of the International Consensus Statement on Prevention and Treatment of Venous Thromboembolism.\(^2\)

The heterogeneity of various available D-dimer assays and discordant versions of the Wells clinical prediction rule make interpretation of available data challenging. Many diagnostic and therapeutic studies have combined or extrapolated analyses of DVT from pulmonary embolism (PE) cohorts. Special subsets of patients, such as those with recurrent or upper extremity DVT and pregnant patients, are often excluded from larger analyses, so documentation of their experience is much less robust. Finally, randomized controlled trials concerning the emerging novel oral anticoagulants have primarily targeted noninferiority. Post marketing experience and direct comparisons are limited, and recommendations for their use are not formally graded by most existing guidelines.
Pathophysiology And Anatomy

Pathophysiology

Formation of a deep venous thrombus is influenced by the elements of the Virchow triad: venous stasis, vascular endothelial injury, and hypercoagulability. The identified risk factors for DVT affect one or more of the elements of this triad and are classified as either intrinsic or extrinsic, and either provoked or unprovoked. (See Table 1.) Intrinsic causes include inherited thrombophilias, the most common of which (in order of decreasing relative risk [RR]) are antithrombin deficiency, protein C or S deficiency, and factor V Leiden and prothrombin gene mutations. Acquired intrinsic causes include malignancy, advanced age (especially > 75 years), antiphospholipid syndrome, nephrotic syndrome, and obesity. Provoked DVT is precipitated by extrinsic factors, most commonly immobilization of > 48 hours’ duration, recent hospitalization, recent surgery, localized or generalized trauma, pregnancy, oral contraceptives or hormone replacement therapy, air travel (> 8 hours in duration), transient infectious disease, and deterioration of general condition or frailty.

One of the strongest risk factors for development of DVT is a history of prior DVT or PE, although previous undiagnosed or silent VTE may account for unidentifiable risk factors. Many patients will have ≥ 1 intrinsic risk factors with a subsequent acquired or extrinsic risk factor. Recognition of the predisposing conditions helps in the risk stratification of patients with suspected DVT and elucidates the potential etiology in patients with confirmed DVT.

If not appropriately diagnosed and treated, DVT has the potential for significant morbidity and mortality, including development of PE, recurrent DVT, or post-thrombotic syndrome. PE is the most common complication; it is usually caused by lower extremity DVT and it accounts for a 1-month mortality rate of 9.4% from first-time DVT. It is estimated that 40% to 50% of patients with DVT may harbor a silent PE. When it is treated, the mortality from DVT drops to < 6%, although the 2-year mortality from DVT may be as high as 20%. Accurate diagnosis is imperative, as the risk of acute disease must be balanced with the risks of treatment with anticoagulation.

Anatomy

The majority (84%) of patients diagnosed with DVT present with lower extremity thrombosis, with smaller percentages presenting with isolated calf (13%) or upper extremity DVT (16%). Although venous drainage flows only in a proximal direction and anatomic variation is common, it is easier to conceptualize the anatomy of the deep veins in the opposite direction, ie proximally to distally. (See Figure 1, page 4.) The inferior vena cava (IVC) bifurcates into the iliac veins, dividing into internal and external branches. When the external iliac passes underneath the inguinal ligament, it is renamed the common femoral vein. At about 5 to 7 cm inferior to the inguinal ligament, the common femoral vein bifurcates into the femoral vein and the deep femoral vein, which courses to the lateral thigh muscles. The femoral vein (also referred to as the "superficial" femoral vein, which is a misnomer in that it is part of the deep venous system) continues posterior to the femoral artery, coursing inferiorly and medially along the upper thigh before passing through the popliteal fossa to become the popliteal vein. At the popliteal fossa, the popliteal vein lies lateral to the popliteal artery, before coursing more posteriorly as it travels distally. At the level of the popliteal trifurcation, the popliteal vein branches into the deep veins of the calf, with the anterior tibial vein coursing anteromedially, the posterior tibial vein posteri- orly, and the peroneal vein laterally. The muscular veins – including the gastrocnemius and soleus veins – branch off the deep veins of the calf, with some debate as to whether or not they should still be considered part of the deep venous system. In contrast to the deep venous system, the superficial venous system includes the greater saphenous vein, which branches off the femoral vein inferior to the inguinal ligament, and the lesser saphenous vein, which commonly branches off the popliteal vein.

Table 1. Risk Factors For Development Of Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>† Antithrombin deficiency</td>
</tr>
<tr>
<td>† Protein C deficiency</td>
</tr>
<tr>
<td>† Protein S deficiency</td>
</tr>
<tr>
<td>† Factor V Leiden</td>
</tr>
<tr>
<td>† Prothrombin gene mutations</td>
</tr>
<tr>
<td>† Antiphospholipid syndrome</td>
</tr>
<tr>
<td>† Homocysteinuria</td>
</tr>
<tr>
<td>† Nephrotic syndrome</td>
</tr>
<tr>
<td>† Immobilization &gt; 48 hours</td>
</tr>
<tr>
<td>† Recent hospitalization or surgery</td>
</tr>
<tr>
<td>† Malignancy</td>
</tr>
<tr>
<td>† Trauma</td>
</tr>
<tr>
<td>† Pregnancy</td>
</tr>
<tr>
<td>† Exogenous hormone use</td>
</tr>
<tr>
<td>† Deterioration in general condition</td>
</tr>
<tr>
<td>† Prior DVT or VTE</td>
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</tbody>
</table>

Abbreviations: DVT, deep venous thrombosis; VTE, venous thromboembolism.
Differential Diagnosis

The signs and symptoms of DVT overlap with many other conditions. (See Table 2.) Overall, the prevalence of confirmed thrombosis in patients suspected of having DVT is about 19%, with rates ranging from 5% in patients with low probability to 53% in patients with high probability for DVT.20 As such, the majority of patients presenting with signs or symptoms suggestive of DVT will ultimately be diagnosed with alternate conditions. For instance, lower extremity swelling may be caused by pre-existing orthopedic abnormalities or paralysis.21 Table 2 summarizes the findings from a recent outpatient study of 1028 patients suspected of having DVT, only 13.4% of whom were ultimately diagnosed with DVT.22 As many as half of all patients with a history of prior DVT may have persistent pain and swelling in the affected extremity from postthrombotic syndrome, further complicating the clinical evaluation.23

Prehospital Care

There are no published guidelines on prehospital management of DVT. Since the primary acute concern in patients with suspected DVT is progression to PE, emergency medical services personnel should be cognizant of the patient with a swollen painful lower extremity who is or becomes hemodynamically unstable or who develops chest pain, shortness of breath, or other signs of acute cardiopulmonary distress. Management should consist of supportive care and transport to an appropriate facility. The stable patient with suspected DVT may be transported by a basic life support ambulance. If the patient is or becomes unstable and resources are available, transport via an advanced life support provider should be considered.

Emergency Department Evaluation

History And Physical Examination

The textbook presentation of lower extremity DVT consists of unilateral pain, swelling, edema, erythema, warmth, tenderness to palpation along the deep venous system, secondary dilation of superficial collateral veins or a palpable venous cord, and, of course, the classic Homans sign (demonstrated by eliciting of calf pain with passive, abrupt dorsiflexion of the foot). As every practicing emergency clinician knows, however, actual clinical presentations of DVT can be insidiously subtle and nonspecific, obscuring which variables are most helpful in the clinical diagnosis of DVT.

To address this uncertainty, Goodacre et al performed a meta-analysis of over 50 diagnostic cohorts with suspected DVT to evaluate test characteristics of these variables.24 Based on the strongest positive

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Table 2. Differential Diagnosis For Suspected Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strain / tear / hematoma</td>
<td>16.0%</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>13.4%</td>
</tr>
<tr>
<td>Chronic venous insufficiency</td>
<td>12.6%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>10.9%</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>9.4%</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.8%</td>
</tr>
<tr>
<td>Baker (popliteal) cyst</td>
<td>3.9%</td>
</tr>
<tr>
<td>Other</td>
<td>29%</td>
</tr>
</tbody>
</table>

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likelihood ratios (LR+) with 95% confidence intervals (CI), the features that proved independently predictive of DVT included malignancy, history of previous DVT, recent immobilization, difference in calf diameter, and recent surgery. In contrast, Homans sign, calf pain, calf swelling, and obesity did not carry high enough LR+ to serve as reliable indicators of DVT. (See Table 3) No single feature had a low enough negative likelihood ratio (LR-) to reliably exclude DVT, but absence of calf swelling (LR- 0.67; 95% CI, 0.58-0.78) and lack of difference in calf diameter (LR- 0.57; 95% CI, 0.44-0.72) may indicate a slight reduction in the likelihood of DVT.

Not surprisingly, it is more effective to look at a combination of the clinical features, risk factors, and alternate diagnoses than to focus on isolated variables. For instance, a high Wells score incorporating a scripted combination of the above factors (see Table 4) yielded a much more predictive LR+ of 5.2 (95% CI, 4.0-6.0) while a low Wells score rendered the disease less likely, with an LR- of 0.25 (95% CI, 0.21-0.29). When physicians dichotomized their clinical judgment to high versus low, high-probability estimations resulted in an LR+ of 6.2 (95% CI, 1.0-40.0) while low-probability estimations were more fine-tuned at an LR- of 0.18 (95% CI, 0.13-0.26).

When the clinical suspicion for DVT is high, the emergency clinician should simultaneously assess for the complications of DVT. In addition to PE, DVT with massive clot burden can cause a severe form of venous obstruction known as phlegmasia cerulean dolens, which is characterized by sudden-onset swelling, bluish discoloration, and even loss of arterial pulses that can lead to gangrene and loss of the limb. Prompt consultation for thrombolysis or surgical thrombectomy is indicated in this situation. More common is concurrent or long-term postthrombotic syndrome, which affects up to one-half of patients (especially those with recurrent ipsilateral DVT) and causes symptoms of venous insufficiency, persistent pain and swelling, skin discoloration, varicose veins, and, in severe cases, nonhealing lower extremity ulcerations.

### Risk Stratification

Since its inception in 1995, the Wells clinical model has been the most often-cited prediction rule for stratifying pretest probability of suspected first-time lower extremity DVT. Wells et al used signs and symptoms, risk factors, and the potential for alternative diagnoses to prospectively score outpatients referred for suspected DVT as having either low (< 0 points), moderate (1-2 points), or high (≥ 3 points) pretest probability. These risk groups corresponded to a DVT prevalence of 5%, 33%, and 85% on venography, respectively (P < .001), while demonstrating high interobserver reliability (kappa = 0.85) using their original 12-point clinical model.

### Table 3. Diagnostic Value Of Clinical Features Of Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>LR+</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td><strong>Highly Predictive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>2.71</td>
<td>2.16-3.39</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>2.25</td>
<td>1.57-3.23</td>
</tr>
<tr>
<td>Recent immobilization</td>
<td>1.98</td>
<td>1.70-2.30</td>
</tr>
<tr>
<td>Difference in calf diameter</td>
<td>1.80</td>
<td>1.48-2.19</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>1.76</td>
<td>1.40-2.20</td>
</tr>
<tr>
<td><strong>Less Predictive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homans sign</td>
<td>1.40</td>
<td>1.18-1.66</td>
</tr>
<tr>
<td>Calf pain</td>
<td>1.08</td>
<td>0.96-1.20</td>
</tr>
<tr>
<td>Calf swelling</td>
<td>1.45</td>
<td>1.25-1.69</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.85</td>
<td>0.59-1.23</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep venous thrombosis; LR+, positive likelihood ratio; CI, confidence interval.

### Table 4. Wells Clinical Model For Predicting The Pretest Probability Of Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Clinical Character</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within previous 12 wk requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>*Previously documented deep venous thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep venous thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

Three-tiered scoring method: High ≥ 3; moderate = 1 to 2; low < 0. Two-tiered scoring method: Likely > 2; unlikely < 1.

In 1997, using a simplified 9-point version of this model, Wells et al prospectively demonstrated the safety of a more focused application of serial ultrasounds tailored to pretest probability by eliminating the traditional repeat ultrasound at 1-week follow-up in patients with low pretest probability of DVT. Differences in the prevalence of DVT in the low, moderate, and high pretest probability groups were maintained at 3%, 17%, and 75%, respectively (P < .00001), while interobserver reliability between study nurses and physicians remained high (kappa = 0.75). Yet another modification of the Wells clinical model accounts for inclusion of patients with previously documented DVT by adding a point to the clinical score for this history, while also differentiating pretest probability into "likely" versus "unlikely" categories. In this 2003 iteration of the Wells criteria, Wells et al randomized 1096 outpatients with suspected DVT to either initial ultrasound or D-dimer testing, and the results demonstrated a safe reduction in ultrasounds in unlikely patients via the alternative use of D-dimer. Patients who were prospectively scored as clinically likely to have DVT demonstrated a 28% rate of DVT on 3-month follow-up, compared with a 5.5% rate in the clinically unlikely category.

In 2006, Wells et al revisited their earlier 3-tiered clinical model and similarly modified it with the additional point for prior history of DVT. (See Table 4, page 5.) A systematic review of 14 prospective cohorts that included 8239 outpatients with suspected DVT revealed pooled prevalences of 5%, 17%, and 53% for DVT in the low, moderate, and high pretest probability categories, respectively. The 3-tiered stratification of pretest probability forms the suggested basis for tailoring the diagnostic work-up toward a patient with suspected DVT in multiple current guidelines. While available guidelines agree that a negative D-dimer is sufficient initial testing in low pretest probability groups, the ACCP additionally advocates for the use of initial D-dimer testing in moderate pretest probability patients under specific conditions. (See Clinical Pathway for the Diagnostic Evaluation of a Suspected First Lower Extremity DVT, page 14.)

Despite how widely the Wells clinical score is cited in the literature, its comparative performance against clinician gestalt remains unclear. Although dedicated studies are limited, Goodacre et al suggested similar performance between unstructured clinician assessments and standardized Wells scoring. A more recent single-center prospective cohort with a high prevalence of DVT (47%) reported an LR+ of 6.82 for empirical estimation of high probability by vascular specialists versus an LR+ of 2.23 for a likely score via Wells criteria applied by emergency physicians. This suggests that, with the appropriate experience, empirical estimation may be as predictive as, if not more predictive than, Wells scoring. Nonetheless, its explicit standardization and ease of application continue to make the Wells scoring tool ideal for both ongoing research and clinical practice.

Additional research evaluates the interobserver variability of the Wells clinical model, as well as its applicability both to broader and more specific populations. External calculations of interobserver variability using the score have ranged from a kappa of 0.58 between resident and senior vascular medicine specialists to 0.74 between emergency physicians and nurse practitioners using 3-tiered Wells scoring. In 2005, Oudega et al suggested that the Wells criteria may not perform as reliably in the primary care setting, although the earlier version of Wells scoring used in this analysis did not account for prior documented DVT. Subgroup analysis of a combined meta-analysis of 10,002 patients has uncovered additional insights with regard to patients with prior history of DVT and active malignancy. In 941 patients with suspected recurrent DVT, correction from the original Wells criteria to the modified version (by adding a point for prior history of DVT) improved the false-negative rate of DVT from 2.5% (95% CI, 1.2-5.4) to 1.0% (95% CI, 0.6-1.6). However, subgroup analysis of 834 patients with active cancer revealed that the combination of an unlikely score and a negative D-dimer resulted in a higher miss rate of 2.2% (95% CI, 0.5-8.6), suggesting that imaging may have stronger benefit in this subset of patients than risk stratification and laboratory testing alone.

## Diagnostic Studies

### D-dimer

The D-dimer is considered a nonspecific but sensitive biomarker for VTE. Because it may be elevated in a number of nonthrombotic conditions (eg, recent surgery, infection, trauma, malignancy, pregnancy, stroke, and advanced age), D-dimers are more helpful in excluding the diagnosis of VTE with a negative result in the appropriately risk-stratified patient than in confirming VTE when positive.

The various methods of D-dimer testing result in different sensitivities and specificities for VTE that should be viewed as institution-specific, based on the particular type of assay used. Microplate enzyme-linked immunoassays (ELISAs) and newer-generation quantitative latex agglutination (or immunoturbidimetric) assays are considered highly sensitive for DVT (93%-94% sensitive), whereas whole blood D-dimer assays such as SimpliRED are only moderately sensitive (at 83%), although they offer a more rapid turnaround time and demonstrate a higher specificity (approximately 71%).

Given the current state of numerous coexisting D-dimer assays and techniques across laboratories, the astute clinician should be familiar with local
Laboratory practices and maintain awareness of technique-specific units of measurement (e.g., fibrinogen equivalent units [FEU] vs D-dimer units [DDU]) and laboratory-specific variable magnitudes of measurement that are not always easily converted from one to another.\(^{36}\)

Laboratory variability notwithstanding, for the purposes of excluding lower extremity DVT, a negative D-dimer result should be interpreted within the context of the test method’s degree of sensitivity (moderate vs high) and the patient’s clinical pretest probability of DVT.\(^1\) (See Table 3, page 5; and Clinical Pathway For The Diagnostic Evaluation Of A Suspected First Lower Extremity DVT, page 14.) A negative result using a moderate-sensitivity assay may be sufficient to safely rule out DVT without further testing in a patient with low pretest clinical probability; however, a moderate-risk patient would need at least a negative high-sensitivity D-dimer in order to complete the workup without imaging. In patients with moderate to high pretest probability of DVT, a negative D-dimer result, in combination with an initial negative proximal compression ultrasound, may safely eliminate the need for follow-up serial or initial whole-leg ultrasound. There is insufficient evidence to support the safety of using only D-dimer to rule out DVT in high-risk patients. The practice is inefficient (fewer than 15% of high-risk outpatients will yield a negative result\(^{27}\)), and relying on D-dimer results without imaging in high-risk patients is not recommended.\(^1\)

**Adjusted D-dimer Thresholds**

Although D-dimer testing is generally interpreted in a binary manner, using the traditional cut-off (i.e., > 500 mcg/L FEU or < 500 mcg/L FEU) to yield a positive or negative result, more recent studies advocate adjusting the D-dimer threshold in select patient groups to improve specificity without sacrificing sensitivity. Newer literature suggests that future strategies may allow for routine use of higher D-dimer cut-offs in patients with predefined low pretest probability and for elderly patients. Considerations for D-dimer in recurrent DVT, DVT during pregnancy, and upper extremity DVT are discussed in the “Special Populations” section (page 12).

In 2004, a retrospective study demonstrated that D-dimer test specificity could be improved, while maintaining equally high negative predictive values, by using a higher D-dimer cut-off in patients with low pretest probability of DVT.\(^{38}\) A 2013 follow-up prospective randomized multicenter controlled trial stratified and studied the safety of using a higher threshold of < 1 mcg/mL FEU for outpatients with low pretest probability of suspected first-time DVT, compared with the standard threshold of < 0.5 mcg/mL.\(^{37}\) Both testing strategies resulted in similar rates of VTE at 3-month follow-up in patients with low pretest probability (0.0% vs 0.3%), while also reducing the number of ultrasounds in this group at an absolute rate of 21%. The safety of this approach and its ability to decrease the initial number of ultrasounds was also externally validated in a post hoc analysis of a population with a much higher DVT prevalence (22% vs 7%).\(^{39}\)

Because D-dimer levels increase with age, traditional cut-off values have less utility in elderly patients for excluding VTE (e.g., 500 mcg/L FEU).\(^{40,44}\) In response, there has been growing interest in applying age-adjusted cut-offs for patients aged > 50 years, determined by multiplying the patient’s age in years times 10. For example, a patient who is 80 years old would be allowed an age-adjusted cut-off of up to 800 mcg/L FEU.

A 2013 meta-analysis of 12,497 patients using age-adjusted D-dimer cut-offs for suspected VTE (either PE or DVT) demonstrated higher specificities using age-adjusted cut-offs while still maintaining a sensitivity > 97% in all age groups.\(^{42}\) The use of age-adjusted D-dimer cut-offs for DVT was adapted from the use of a retrospectively validated strategy with PEs.\(^{43}\) A DVT-specific meta-analysis combining cohorts with various D-dimer assays and versions of the Wells criteria found a higher exclusion rate of DVT in 1672 patients with nonhigh probability when using an age-adjusted cut-off (51%) versus the exclusion yield with the standard 500 mcg/L FEU cut-off (42%), while still maintaining similar false-negative rates in the age-adjusted (0.8%) and standard (0.7%) groups.\(^{44}\) This has also been retrospectively validated in the primary care and outpatient DVT referral settings in patients with low clinical probability.\(^{45,46}\)

More recently, a prospective validation study of 3346 patients using age-adjusted D-dimer thresholds to exclude suspected PE demonstrated a false-negative rate of 0.3%,\(^{47}\) lending further credibility to the movement toward age-adjusted thresholds. If the DVT evidence continues to mirror the PE trend, a similar prospective validation for DVT can be expected in the near future.

**Imaging Studies**

Although rarely utilized in recent years due to the advances in ultrasonography, contrast venography has, historically, been the gold standard for the diagnosis of lower extremity DVT. After cannulating and injecting radiopaque dye into the distal venous system, the diagnosis is made by visualization of filling defects, abrupt termination of the dye column, nonfilling of the venous system, or diversion of flow.\(^{48}\) Patients with an adequate, negative study demonstrate a 1.3% (95% CI, 0.2-4.4) risk of developing DVT within 3 months.\(^{1,21}\) However, this method has many limitations, including the need for invasive testing, failure to cannulate an appropriate vein in the dorsal foot, inadequate visualization of veins, high interobserver variability of the results, and even postprocedure thrombosis.\(^{21}\) Despite these shortcomings, contrast venography established the < 2% risk threshold standard against which modern forms of diagnostic
Ultrasound

Venous duplex ultrasonography of the proximal deep veins is the most common means of evaluating for the presence of DVT.\textsuperscript{49,50} Duplex ultrasonography combines 2-dimensional grayscale (B-mode) imaging with Doppler color flow or spectral imaging. Imaging of the deep venous system is performed from the proximal common femoral vein through the popliteal trifurcation.\textsuperscript{51} DVT is confirmed by a combination of the following: abnormal venous compression on B-mode ultrasound (normally, the vein should fully collapse with compression); the presence of an echogenic thrombus within the lumen of the vein; abnormal Doppler color flow or visualization of filling defects with color Doppler; or abnormal spectral Doppler flow.\textsuperscript{50,52} (See Figure 2.)

Meta-analysis of duplex ultrasonography compared with venography demonstrates a sensitivity of 96.5% (95% CI, 95.1-97.6) and specificity of 94.0% (95% CI, 92.8-95.1) for diagnosis of proximal DVT by duplex ultrasound.\textsuperscript{50} Limitations of duplex ultrasonography include limited evaluation of DVT proximal to the common femoral vein (ie, iliac veins), inability to visualize the femoral vein within the adductor canal, and, with traditional proximal duplex ultrasonography, nonimaging of the calf veins.\textsuperscript{53} Because the risk of propagation of an undiagnosed distal calf vein thrombus could be as high as 25%, serial ultrasonography at 1 week was traditionally recommended for all patients.\textsuperscript{53,54} However, later literature found only a 1.3% yield of propagation on repeat ultrasound (95% CI, 0.97-1.9).\textsuperscript{55} Utilization of a risk stratification scheme may eliminate the need for the follow-up ultrasound. In a low-risk population (DVT unlikely), Wells et al found that only 1.4% (95% CI, 0.4-3.8) had DVT on follow-up after a single proximal ultrasound, calling into question the need to obtain repeat ultrasounds in patients who are risk stratified with unlikely probability of DVT.\textsuperscript{27,50}

Whole-leg duplex compression ultrasonography can also be performed as an extension of the standard proximal duplex compression ultrasound. Because both the proximal and calf veins are studied with whole-leg ultrasonography, alternative diagnoses (such as superficial thrombophlebitis or musculoskeletal pathology) are more readily recognized and isolated distal calf thrombosis may be revealed. Especially important in an ED population, a negative whole-leg ultrasound may obviate the need for a repeat study in appropriately stratified patients.\textsuperscript{55-57} However, evaluation of the distal veins is significantly less accurate than the proximal veins, with a pooled sensitivity of 63.5% (95% CI, 59.8-67.0) and specificity of 93.8% (95% CI, 93.1-94.4).\textsuperscript{50} Other disadvantages of whole-leg ultrasound include the increased complexity of the examination, increased time to perform the examination, an increase in the proportion of technically inadequate examinations, and the potential for overtreatment of distal calf thrombi that may not pose significant risk for propagation.\textsuperscript{58}

Many studies that compared serial proximal compression ultrasound with whole-leg ultrasound (while withholding anticoagulation after initial negative studies) have demonstrated that both strategies have a similar incidence of VTE on 3-month follow-up (0.9%-2.0% for proximal compression ultrasound vs 1.2% for whole-leg ultrasound).\textsuperscript{57,59} However, whole-leg ultrasound may diagnose more DVT than needs to be treated, with isolated distal DVT accounting for 52.1% of diagnosed DVT in a meta-analysis of whole-leg ultrasonography.\textsuperscript{23,60}

When determining the role of ultrasound in the diagnostic workup, pretest probability for DVT should be risk stratified so that diagnostic testing can be tailored accordingly.\textsuperscript{1,2,8} (See Clini-
Point-Of-Care Emergency Ultrasound

Focused point-of-care ultrasound has become commonplace in the practice of emergency medicine, and examination of the lower extremities for DVT is among the core ultrasound applications for emergency physicians. Unlike a comprehensive duplex compression ultrasound, focused emergency ultrasound consists of a 2-point compression-only examination focusing on the common femoral vein and the popliteal vein. Using a linear 5 to 10 MHz probe, the common femoral vein is compressed serially from proximal to the saphenofemoral junction distally past the confluence of the deep femoral vein and femoral vein. The popliteal vein is then compressed from the popliteal trifurcation proximally. Studies have demonstrated that point-of-care lower extremity ultrasound is fast and accurate, and decreases time to disposition in the ED. A recent meta-analysis of ultrasound performed by emergency physicians demonstrated a pooled sensitivity of 96.1% (95% CI, 90.6-98.5) and specificity of 96.8% (95% CI, 94.6-98.1) in the evaluation of DVT. Potential areas of concern for point-of-care lower extremity ultrasound arise due to the inability to visualize of certain parts of the anatomy, including the femoral vein along the course of the leg, the calf veins, and, more proximally, the iliac veins (where the addition of Doppler findings can help identify thrombi). Also, the compliance rate for recommended 5- to 7-day serial studies can be low in the ED population. The rate at which an isolated DVT in the femoral vein is not visualized in either the common femoral vein or in the popliteal vein in a 2-point compression ultrasound has not been established.

Alternative Imaging Modalities

Computed Tomography Venography

In a meta-analysis, CT venography (which involves helical CT imaging of the lower extremities following venous injection of contrast) demonstrated a pooled sensitivity of 95.9% (95% CI, 93.0-97.8) and specificity of 95.2% (95% CI, 93.6-96.5) for lower extremity DVT. Most of the included studies compared CT venography to compression duplex ultrasonography, reported only proximal DVT, and evaluated for DVT as a part of a PE workup. CT venography has several advantages: it is noninvasive, capable of diagnosing pelvic or iliac vein thrombosis, and it can be performed in conjunction with CT pulmonary angiography to increase the sensitivity of evaluation for VTE. CT venography can also be used to evaluate for DVT in patients with indeterminate or technically inadequate compression duplex ultrasound studies or in cases where performance of a compression duplex ultrasound would be impossible, such as for a patient with an overlying cast. Disadvantages of CT venography include the risks involved with ionizing radiation and intravenous contrast administration, as well as lower sensitivity.

Magnetic Resonance Imaging

MRI also has occasions for use in the diagnosis of DVT. Several different techniques have been documented, including visualization of blood flow without administration of contrast (time-of-flight or phase-contrast venography MRI), MRI with intravenous gadolinium contrast, and magnetic resonance direct thrombus imaging. A meta-analysis of MRI demonstrated a pooled sensitivity of 91.5% (95% CI, 87.5-94.5), with a higher sensitivity for proximal DVT than distal DVT (93.9% vs 62.1%), and a pooled specificity of 94.8% (95% CI, 92.6-96.5). Although it avoids the ionizing radiation of CT venography, MRI is more costly, more time-consuming, and less frequently available. However, it remains an alternative for patients in whom compression duplex ultrasound is nondiagnostic and for whom CT or contrast venography is contraindicated.

Current guidelines recommend against the routine use of CT venography or MRI in patients with suspected first (Grade 1C) or recurrent (Grade 1B) lower extremity DVT. If subtle ultrasound findings or extensive unexplained swelling with high clinical suspicion suggest the presence of an iliac vein DVT, use of CT venography or MRI should be considered (Grade 1C).

Treatment

Treatment for acute DVT is divided into 3 phases: (1) initial (0 to ~7 days), (2) long-term (~7 days to
-3 months), and (3) extended (> ~3 months). Most cases of proximal DVT and some cases of severe or high-risk distal DVT will be treated with anticoagulation in the initial and long-term phases, with adjunct recommendations for early ambulation and compression therapy to prevent or decrease sequelae of postthrombotic syndrome. New oral direct inhibitors, which act on factor Xa (eg, rivaroxaban and apixaban) or thrombin (eg, dabigatran), are added to the array of anticoagulant options, and some offer the advantages of monotherapy and once-daily dosing in the initial phase of anticoagulation. Select patients may require longer durations of therapy in the extended phase of anticoagulation; additionally or alternatively, they may benefit from specialized interventions ranging from IVC filters to thrombolytics or operative thrombectomies. (See Clinical Pathway For Treatment Of Lower Extremity DVT, page 15.)

**Initial Anticoagulation**

Parenteral anticoagulation has long been the mainstay of first-line DVT treatment to prevent extension or recurrence of clots (Grade 1B). Provided there is no renal insufficiency or other contraindications, fixed-dose subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux are preferred (Grades 2B and 2C, respectively) over unfractionated heparin (UFH), offering greater convenience, adaptability to the outpatient setting, and lower potential for heparin-induced thrombocytopenia. Meta-analysis of 23 randomized controlled trials that compared LMWH to UFH for VTE demonstrated a favorable decrease in recurrent VTE (odds ratio [OR], 0.70; 95% CI, 0.57-0.85), major hemorrhage (OR, 0.58; 95% CI, 0.40-0.83), and death (OR, 0.77; 95% CI, 0.63-0.93) with LMWH. Once-per-day dosing of LMWH at the same total daily dose (eg, 2 mg/kg once daily vs 1 mg/kg twice daily) has shown no significant increases in bleeding, extension, or recurrence compared with twice-daily dosing and is the preferred regimen (Grade 2C). Fondaparinux proved noninferior to LMWH in a randomized double-blind trial comparing the 2 regimens. However, there are some caveats: LMWH and fondaparinux will accumulate in patients with renal insufficiency (creatinine clearance < 30 mL/min), and neither has reliable monitoring capabilities or effective reversal agents (although protamine and recombinant factor VIIa may show partial response). Like LMWH and fondaparinux, rivaroxaban and apixaban are, in part, renally excreted.

**Novel Oral Anticoagulants**

The novel oral anticoagulants offer an attractive and potentially game-changing alternative to the more traditional parenteral heparins and oral vitamin K antagonists (VKAs). (For more information on new oral anticoagulants, see the October 2013 issue of Emergency Medicine Practice, available at: www.ebmedicine.net/NOACs) Their use is largely expanded from prior experiences with these medications for postoperative DVT prevention and stroke prevention in atrial fibrillation. Open-label randomized trials of the direct factor Xa inhibitor, rivaroxaban, in 3449 patients with DVT and 4832 patients with PE demonstrated noninferior rates of recurrent VTE and decreased rates of major bleeding (hazard ratio, 0.54; 95% CI, 0.37-0.79; P = .002) in pooled analysis compared with standard LMWH/VKA therapy, and it was the first of the novel oral anticoagulants to obtain Food and Drug Administration (FDA) approval for acute VTE treatment in November 2012. More recently, in August 2014, the FDA approved another factor Xa inhibitor, apixaban (Eliquis®), for initial therapy of acute VTE, following on the heels of its randomized double-blinded trial (N = 5395 patients with combined acute VTE) that demonstrated noninferiority to LMWH/warfarin as well as significantly decreased rates of major bleeding (RR, 0.31; 95% CI, 0.17-0.55; P < .001).

Although the risk of bleeding appears lower, the reversal agents are still in development and the partial reversal efficacy of prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), and recombinant human factor VIIa are being investigated.

Cost-effectiveness calculations appear to favor oral anticoagulants over combination LMWH/VKA therapy after accounting for medication pricing, shorter hospital stays, and costs of medication administration and INR monitoring. Regardless of the type of medication selected, initial therapy should be started immediately and continued for a minimum of 5 days, until maintenance or long-term anticoagulation reaches therapeutic levels (Grade 1B). The ACCP guidelines even suggest considering empirical initial anticoagulation while awaiting confirmatory diagnosis in patients with high clinical suspicion (Grade 2C) or in patients with intermediate clinical suspicion when delays to diagnosis > 4 hours are anticipated (Grade 2C).

**Long-Term Anticoagulation**

Although the long-term (ie, maintenance) phase of anticoagulation therapy through the first 3 months may have previously fallen beyond the scope of ED care, growing prioritization for outpatient treatment of acute DVT – as well as return visits for suspected bleeds – necessitate that the up-to-date emergency clinician be familiar with these regimens as well. Therapeutic options for maintenance therapy range from continuation of LMWH to transitioning to oral VKAs or a new oral direct inhibitor anticoagulant.

In noncancer patients, VKAs have traditionally been the oral maintenance anticoagulation agents of choice.
Nonetheless, they require the ability to establish close INR monitoring and dietary counseling, are notorious for drug–drug interactions, and necessitate initial parenteral therapy to bridge the transition to therapeutic INR levels between 2 and 3. To avoid unnecessary and prolonged hospital stays, guidelines recommend commencing VKA therapy on the first day of diagnosis and continuing parenteral therapy for a minimum of 5 days until the INR is therapeutic for 24 hours (Grade 1B). There is some debate as to the quantity of the initial loading dose (5 mg or 10 mg orally). Oral VKAs have long-standing proven methods of anticoagulation reversal with vitamin K, fresh frozen plasma, and, for life-threatening bleeds, PCC.

Of the new oral anticoagulants, rivaroxaban and apixaban offer the added benefit of monotherapy from the time of initial anticoagulation; they are also associated with a lower risk of bleeding than the standard LMWH/VKA combination. As an alternative, dabigatran, a direct thrombin inhibitor, reflects similar rates of recurrent VTE, major bleeding, and death compared with VKAs, although it requires initial bridging with parenteral anticoagulation. A fourth new oral anticoagulant, the factor Xa inhibitor edoxaban (Savaysa®), is currently under FDA review for long-term therapy following initial parenteral therapy. It also demonstrated noninferiority to VKAs in randomized, double-blind testing (N = 8292) and, additionally, it reflected decreased rates of clinically relevant bleeding (hazard ratio, 0.81; 95% CI, 0.71-0.94; P = .004). However, as previously discussed, unlike VKAs, the new oral anticoagulants currently lack a dedicated reversal agent in the setting of acute bleeding, and their varying rates of renal excretion limit their use in patients with decreased creatinine clearance.

Patients with active cancer carry a higher risk of recurrent VTE, bleeding, and variable responses to traditional VKA therapy. Systematic review of randomized trials has shown LMWH to be superior to VKA therapy in this population, with a 6.7% rate of recurrent VTE in the LMWH arm, compared with 12.9% in the VKA group (RR, 0.53; 95% CI, 0.36-0.76; P = .0007). Subgroup analysis combining the DVT and PE trials for rivaroxaban (n = 597 patients) suggests a net clinical benefit with rivaroxaban (hazard ratio, 0.60; 95% CI, 0.36-0.99) after accounting for trends toward decreased recurrent VTE (hazard ratio, 0.69; 95% CI, 0.36-1.33) and major bleeds (hazard ratio, 0.53; 95% CI, 0.23-1.23), but the overall experience with this new class of medications in this subset of patients is still limited. In the meantime, daily LMWH injections for at least 6 months remain the general first-line recommendation for long-term and extended-term treatment in patients with active cancer.

**Extended Anticoagulation**

For most uncomplicated acute DVT in noncancer patients, 3 months of treatment are recommended (Grade 1B). Extension of therapy beyond this duration, generally using the same anticoagulant agent used for long-term therapy, may depend on presence or absence of provoking factors (eg, recent surgery), known hypercoagulability, prior history of DVT, active malignancy, bleeding risk, and, more recently, the use of D-dimer assays to predict future VTE recurrence. To be fully aware of the risks of bleeding, potential reversal agents (or lack thereof), and treatment alternatives, emergency clinicians should familiarize themselves with both the old and the new anticoagulants.

**Inferior Vena Cava Filters**

An IVC filter is a permanent or retrievable (optional) vascular filter designed to mechanically trap large emboli and prevent massive PE in the approximately 4% of patients with DVT who have contraindications to anticoagulation or who have recurrent PE while they are therapeutically anticoagulated. Placement of an IVC filter might also be appropriate for DVT patients who are pregnant or have cancer. An IVC filter may also be considered prophylactically in high-risk patients with significant trauma or spinal surgery. Current guidelines recommend use of an IVC filter in patients with acute proximal DVT, as well as patients for whom there are contraindications for anticoagulation (Grade 1B). The Society of Interventional Radiology makes further recommendations regarding the choice of retrievable versus permanent filters based on the patient’s expected duration of elevated risk for PE or contraindication for anticoagulation.

No randomized controlled studies compare IVC filter placement to anticoagulation, and no trials compare the various filter designs. The Prevention du Risque d’Embolie Pulmonaire par Interruption Cave (PREPIC) study found that, in comparison with anticoagulation alone, placement of an IVC filter in combination with anticoagulation decreased the rate of PE (15% vs 9%; RR, 0.37; 95% CI, 0.17-0.79), increased the rate of recurrent DVT (RR, 1.52; 95% CI, 1.02-2.27), and had no effect on development of postthrombotic syndrome (RR, 0.87; 95% CI, 0.66-1.13) or death (RR, 0.97; 95% CI, 0.74-1.28). A subsequent Cochrane review (a major component of which was the PREPIC study) reached similar conclusions. Complications of IVC filter placement include DVT, filter migration or embolization, and IVC stenosis or perforation, with complication rates increasing in relation to prolonged duration of the placement procedure. Of course, there is an elevated risk of thrombogenicity with the presence of any intravascular foreign body. Given the risk of DVT, the ACCP guidelines recommend the use of a conventional course of anticoagulant medication for patients in whom an IVC filter has been placed if the risk of bleeding has resolved (Grade 2B).
Thrombolysis And Thrombectomy

Treatment modalities that remove the thrombus have the potential to immediately increase the patency of the vein and decrease the short-term and long-term effects of DVT, including vascular compromise, PE, and postthrombotic syndrome. The available modalities include systemic thrombolysis, catheter-directed thrombolysis, interventional mechanical clot removal, or surgical thrombectomy. Early thrombus removal strategies are preferred in patients with limb-threatening venous ischemia due to iliofemoral DVT (eg. phlegmasia cerulean dolens) (Grade 1A).4,70

Treating lower extremity venous thrombosis with thrombolysis (as opposed to anticoagulation) results in active lysis of the clot, with disadvantages primarily related to the increased risk of bleeding.91 Thrombolysis can be performed using either systemic thrombolytic therapy or localized catheter-directed therapy, with or without mechanical thrombus fragmentation or aspiration (pharmacomechanical thrombolysis). Catheter-directed thrombolysis achieves clot lysis more rapidly and with lower doses of thrombolytic agents than systemic thrombolysis, and pharmacomechanical thrombolysis can, potentially, further shorten the procedure and reduce the necessary dose of thrombolytic medication.4,70

A Cochrane review demonstrated significantly more complete clot lysis with thrombolysis (systemic or localized) than with anticoagulation at follow-up within 1 month (RR, 4.91; 95% CI, 1.66-14.53) and > 6 months (RR, 2.37; 95% CI, 1.48-3.80), as well as decreased rates of postthrombotic syndrome (RR, 0.64; 95% CI, 0.52-0.79). Patients treated with thrombolysis had an increased risk of bleeding (RR, 2.23; 95% CI, 1.41-3.52) but no change in occurrence of PE (RR, 1.00; 95% CI, 0.33-3.05) or recurrent DVT (RR, 1.41; 95% CI, 0.37-5.40). There were also no changes in early mortality within 1 month (RR, 0.76; 95% CI, 0.32-1.89) or intermediate mortality within 6 years (RR, 1.12; 95% CI, 0.319-1.89).91 There is a paucity of studies directly comparing systemic to catheter-directed thrombolysis. In one study, patients treated with catheter-directed thrombolysis had better preserved valvular competence (44% vs 15%; P = .049), less deep venous reflux (44% vs 81%; P = .03), and a trend toward improved venous patency in comparison with patients treated with systemic thrombolysis.92 When comparing catheter-directed thrombolysis to anticoagulation alone and systemic thrombolysis to anticoagulation alone, benefits and risks are similar.91

Current guidelines recommend the use of anticoagulant therapy over both systemic and catheter-directed thrombolysis (Grade 2C) and advise that thrombolysis should be considered only in patients meeting all of the following criteria: iliofemoral DVT, < 14 days since onset of symptoms, good functional status, life expectancy of ≥ 1 year, low risk of bleeding, and no other contraindications to thrombolytic therapy.4

Surgical Management

Historically, prior to development of anticoagulant medications, surgical thrombectomy was the treatment for iliofemoral DVT; now it is reserved for patients who have contraindications to thrombolysis or for whom other treatment modalities have failed.93 Current recommendations (Grade 2C) state that operative thrombectomy should be considered only if all of the following criteria are present: iliofemoral DVT, < 7 days since onset of symptoms, good functional status, life expectancy of ≥ 1 year, and readily available resources and expertise.4,70 Surgical thrombectomy involves a venotomy and removal of the clot. Embolization is prevented by placement of a proximal occluding balloon catheter and the use of positive pressure ventilation to reverse blood flow in the IVC.94 Benefits of surgical thrombectomy for iliofemoral DVT include increased venous patency (75%-80%, compared with 35% for anticoagulation alone), preservation of venous valve competency, and fewer postthrombotic complications.53,94 Risks include blood loss, embolization of thrombus, and development of postprocedure DVT due to endothelial disruption.95 Due to additional postthrombectomy risk of DVT, it is recommended that patients receive anticoagulation postoperatively if there are no contraindications.4

Special Populations

Recurrent Deep Venous Thrombosis

The diagnosis of recurrent DVT is complicated by a number of factors. Although the Wells clinical model was modified to allow for inclusion of patients with prior DVT, many earlier cohort studies excluded patients with a documented history of DVT. Patients with prior DVT are prone to postthrombotic syndrome of the affected leg, which can be difficult to distinguish from a new thrombotic episode. Ultrasoundography may pose technical difficulties in interpretation of chronic versus acute thrombus in an ipsilateral extremity that still bears residual abnormalities, requiring direct comparison with the exact location and venous diameters of prior thrombi during compression.

A handful of studies have evaluated the utility of D-dimer in this more complicated subset of patients. Rathburn et al prospectively evaluated 300 consecutive patients with suspected recurrent DVT, conducting sensitive D-dimer tests on all the patients.95 They found a 0.75% rate of confirmed thromboembolism on 3-month follow-up (95% CI, 0.02-4.09), which increased to 1.5% (95% CI, 0.18-53%) when including an initially indeterminate result in a patient whose repeat acute thrombosis was confirmed just outside the 3-month
window. Bates et al reported a 98% negative predictive value (95% CI, 96-99) for a negative D-dimer result from their prospective multicenter cohort study.\textsuperscript{96}

Noting these diagnostic limitations, coupled with early but promising results from unstratified D-dimer testing, the ACCP guidelines suggest 1 of 3 diagnostic workup options for this population, as appropriate\textsuperscript{1}: (1) a single highly sensitive D-dimer (especially if the prior ultrasound is not available for comparison), followed by a proximal compression ultrasound if the D-dimer is positive; (2) serial proximal compression ultrasounds on day 1 and day 7 (±1); or (3) negative initial proximal compression ultrasound with a concurrent initial D-dimer (of either moderate or high sensitivity), with no need for follow-up testing if the D-dimer is negative. Patients whose ultrasounds are abnormal but equivocal for acute thrombus (particularly if there is no prior ultrasound for direct comparison) are advised to undergo either a more rapid follow-up ultrasound prior to the 1-week ultrasound or a formal venography for confirmation. During serial testing, it is considered safe to withhold anticoagulation.\textsuperscript{1,96}

The next progression in the diagnosis of acute recurrent DVT is to incorporate risk stratification into this diagnostic algorithm. Previously, a small prospective study of 105 patients used the combination of dichotomized, modified Wells scoring and D-dimer testing to evaluate the safety of this management approach. Although the subset of patients unlikely to have DVT with a negative D-dimer accounted for only 15% of evaluated patients in this population with a high (45%) prevalence of DVT, none of these 6 patients had a DVT on 3-month follow-up.\textsuperscript{97} More recently, subgroup analysis of a combined meta-analysis of 10,002 patients with suspected DVT yielded 941 patients with a prior confirmed history of DVT.\textsuperscript{32} Using the original Wells criteria in this subset risked a 2.5% rate of DVT in patients with low pretest probability and a negative D-dimer (95% CI, 1.2-5.4). However, using the modified version of scoring, whereby an additional point is added for previous DVT, the combination of a low-risk score (< 1) with a negative D-dimer resulted in a more acceptable miss rate of 1.0% (95% CI, 0.6-1.6). This suggests that using the modified Wells scoring and a negative D-dimer is likely safer in ruling out recurrent acute DVT than using an unstratified approach. The data are still not as robust as for diagnosis of first-time DVT, and larger prospective validations specific to this population and the use of risk stratification are needed.

Isolated Deep Distal Vein Thrombosis

The clinical significance and treatment of isolated deep distal vein thrombosis (IDDVT) remains controversial. IDDVT can occur anywhere in the distal veins of the calf, including the deep calf veins (peroneal, posterior tibial, and anterior tibial veins) and the muscular veins (soleus and gastrocnemius veins). Together, isolated deep calf vein thrombosis and isolated calf muscle vein thrombosis comprise IDDVT, although there is some debate as to whether or not the calf muscle veins should be considered part of the deep venous system.\textsuperscript{19}

Most DVT starts in the calf; the historic rate of extension to the proximal veins – generally occurring within the first 2 weeks – is up to 25%. Recent studies have documented lower rates of propagation to the proximal veins (8%-16%), with a 1.6% to 3.4% risk of PE.\textsuperscript{19,53,98} In thrombosis isolated to the muscular veins, only 3% propagate to the proximal veins.\textsuperscript{99} Furthermore, up to 90% resolve spontaneously without treatment.\textsuperscript{19,53,98} In a review of studies diagnosing calf vein DVT by either venography or whole-leg ultrasound, the overall prevalence of DVT ranged between 14% and 37%, 23% to 59% of whom were diagnosed with isolated calf DVT.\textsuperscript{19} Patients with isolated calf DVT are more likely to be younger, have transient provoking risk factors (eg, hospitalization, recent surgery, trauma, or travel), and, therefore, have a decreased rate of DVT recurrence, compared with patients who have proximal DVT (2.6% vs 8.4%).\textsuperscript{19,98}

Treatment of isolated distal DVT must balance these lower risks of propagation, embolization, and recurrence with the reduced benefits of treatment and the risks of anticoagulation.\textsuperscript{100} The goal of diagnosis in this population is to identify the subset that would actually benefit from therapy,\textsuperscript{4} in contrast with patients who should be observed via serial ultrasounds for propagation of thrombus to the proximal system. There is a paucity of studies regarding this treatment paradigm. A 2012 meta-analysis identified 8 studies, with a total of 454 patients, and found a decrease in PE (OR, 0.12; 95% CI, 0.02-0.77; P = .03) and thrombus propagation (OR, 0.29; 95% CI, 0.14-0.62; P = .04) with anticoagulation.\textsuperscript{101} A 2012 review also acknowledged the heterogeneity of the literature but noted that unprovoked calf DVT (including a history of malignancy or thrombophilia) has been demonstrated to be more likely to propagate than provoked calf DVT (such as that occurring after trauma or surgery); that there was no benefit to extending anticoagulation from 6 weeks to 12 weeks in low-risk patients with transient risk factors, and that the risk of major bleeding after treatment with anticoagulants ranged from 0% to 6%.\textsuperscript{98}

Current guidelines have mixed recommendations regarding treatment of distal DVT. The International Consensus Statement recommends 3 months of anticoagulation for distal DVT,\textsuperscript{2} while the ACCP guidelines caution that routine treatment of distal calf veins is not warranted, as the risk of bleeding from anticoagulation can outweigh the relatively low risk of propagation or extension into a clinically significant VTE. As such, only serial imaging of the lower extremities for the first 2 weeks is recommended in patients with isolated provoked distal DVT without severe symptoms or risk factors for extension (Grade 2B). Anticoagulation should be reserved only for patients with severe symptoms or
Clinical Pathway For The Diagnostic Evaluation Of A Suspected First Lower Extremity Deep Venous Thrombosis

Suspected first lower extremity DVT

Determine clinical pretest probability (Grade 2B)

Low probability

D-dimer\(^a\)
- Low probability: moderate- or high-sensitivity test
- Moderate probability: high-sensitivity test (Grade 1B)

NEGATIVE

No DVT (Grade 1B)

Was patient previously stratified as low probability?

YES

Treat for DVT (Grade 1B)

NEGATIVE

SERIAL PROXIMAL US\(^b\)
- Moderate probability (Grade 1B-C)
- High probability (Grade 1B)

POSITIVE

Treat for DVT (Grade 1B)

NEGATIVE

No DVT\(^c\) (Grade 1B)

Moderate probability

Proximal US (Grade 1B)

POSITIVE

Treat for DVT (Grade 1B)

NEGATIVE

D-dimer\(^c\)
- Moderate probability: moderate- or high-sensitivity test (Grade 1C)
- High probability: high-sensitivity test (Grade 1B)

POSITIVE

High risk of propagation or severe symptoms? (See "Ultrasound" section, page 8)

NEGATIVE

Serial US (Grade 2C)

Treat for DVT (Grade 2B)

Isolated distal DVT

Whole-leg US\(^d\)
(Grade 1B)

POSITIVE

Treat for DVT (Grade 1B)

NEGATIVE

No DVT\(^d\) (Grade 1B)

High risk of propagation or severe symptoms? (See "Ultrasound" section, page 8)

NO

Proximal DVT

Test for DVT (Grade 1B)

NEGATIVE

Serial US (Grade 2C)

Extensive unexplained swelling in patient with high probability should prompt consideration of isolated iliac DVT.

Abbreviations: DVT, deep venous thrombosis; US, ultrasound.


\(^a\) Preferred initial strategy for patients with low probability (Grade 2B) and for select patients with moderate probability (see "D-dimer" section, page 6).

\(^b\) Whole-leg US may be preferred in patients unable to return for serial testing and for those with severe symptoms or at high risk for propagation of distal DVT.

\(^c\) Alternative acceptable strategy if moderate risk would be to proceed to whole-leg US (Grade 1B).

\(^d\) Extensive unexplained swelling in patient with high probability should prompt consideration of isolated iliac DVT.

\(^e\) Alternative acceptable strategy if moderate risk would be to proceed to whole-leg US (Grade 1B).
Clinical Pathway For Treatment Of Lower Extremity Deep Venous Thrombosis

Treatment indicated for lower extremity DVT

Complicated DVT or contraindications to anticoagulation?

NO

Start initial anticoagulation

- Parenteral: LMWH\(^a\) SC or UFH IV or fondaparinux\(^a\) SC (Grade 1B)
  or
  - NOAC: rivaroxaban PO or apixaban PO (Ungraded\(^b\))

NO

Outpatient treatment appropriate?

- Adequate outpatient follow-up
- Adequate home circumstances
- No significant comorbidities
- Normal renal function

YES

Transition to long-term outpatient anticoagulation (Grade 1B)

- Parenteral bridge (5 days): LMWH or fondaparinux (Grade 1B) and initiation of oral VKA\(^c\) until INR 2-3 (Grade 1B) or dabigatran (Ungraded\(^b\))
  or
  - Continuation of NOAC: rivaroxaban or apixaban (Ungraded\(^b\))
  or
  - Continuation of parenteral therapy in select populations (eg, active cancer) (Grade 2B)

Inpatient treatment

Treatment complications or failure?

YES

Outpatient treatment

- Long-term anticoagulation for a minimum of 3 months (Grade 1B)
- Consideration of extended anticoagulation (>3 months) in select patients (eg, active cancer or second unprovoked DVT) (Grade 1B)
- Adjuvant measures (eg, compression stockings (Grade 2B), early ambulation (Grade 2C))

NO

Other treatments (see text)

- IVC filter (Grade 1B)
- Catheter directed thrombolysis (Grade 2C)
- Systemic thrombolysis (Grade 2C)
- Surgical thrombectomy (Grade 2C)

Abbreviations: ACCP, American College of Chest Physicians; DVT, deep venous thrombosis; INR, international normalized ratio; IV, intravenous; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant; PO, by mouth; SC, subcutaneous; UFH, unfractionated heparin; VKA, vitamin K antagonist.

\(^a\) Preferred initial strategy. (Grade 2C)
\(^b\) No ACCP grade of recommendation available at time of publication of guidelines. Studies have demonstrated noninferiority compared with standard treatment. LMWH (Grade 2C) or VKA antagonist (Grade 2B) suggested over NOAC.
\(^c\) Preferred regimen (Grade 2C).

with risk factors for extension (Grade 2C). These risk factors include positive D-dimer, extensive thrombosis (eg, >5 cm in length, >7 mm maximum diameter, or involving multiple veins), lack of reversible provoking factor, active cancer, history of VTE, and inpatient status. If anticoagulation therapy is chosen, the ACCP guidelines currently recommend the full 3-month duration of therapy for distal DVT; however, as discussed above, shorter durations may be equally effective in select populations.

Deep Venous Thrombosis In Pregnancy

Pregnancy is a known risk factor for VTE and VTE is a leading cause of maternal mortality, yet pregnant patients have routinely been excluded from studies of suspected DVT (including the development of Wells clinical score). Further complicating the presentation, pregnant patients may exhibit very different characteristics from the general population. As pregnancy progresses, patients are more likely to develop leg swelling and discomfort independent of DVT. D-dimer levels also rise with advancing gestational age, prompting proposals to consider validating higher testing thresholds for this population.

In addition, there are anatomic variations in pregnancy-related DVT. More than 80% of pregnancy-related DVT involves the left lower extremity, and 17% is missed by proximal compression ultrasounds. Anticoagulation is chosen, the ACCP guidelines currently recommend the full 3-month duration of therapy for distal DVT; however, as discussed above, shorter durations may be equally effective in select populations.

Use Of Anticoagulant Agents In Pregnancy

Heparins, both unfractionated heparin and LMWH, do not cross the placenta and are considered safe for use in pregnancy, whereas VKAs cross the placenta, are potentially teratogenic, and can cause bleeding in the fetus. Also, during pregnancy, there is a decreased anticoagulant response to unfractionated heparin, as well as the potential for heparin-induced thrombocytopenia. Therefore, according to both the ACCP and ACOG recommendations, the treatment of choice for DVT in pregnancy is LMWH (Grade 1B), with adjustment of dosing to account for the pharmacokinetics of pregnancy.

Anticoagulation should be continued through the first 6 weeks of the postpartum period and for a minimum of 3 months (Grade 2C), although studies supporting this recommendation tend to be retrospective and observational in nature. Use of LMWH is supported over VKAs for treatment of VTE in all trimesters of pregnancy (Grade 1A in first trimester, Grade 1B in second and third trimesters) and during imminent delivery (Grade 1A). There are limited data regarding the use of fondaparinux and no data regarding the use of the novel oral anticoagulants in pregnancy. Based on this evidence, the ACOG and ACCP guidelines recommend limiting the use of fondaparinux to patients with severe reactions to heparin (Grade 2C) and avoiding the use of the novel oral anticoagulants during pregnancy (Grade 1C).

Upper Extremity Deep Venous Thrombosis

Upper extremity DVT tends to have a different etiology, and it is much less common than lower extremity DVT, occurring in 10% to 15% of documented cases.
of VTE, with an incidence of approximately 0.4 to 1 per 10,000 persons per year.\textsuperscript{13,14} Complications from upper extremity DVT are also less frequent, with a lower risk of pulmonary embolism (4%-6% for upper extremity DVT vs 15%-32% for lower extremity DVT), fewer recurrences (2%-5% vs 19%), and lower rates of postthrombotic syndrome (5% vs 29%).\textsuperscript{110,111}

Anatomically, the deep venous system of the upper extremity, from proximal to distal, consists of the subclavian vein, which passes underneath the clavicle and exits the thoracic outlet under the first rib, becoming the axillary vein. The axillary vein then passes underneath the teres major muscle, becoming the brachial vein, which then courses inferiorly alongside the brachial artery and the median nerve medial to the humerus. Numerous anastomoses with the superficial venous system (the basilic and cephalic veins) occur before the veins enter the cubital fossa, becoming the superficial veins of the forearm.

Twenty percent of upper extremity DVT is of primary etiology, such as from venous thoracic outlet obstruction as a result of anatomic abnormalities or effort-induced repetitive microstress of the vessels (Paget-Schroetter syndrome). The remaining 80% has a secondary etiology, such as indwelling catheters or pacemaker wires, surgery, or trauma.\textsuperscript{110} Older age (average age of 38 years for upper extremity DVT vs 49 for lower extremity DVT), obesity, oral contraceptive use, thrombophilia (18% for upper extremity vs 39% for lower extremity), and malignancy are less common etiologies of upper extremity DVT than lower extremity DVT.\textsuperscript{110,111}

Like lower extremity DVT, the presentation of upper extremity DVT can be subtle; pain, swelling, edema, paresthesias, discoloration, and weakness are common signs and symptoms.\textsuperscript{110} However, unlike the well-established diagnostic paradigm for the evaluation of lower extremity DVT, there is a paucity of data regarding the evaluation of upper extremity DVT.\textsuperscript{11}

With ultrasonography emerging as the preferred imaging test,\textsuperscript{110} meta-analysis has demonstrated an overall sensitivity of 97% (95% CI, 90-100) and specificity of 96% (95% CI, 87-100), with no improvement in accuracy upon adding color Doppler.\textsuperscript{112} Compression ultrasonography is limited by the inability to visualize or compress the proximal central deep veins due to the overlying bony structures.\textsuperscript{110}

**Risk Stratification**

A 2008 study developed and validated a clinical prediction score for upper extremity DVT.\textsuperscript{113} The score adds 1 point each for pain, edema, and the presence of foreign venous material (eg, catheter or pacemaker), and subtracts 1 point if an alternative diagnosis is more likely. A score of 0 or -1 is considered low risk, although upper extremity DVT may be diagnosed in 13% of patients. A score of 1 is considered intermediate risk, with a 38% prevalence of upper extremity DVT, while a score of > 2 is considered high risk, with a 69% prevalence of upper extremity DVT in the validation study.\textsuperscript{113} The use of D-dimer testing has not been well studied in the evaluation of upper extremity DVT, although one study of 52 patients reported a sensitivity of 100% (95% CI, 78-100) and specificity of 14% (95% CI, 4-29).\textsuperscript{114} CT venography and MRI have not been well studied in the evaluation of upper extremity DVT, but may have a role in the diagnosis of the proximal upper extremity deep veins that are not amenable to compression ultrasonography.\textsuperscript{1,115}

**Diagnosis**

The current ACCP guidelines recommend initial evaluation for upper extremity DVT with compression duplex ultrasonography (Grade 2C) followed by testing with a moderate or highly sensitive D-dimer; serial ultrasound; or imaging with venography, CT, or MRI if there is a high clinical suspicion and the initial ultrasound is negative (Grade 2C). Upper extremity DVT can be excluded in patients with a negative compression duplex ultrasound and subsequent negative D-dimer, CT, MRI, or venography (Grade 1C). Patients in whom the initial compression duplex ultrasound was negative, with a subsequent positive D-dimer, and those with a suboptimal compression duplex ultrasound should undergo venography (Grade 2B), unless there is a compelling alternative diagnosis (Grade 2C).

A multicenter trial of 406 patients suspected of having upper extremity DVT validated the use of a diagnostic algorithm consisting of sequential application of clinical risk stratification, D-dimer testing, and compression ultrasonography. Using the clinical decision rule derived and validated by Constans,\textsuperscript{113} patients were stratified as either unlikely (score of ≤ 1) or likely (score of ≥ 2) to have upper extremity DVT. Patients unlikely to have DVT underwent initial testing with D-dimer, did not undergo further testing if the test was negative, and proved a 0% rate of upper extremity DVT on 3-month follow-up (95% CI, 0.0-4.2). Patients who were likely to have lower extremity DVT underwent compression ultrasonography, followed by combination with D-dimer testing if the ultrasound was negative. The combination of a negative ultrasound and negative D-dimer resulted in a 1.2% rate of upper extremity DVT at 3 months (95% CI, 0.0-6.5). The authors concluded that this diagnostic paradigm was safe and effective in excluding upper extremity DVT with an overall miss rate of 0.4% (95% CI, 0.0-2.2).\textsuperscript{116}

**Treatment**

Since the goals of upper extremity DVT treatment are the same as for lower extremity DVT – namely, prevention of DVT propagation, PE, and recurrence, as well as prevention of postthrombotic syndrome – the treatment strategies have largely been extrapolated from those for lower extremity disease. Strategies include anticoagulation, thrombolysis, surgical thrombectomy, superior vena cava filter placement, and removal of any indwelling venous catheters.\textsuperscript{110}
The current ACCP guidelines recommend initiation of anticoagulation (Grade 1B) and continuation of anticoagulation for at least 3 months (Grade 2B). LMWH is preferred over UFH (Grade 2C). Data from 4 observational studies with a total of 209 patients demonstrate a 1.9% rate of recurrence after treatment, with no cases of PE. Indwelling venous catheters should not be removed as long as the need for them persists and the catheters remain functional (Grade 2C); however, anticoagulation should be continued for as long as the catheter remains in place (Grade 2C). In a study of 74 patients with catheter-related upper extremity DVT treated with LMWH (dalteparin), no patients had catheter failure or extension of DVT resulting from leaving the catheter in place. Catheter-directed or systemic thrombolysis may be performed for patients with severely symptomatic massive upper extremity DVT and a low risk of bleeding (Grade 2C), but anticoagulation is preferred over thrombolysis (Grade 2C). Catheter-directed or surgical interventions should be reserved for patients with persistent symptoms and failure of anticoagulation or thrombolysis. Patients found to have venous thoracic outlet obstruction may need to undergo surgical decompression, which, generally, has good outcomes.

### Controversies And Cutting Edge

As discussed throughout this review, new strategies in the management of DVT are numerous, with still more anticipated in the near future.

The Wells clinical score has undergone several rounds of modifications over the years, improving its ease of use and expanding its applicability to patients with prior DVT, although perhaps it still requires further modification in the setting of active malignancy. Despite its standardized scoring rubric, its interobserver variability is less consistent in external studies and it may not necessarily improve upon clinical gestalt for more experienced providers. In the laboratory, higher D-dimer thresholds are being tested in select populations, including the

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**Risk Management Pitfalls For Deep Venous Thrombosis**

(Continued on page 19)

1. **“The patient was high-risk, but had a negative D-dimer.”** Sole use of D-dimer tests in high-risk patients is not recommended, as there is insufficient evidence supporting their safety when they are not used in combination with ultrasonography. The majority of high-risk patients may have a positive D-dimer for alternative reasons, so starting with this test is also generally low-yield.

2. **“Radiology confirmed DVT of the calf, so I anticoagulated as I normally do.”** For routine, provoked, isolated distal DVT without severe symptoms or risk factors, the risk of bleeding posed by anticoagulation treatment likely outweighs the risk of propagation of distal thrombi into the proximal venous system. Thus, current ACCP guidelines recommend serial ultrasounds instead of routine anticoagulation in uncomplicated distal DVT. However, this decision may be discussed with patients to determine their degree of comfort with this plan.

3. **“Although cancer is a risk factor for DVT, his Wells clinical score identified him as unlikely to have DVT and he had a negative D-dimer.”** Based on subgroup analysis of patients with active cancer, an unlikely Wells clinical score and negative D-dimer resulted in a > 2% risk of acute DVT. Thus, the combination does not appear to be safe for use in this particular subset of patients who harbor a higher risk for DVT.

4. **“I told the patient to follow up for a repeat ultrasound, but he took a long flight the following day anyway. What else could I have done?”** After a negative proximal ultrasound, a patient with moderate to high pretest probability of disease still needs additional testing to safely rule out DVT. While this has traditionally taken the form of a serial ultrasound at 1 week, if the patient is unable or unwilling to follow up, a negative concurrent D-dimer test on the initial ED visit or a negative whole-leg ultrasound may obviate the need for follow-up testing. Alternatively, a discussion with the patient about the potential benefit versus harm of empiric anticoagulation could be considered, given his impending travel.

5. **“The patient did not want to be admitted and was afraid of needles for self-injecting LMWH, so I decided to try a new oral anticoagulant as an outpatient regimen.”** Not all of the new oral anticoagulants are suitable for both initial and long-term anticoagulation in the treatment of acute DVT. Dabigatran, for instance, currently requires a parenteral bridge during the initial anticoagulation period. In addition to ensuring normal creatinine clearance and close outpatient follow-up, the emergency clinician should advise the patient as to the uncertainties of reversing anticoagulation in the setting of acute bleeding.
low-risk group and the elderly. The use of D-dimers in the workup for suspected DVT that is recurrent, occurs during pregnancy, or affects the upper extremities is actively debated, with new clinical prediction rules being tested and validated in these special populations.

The use of ultrasonography has become commonplace under the weakly supported recommendation that all patients require serial proximal ultrasounds to exclude propagation of potentially undiagnosed distal DVT. However, patients at low risk for DVT likely do not require serial imaging, nor do all patients ultimately require imaging of the whole leg. Controversy still surrounds the definition, significance, risk of extension, treatment, and even the need to diagnose isolated distal DVT. Selective serial observation may be superior to routine treatment of isolated distal DVT, and shorter courses of anticoagulation may be as effective as standard therapy.

Current recommendations now advocate for outpatient management of acute proximal DVT, when possible. Although there is uncertainty regarding the reversal strategy for the new oral anticoagulants, they appear to pose a lower risk of bleeding than the standard LMWH/VKA combination therapy. As experience with these medications grows, a more comprehensive incorporation of the new oral anticoagulants into treatment guidelines for DVT can be anticipated in the coming years.

### Disposition

Admission for parenteral anticoagulation was previously the expected disposition for most patients newly diagnosed with acute DVT, but newer guidelines open the doors—and, in fact, show preference—for outpatient treatment, when possible (Grade 1B). Assuming the patient has normal renal function, the appropriateness of an outpatient strategy is strongly dependent on the patient’s reliability for follow-up and associated social factors, including potential ability to either learn how to self-inject LMWH or to arrange for services to administer these medications and to conduct laboratory testing.

The evidence behind the safety of outpatient

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**Risk Management Pitfalls For Deep Venous Thrombosis**

(Continued from page 18)

6. **“The ultrasound was negative. How was I supposed to know the patient still needed another ultrasound a week later?”**

   A single initial proximal ultrasound in a patient with moderate to high pretest probability of DVT does not rule out the possibility of distal thrombosis in the calf veins. Particularly in the first 2 weeks, distal DVT may carry up to a 25% risk of propagation to the proximal venous system where it becomes more clinically significant and poses the threat of PE.

7. **“The patient had a prior DVT but was still low-risk and had a negative D-dimer. I didn’t know there were multiple versions of the Wells clinical score.”**

   Be sure to add an additional point to the Wells clinical score for history of previous DVT, as the earlier versions excluded patients with suspected recurrent DVT. Without this modification, an unlikely score with a negative D-dimer can still result in > 2% risk of acute DVT.

8. **“The patient had cancer and did not want to be admitted, so I offered LMWH and an oral VKA as an outpatient regimen.”**

   Patients with cancer do not respond as well to oral VKA therapy, which results in higher rates of recurrent VTE compared with LMWH. First-line recommended therapy for cancer patients with acute DVT consists of daily LMWH injections for a minimum of 6 months.

9. **“The D-dimer was negative, though I don’t know what kind of test my hospital uses.”**

   Knowing the sensitivity of the D-dimer test used in one’s institution allows for better interpretation of the result within the context of a patient’s pretest probability of DVT. Some laboratories still use semiquantitative tests, which are faster and more specific, but they perform at a lower sensitivity. While a patient with low pretest probability for DVT can be ruled out with a D-dimer of either moderate or high sensitivity, only a highly sensitive test is sufficient to rule out DVT in a patient with moderate pretest probability of DVT without the use of imaging.

10. **“I had high suspicion, but the patient had 2 negative serial compression ultrasounds, so I assumed the workup was complete.”**

   A patient with high pretest probability of DVT and negative serial ultrasounds may still need to undergo imaging of the pelvic veins, especially if the swelling is extensive and includes the thigh and buttocks. Of note, pregnant patients with DVT have a higher prevalence (17%) of isolated iliac vein thrombosis.
treatment is derived from systematic reviews of studies that randomized patients to either home treatment (with LMWH) or inpatient treatment (with either LMWH or UFH). Patients treated at home had a lower recurrence of VTE (RR, 0.61; 95% CI, 0.42-0.90) and trended toward lower mortality (RR, 0.72; 95% CI, 0.45-1.15) and fewer major bleeds (RR, 0.67-1.36). Significant limitations to these studies, however, include high rates of exclusion as well as the fact that the majority of inpatients were treated with UFH. Only 1 small study (N = 201) used LMWH in its inpatient arm, reporting no increase in combined rates of VTE, PE, or major bleeding (3% vs 3.9%), while effectively halving the overall costs from an economic standpoint. Although the quality of evidence is only moderate, the estimated savings of $500 to $2500 per patient are attractive enough, in the absence of evidence of increased complications, to warrant a strong recommendation from the ACCP for outpatient treatment. Deliberation of disposition options should, of course, incorporate individual patient preferences.

If the patient’s home conditions and likelihood of reliable follow-up are inadequate or the patient’s renal function is limited, inpatient admission is indicated for treatment of DVT. Patients with inadequate creatinine clearance or a higher risk of bleeding, or patients scheduled for procedures that could require rapid reversal of anticoagulation, usually benefit from parenteral UFH, rather than LMWH. Complicated DVT may require alternatives to standard anticoagulation, such as IVC filters, or intravenous direct thrombin inhibitors in the case of heparin-induced thrombocytopenia. Extensive clot burden may, rarely, precipitate phlegmasia cerulean dolens, which can require immediate operative thrombectomy or thrombolysis.

### Summary

DVT is a common disease with potential for mortality from PE and morbidity ranging from the common postthrombotic syndrome to rare loss of limb. Although the clinical signs and symptoms of DVT can be subtle, the diagnostic evaluation can benefit from risk stratification of pretest probability, followed by a systematic workup that includes ultrasonography and/or D-dimer testing. If there are no contraindications, treatment of confirmed DVT consists of a combination of initial and long-term therapy for anticoagulation, the options for which include UFH, LMWH, VKAs, and, more recently, the novel oral anticoagulant agents. Future developments in the management of this disease include fine-tuning risk stratification, particularly for certain subsets of patients (ie, those with active cancer and pregnant patients) and, pending postmarketing data and availability of a reversal strategy, identification of patients who can benefit from the new oral anticoagulants as the treatment of DVT increasingly shifts to the outpatient setting.

### Case Conclusions

For the 42-year-old woman with a family history of protein S deficiency, you initially recommended a repeat serial ultrasound at 1 week to rule out the possibility of distal clots that could migrate proximally. Because her symptoms were mild, there was likely no need for interim anticoagulation between studies. However, the patient remained anxious, so you offered the possibility of a same-day D-dimer test instead. The test came back negative and she was reassured to follow up with her primary care doctor.

You decided to order a D-dimer test on the 22-year-old man sent from the clinic. Although you knew that your lab used SimpliRED®, you risk stratified the patient into the low pretest probability group using the Wells clinical score and were relieved to know that a single negative test result – even if only moderately sensitive – is sufficient to rule out DVT in an otherwise healthy patient.

After carefully analyzing the risks and benefits of the available treatment options and ensuring that your third, previously admitted patient had a normal creatinine clearance, you were able to arrange for the nurse to teach him to self-inject LMWH at home. You gave him a prescription for 5 days’ worth of LMWH and started him on warfarin 10 mg for that night and the next day. You also counseled him on dietary constraints while taking VKAs, provided strict instructions to follow up with his primary care doctor for further monitoring and INR checks, and specified clear return precautions.

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**Cost-Effective Strategies**

- Not every patient needs an ultrasound on initial diagnostic workup. Risk stratification and a D-dimer can preclude the need for ultrasound in low-risk patients, and, if the D-dimer is highly sensitive, in moderate-risk patients without active cancer.
- Point-of-care, focused emergency ultrasound is accurate in diagnosing proximal lower extremity DVT and decreases length of stay in the ED.
- Not every patient needs a repeat proximal ultrasound. Risk stratification into the low pretest probability group can obviate the need for further testing. For patients identified as having moderate to high pretest probability, a repeat ultrasound may be avoided if a concurrent D-dimer on the initial visit is negative or if a whole-leg (instead of a proximal ultrasound) is performed and results are negative.
- Consider outpatient treatment of acute DVT if the patient has good follow-up, an adequate home situation, and normal renal function.
References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


30. Dewar C, Corretge M. Interrater reliability of the Wells score as part of the assessment of DVT in the emergency depart-
ment: agreement between consultant and nurse practitioner. 


Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. 


BMJ. 2014;348:g1340. (Meta-analysis; 10,002 patients) 33.


Bockenstedt P. D-dimer in venous thromboembolism. 


Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. 


Linkins LA, Bates SM, Ginsberg JS, et al. Use of different D-dimer levels to exclude venous thromboembolism depending on clinical pretest probability. 


J Thromb Haemost. 2007;5(9):1869-1877. (Post hoc analysis of prospective trials; 1721 patients) 42.

Schouten HJ, Geersing GJ, Koek HL, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. 

BMJ. 2013;346:f2492. (Meta-analysis; 12,497 patients) 43.


BMJ. 2010;340:c1475. (Retrospective; 5132 patients) 44.

Dowma RA, Tan M, Schutgens RE, et al. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. 

Haematologica. 2012;97(10):1507-1513. (Retrospective; 2818 patients) 45.


BMJ. 2012;344:e2985. (Retrospective; 1374 patients) 46.

Hamblin AD, Cairns K, Keeling DM. The use of age-dependent D-dimer cut-off values to exclude deep vein thrombosis. 

Reply to “Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded”. 

Haematologica. 2012;97(10):1507-1513. (Retrospective; 6599 patients) 47.


Archives of Surgery. 1972;104(2):134-144. (Review) 49.


McMaster Diagnostic Imaging Practice Guidelines Initiative. 


American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of peripheral venous ultrasound examinations. 


Kearon C. Natural history of venous thromboembolism. 


Kearon C, Julian JA, Becker DM. Calf deep venous thrombosis. A wolf in sheep’s clothing? 


Thromb Haemost. 2003;89(2):221-227. (Prospective cohort study, 623 patients) 56.


Thromb Haemost. 2003;89(2):228-234. (Prospective observational cohort study; 1646 patients) 57.


Br J Haematol. 2011;146(3):422-430. (Prospective observational cohort study; 212 patients) 59.

Bernardi E, Camporese G, Buller HR, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. 

JAMA. 2008;300(14):1653-1659. (Randomized controlled trial, 2465 patients) 60.


2379 patients)
68. Goodman LR, Stein PD, Matta F, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. *AJR Am J Roentgenol.* 2007;189(5):1071-1076. (Prospective randomized controlled study; 711 patients)
CME Questions

1. Which of the following veins is part of the superficial venous system, rather than the deep venous system?
   a. Superficial femoral vein
   b. Greater saphenous vein
   c. Anterior tibial vein
   d. Peroneal vein

2. Which of the following features most increases the likelihood of having an acute DVT?
   a. Homans sign
   b. Calf swelling
   c. High Wells score
   d. History of malignancy

3. Which of the following risk factors was a later addition to the original Wells clinical score?
   a. Active malignancy
   b. Prior history of DVT
   c. Age > 75 years
   d. Alternate diagnosis at least as likely as DVT

4. In addition to the popliteal vein, which of the following veins is evaluated during focused point-of-care emergency ultrasound evaluation for DVT?
   a. Posterior tibial vein
   b. External iliac vein
   c. Common femoral vein
   d. Saphenous vein

5. Which of the following anticoagulants is safe to give to a patient with renal insufficiency?
   a. UFH
   b. Warfarin
   c. LMWH
   d. Dabigatran
   e. A and B

6. Which of the following anticoagulants has proven methods of reversal?
   a. Warfarin
   b. LMWH
   c. Fondaparinux
   d. Rivaroxaban

7. Which of the following anticoagulants is considered first-line long-term therapy for patients with active cancer?
   a. UFH
   b. LMWH
   c. Fondaparinux
   d. Oral VKA

8. In a patient with low pretest probability of DVT, which of the following is NOT an appropriate initial diagnostic test?
   a. Moderate-sensitivity D-dimer
   b. High-sensitivity D-dimer
   c. Proximal compression ultrasound
   d. Whole-leg ultrasound

9. In a patient with moderate pretest probability of DVT, which of the following is NOT an appropriate initial diagnostic test?
   a. Moderate-sensitivity D-dimer
   b. High-sensitivity D-dimer
   c. Proximal compression ultrasound
   d. Whole-leg ultrasound

10. In a patient with high pretest probability of DVT, which of the following is appropriate as an initial diagnostic test?
    a. High-sensitivity D-dimer
    b. Proximal compression ultrasound
    c. Whole-leg ultrasound
    d. B or C
    e. A, B, or C
Emergency Department Management Of The Alcohol Withdrawal Syndrome

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Alcoholism is a prevalent medical and psychiatric disease and, consequently, alcohol withdrawal syndrome is encountered frequently in emergency departments. Uncomplicated alcohol withdrawal, or alcohol withdrawal tremor, is the most common and least severe manifestation of alcohol withdrawal syndrome; it can commonly be managed on an outpatient basis with oral benzodiazepines. Alcohol withdrawal seizure and alcoholic hallucinosis are the first manifestations of so-called complicated alcohol withdrawal. They generally signify the need for inpatient alcohol detoxification and, often, the use of intravenous benzodiazepines. Delirium tremens is the most severe and life-threatening form of alcohol withdrawal. The key diagnostic criteria for delirium tremens are an alteration in awareness or attention (delirium) and tremor. Patients commonly manifest hyperadrenergic signs and symptoms that necessitate intensive care unit admission, intravenous benzodiazepines, and, frequently, adjunctive pharmacotherapy. An aggressive front-loading approach with benzodiazepines is proposed and the management of benzodiazepine-resistant disease is addressed.

Evaluation Of Potential Upper Gastrointestinal Bleeding In The Emergency Department

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Upper gastrointestinal bleeding in the emergency department can occur from a wide variety of conditions with a similarly wide range of disease severity. While the initial evaluation and stabilization is standard for nearly all causes of bleeding, beyond these initial steps, it is crucial to distinguish between bleeding from a variceal or nonvariceal source. Treatments such as antibiotics and somatostatin analogues may benefit patients with variceal bleeding, while therapies such as proton pump inhibitors have limited utility in this subset of patients but may benefit those bleeding from nonvariceal sources. Patients with ongoing bleeding and hemodynamic instability may benefit from emergent endoscopy. There are several risk stratification scoring systems for patients with upper gastrointestinal bleeding; however, to date, there is limited evidence to identify low-risk patients who are suitable candidates for outpatient treatment.
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