

in the clinic

Deep Venous Thrombosis

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Venous thromboembolism (VTE) is a relatively common and potentially life-threatening condition that affects approximately 100 persons per 100 000 per year in the United States (1). About one third of patients with VTE present with features of pulmonary embolism (PE), and two thirds present with features of deep venous thrombosis (DVT). Treated DVT has an excellent prognosis. The probability of fatal PE is 0.4% and the probability of nonfatal thromboembolism is 3.8% over a 3- to 6-month treatment period (2).

Prevention

What factors increase the risk for DVT?

The main risk factors for VTE are recent surgery (especially major general surgery, hip or knee replacement, or knee arthroscopy), trauma (especially major trauma, spinal injury, or fracture of the hip or leg), congestive heart or respiratory failure, a malignant condition, pregnancy, hormone replacement or oral contraceptive therapy, previous VTE, hereditary thrombophilia, increasing age, and immobility (3).

Hospitalization is independently associated with an 8-fold increase in the relative risk for VTE (4). Among surgical patients, a number of patient-related factors predict the risk for postoperative VTE. These include female sex, higher American Society of Anesthesiologists class, ventilator dependence, preoperative dyspnea, disseminated cancer, chemotherapy within 30 days, >4 U packed erythrocyte transfusion in the 72 hours before surgery, albumin <3.5 mg/dL, bilirubin >1.0 mg/dL, sodium >145 mmol/L, hematocrit <38%, type of surgical procedure, emergency surgery, complexity of the procedure, and infected or contaminated wounds (5). In general, cardiovascular risk factors also increase the risk for VTE.

A meta-analysis of case-control and cohort studies with a total of 63 552 patients showed that relative risk for VTE was 2.33 for obesity (95% CI, 1.68 to 3.24), 1.51 for hypertension (CI, 1.23 to 1.85), 1.42 for diabetes mellitus (CI, 1.12 to 1.77), 1.18 for smoking (CI, 0.95 to 1.46), and 1.16 for hypercholesterolemia (CI, 0.67 to 2.02) (6).

Air flights longer than 6 to 8 hours are also associated with an increased risk for DVT (7, 8).

Should clinicians screen specific types of patients for DVT?

Guidelines from the American College of Chest Physicians recommend against routinely screening asymptomatic patients for DVT, even those at increased risk (9). Ultrasound imaging, plethysmography, and D-dimer measurement all have low sensitivity for detecting asymptomatic DVT in such patients (10).

If patients are at high risk for DVT, primary prophylaxis with heparin (and warfarin if the risk is ongoing) should be initiated instead of screening. However, in high-risk patients in whom anticoagulation is contraindicated, ultrasound imaging can be considered as an alternative to prophylactic treatment to determine the need for placement of an inferior vena cava filter.

What modalities should clinicians use to prevent DVT in hospitalized medical patients?

Prophylaxis with subcutaneous heparin (unfractionated heparin 5000 U 2 or 3 times daily or low-molecular-weight heparin [LMWH], such as enoxaparin 40 mg daily), can prevent DVT in at-risk hospitalized medical patients.

A meta-analysis of prophylactic anticoagulation in at-risk medical patients showed significant reductions in any PE (relative risk, 0.43 [CI, 0.26 to 0.71]) and fatal PE (relative risk, 0.38 [CI, 0.21 to 0.69]), a

nonsignificant reduction in symptomatic DVT (relative risk, 0.47 [CI, 0.22 to 1.00]), a nonsignificant increase in major bleeding (relative risk, 1.32 [CI, 0.73 to 2.37]), but no effect on all-cause mortality (relative risk, 0.97 [CI, 0.79 to 1.19]) (11).

LMWH has some advantages over unfractionated heparin as prophylaxis for hospitalized medical patients because it is associated with a lower risk for DVT and PE (12).

Guidelines recommend graduated compression stockings for hospitalized medical patients with a contraindication to anticoagulant prophylaxis (13), but this is based on limited evidence (14, 15).

What modalities should clinicians use to prevent DVT in hospitalized surgical patients?

Clinicians should consider prophylaxis with subcutaneous heparin (unfractionated heparin 5000 U 2 or 3 times daily or LMWH, such as enoxaparin 40 mg daily) to prevent DVT in hospitalized surgical patients. Low-dose unfractionated heparin reduces the risk for fatal postoperative PE from 0.7% to 0.1% (16) and is associated with a relatively low rate of major or minor bleeding complications, ranging from <0.1% for retroperitoneal bleeding to 6.9% for injection-site bruising (17).

Although twice-daily heparin dosing causes fewer major bleeding episodes, thrice-daily dosing offers somewhat better efficacy in preventing clinically relevant thrombotic events.

A meta-analysis comparing twice-daily with thrice-daily administration of subcutaneous unfractionated heparin showed that there was no difference in the overall rate (per 1000 patient-days) of VTE (5.4 for twice-daily vs. 3.5 for thrice-daily; $P = 0.87$). However, thrice-daily heparin showed a trend toward a decrease in PE (1.5 for twice daily vs. 0.5 for thrice daily; $P = 0.09$) and in proximal DVT and PE (2.3 for twice daily vs. 0.9 for thrice daily; $P = 0.05$). The risk for major bleeding was significantly increased with thrice-daily heparin

(0.35 for twice daily vs. 0.96 for thrice daily; $P < 0.001$) (18).

Unless there is a contraindication, LMWH or unfractionated heparin is used for prophylaxis in most cases. LMWH is preferred in patients undergoing hip or knee replacement or neurosurgery, patients older than 40 years undergoing general surgery for malignant conditions, and patients with an inhibitor deficiency state. Warfarin may be used in those undergoing hip and knee replacement or other hip surgery. Randomized trials and meta-analysis show superior efficacy of LMWH over unfractionated heparin in high-risk orthopedic patients (19).

In the absence of a clear contraindication, such as severe peripheral arterial disease, fragile skin, or severe edema, graduated compression stockings or intermittent pneumatic compression should be used in primary prophylaxis against postoperative DVT. Mechanical compression can be used as monotherapy in patients for whom the risks of anticoagulation outweigh the benefits.

What modalities should clinicians use to prevent DVT in pregnant patients?

Clinicians should ask pregnant women about personal or family history of VTE at their first prenatal visit. In general, women with previous idiopathic VTE, VTE related to pregnancy or estrogen therapy, or thrombophilia are at higher risk than those with previous VTE related to a temporary risk factor. Clinicians should therefore consider prenatal and postnatal prophylaxis with LMWH for those at higher risk and only postnatal prophylaxis with LMWH for those with previous VTE related to a temporary risk factor.

Recommendations for women with no history of DVT but thrombophilia identified by screening

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- Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *Lancet.* 1975;2:45-51. [PMID: 49649]
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- King CS, Holley AB, Jackson JL, et al. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. *Chest.* 2007;131:507-16. [PMID: 17296655]

depend on the risk associated with the specific thrombophilic disorder. In general, these women do not require prenatal prophylaxis but should be offered postnatal prophylaxis.

Graduated compression stockings have not been widely evaluated in pregnancy as an addition or alternative to prophylaxis with anticoagulants but have been recommended by expert opinion for all pregnant women at risk for VTE unless there are specific contraindications (20).

Some guidelines recommend that persons with a personal or family history of VTE should be screened for thrombophilia (21) because of the increased risk for VTE associated with thrombophilic disorders (hazard ratio, 0.74 to 34.40), depending on the specific disorder (22).

However, given these data and the baseline risk for VTE in pregnancy of approximately 1 in 1000, the greatest absolute risk for VTE in pregnant women with thrombophilia is about 3.4%. The low risk plus the scant evidence supporting the benefit of thromboprophylaxis once a thrombophilic disorder has been identified makes the role of screening pregnant women for thrombophilia uncertain.

What modalities should clinicians use to prevent DVT in nonpregnant patients with thrombophilia?

The thrombophilias or hypercoagulability disorders include a variety of different syndromes with differing risk for VTE (see Box). Lifelong anticoagulation may be appropriate in some patients, but the lack of long-term studies of VTE thromboprophylaxis for patients with hypercoagulability disorders means that recommendations are based on expert opinion (23).

Hypercoagulability disorders are usually identified as a result of

screening after apparently idiopathic VTE, and recommendations for secondary prevention of VTE usually relate to duration of anticoagulation after the initial VTE (see Treatment section). Recommendations for prevention of DVT in patients with thrombophilia but no previous VTE are limited by lack of long-term studies. Because the incidence of VTE in the general population is low, even if some thrombophilias are associated with a substantial relative risk for VTE, the absolute risk is small. Management involves individualized risk-benefit analysis, taking into account interactions of acquired and hereditary factors that determine the risk for VTE. Consultation with a specialist is recommended.

How should physicians counsel patients about DVT prevention during prolonged immobility associated with travel?

Individuals without specific risk factors should consider below-knee compression stockings starting 2 to 3 hours before flights longer than 6 to 8 hours. Individuals at high risk for DVT because of previous VTE or superficial venous thrombosis, coagulation disorders, severe obesity or limited mobility, neoplastic disease within the past 2 years, cardiovascular disease, and large varicose veins should consider a single dose of subcutaneous LMWH 2 to 4 hours before long-haul travel in addition to compression stockings.

A meta-analysis showed that wearing compression stockings reduced the risk for asymptomatic DVT (odds ratio, 0.10 [CI, 0.04 to 0.25]) associated with long air

Types of Thrombophilia

- Antiphospholipid antibodies
- Antithrombin III deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin 20210A
- Hyperhomocysteinuria

- Nurmohamed MT, Rosendaal FR, Büller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet*. 1992;340:152-6. [PMID: 1352573]
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- Scottish Intercollegiate Guidelines Network. Prophylaxis of Venous Thromboembolism: A National Guideline. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2002.
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- Goodacre S, Sutton AJ, Sampson FC. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. *Ann Intern Med*. 2005;143:129-39. [PMID: 16027455]
- Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. 1995;345:1326-30. [PMID: 7752753]

flights, but their effect on symptomatic DVT, PE, and death could not be determined

because no such events occurred during the trials (24).

Prevention... Asymptomatic patients at high risk for DVT, particularly hospitalized medical and surgical patients, should not undergo screening but should receive primary prophylactic anticoagulation with unfractionated heparin or LMWH. Mechanical compression with graduated compression stockings should be considered in all hospitalized patients at risk for VTE who do not have a specific contraindication. For air flights longer than 6 to 8 hours, individuals without specific risk factors should consider wearing compression stockings and those at high risk should consider prophylaxis with a single dose of LMWH. Treatment to prevent DVT in at-risk pregnant women and people with hypercoagulability disorders is controversial and limited by lack of high-quality data. Decision-making involves weighing the risks and benefits of treatment in the individual patient.

CLINICAL BOTTOM LINE

What signs and symptoms should lead clinicians to suspect DVT?

DVT should be suspected in patients with lower limb pain or swelling. Factors that increase the likelihood of DVT include malignant conditions, history of DVT, recent surgery, immobilization, and increased calf diameter >3 cm in the symptomatic leg. Other clinical features, such as warmth, erythema, and Homan sign, have limited diagnostic value (25).

The most extensively evaluated clinical score for DVT is the Wells score, which stratifies patients to high (likelihood ratio, 5.2), intermediate, and low (likelihood ratio,

0.25) risk for proximal DVT (26) (Table 1). Three other scores have been developed that use fewer items than the 9-item Wells score, and another score combines clinical evaluation with D-dimer results to determine the need for ultrasound testing (27–30). Although these scores may be simpler to use than the Wells score, they have yet to be as widely validated.

The Wells score does not accurately stratify risk for distal DVT, has not been validated in certain groups (such as intravenous drug abusers), and does not perform as well in excluding DVT in primary care settings as in hospital settings (31).

Diagnosis

27. Kahn SR, Joseph L, Abenheim L, et al. Clinical prediction of deep vein thrombosis in patients with leg symptoms. *Thromb Haemost.* 1999;81:353-7. [PMID: 10102459]
28. Constans J, Nelzy ML, Salmi LR, et al. Clinical prediction of lower limb deep vein thrombosis in symptomatic hospitalized patients. *Thromb Haemost.* 2001;86:985-90. [PMID: 11686356]
29. Constans J, Boutinet C, Salmi LR, et al. Comparison of four clinical prediction scores for the diagnosis of lower limb deep venous thrombosis in outpatients. *Am J Med.* 2003;115:436-40. [PMID: 14563499]
30. The Amsterdam Maastricht Utrecht Study on thromboEmbolism Investigators. Safely Ruling out Deep Venous Thrombosis in Primary Care. *Ann Intern Med.* In Press.
31. Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. *Ann Intern Med.* 2005;143:100-7. [PMID: 16027451]

Table 1. Modified Wells Clinical Score*

Clinical Characteristic	Score
Active cancer (treatment ongoing, within 6 mo, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 d or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

DVT = deep venous thrombosis.

* The score is obtained by summing the scores for each positive item. The original Wells score (26) categorized patients into low (score ≤0), intermediate (1–2), or high (≥3) risk for DVT. More recent use of the score (33) dichotomizes patients into DVT unlikely (≤1) or DVT likely (≥2).

What is the role of D-dimer testing in diagnosing DVT?

D-dimer testing can be used to effectively rule out DVT in patients with a low or intermediate clinical risk for DVT.

A meta-analysis showed that the 3-month incidence of VTE was 0.4% (CI, 0.04% to 1.1%) among patients with low or intermediate clinical probability of DVT and a normal highly sensitive D-dimer assay concentration and 0.5% (CI, 0.07% to 1.1%) among patients with a low clinical probability of DVT and a normal D-dimer concentration (32).

D-dimer assays generally have good sensitivity but poor specificity for proximal DVT at conventionally set thresholds that define positive results (33). However, specificity varies with pretest clinical probability of DVT and is lower among patients with a high clinical probability of DVT (34). These characteristics mean that D-dimer assay has better diagnostic accuracy and greater clinical utility in patients with a low clinical probability of DVT.

Diagnostic characteristics vary among D-dimer assays. In general, enzyme-linked immunoassay tests have higher sensitivity and lower specificity, whereas whole-blood agglutination assays have lower sensitivity and higher specificity (33). The SimpliRED D-dimer assay is a widely used point-of-care whole-blood agglutination assay. It is not as sensitive as laboratory-based enzyme-linked immunosorbent assay or latex assays, but because it can be used at the point of care, it can rule out DVT in the emergency department or in outpatient practice.

D-dimer sensitivity may be lower in pregnant patients, anticoagulated patients, and those with prolonged clinical symptoms of DVT. D-dimer specificity may be lower in patients with malignant conditions, pregnant patients, anticoagulated patients, and those with a history of DVT (34).

What is the role of venous ultrasonography in diagnosing DVT and what alternate testing modalities are available?

Clinicians should use venous ultrasound to diagnose or exclude DVT in patients with a high clinical probability of DVT or a positive D-dimer result (Figure). If D-dimer testing is unavailable or unreliable, ultrasound should be used in all patients with suspected DVT.

A meta-analysis of 100 cohort studies showed that venous ultrasound has 94% sensitivity for detecting proximal venous thrombosis, 63% sensitivity for distal DVT, and 94% specificity for both (35).

If proximal DVT is detected on ultrasonography, the patient should be treated with anticoagulants without further investigation. Negative ultrasonography results effectively rules out proximal DVT but not distal DVT.

About 1% to 2% of patients with a normal initial ultrasound have calf venous thrombosis that is destined to extend into the proximal veins, generally within 5 to 8 days (36). For this reason, ultrasound is often repeated 1 week later if initial investigation is negative. Repeated ultrasound for all patients may not be a cost-effective use of health care resources, so selection on the basis of D-dimer result may be an appropriate compromise. Because D-dimer testing has higher sensitivity for distal DVT than ultrasound, a patient with a positive D-dimer and initially negative ultrasound has a significant risk for distal DVT, thus meriting repeated ultrasonography.

Duplex ultrasonography using compression ultrasound and color-flow Doppler has higher sensitivity for detecting distal DVT but slightly lower specificity than ultrasound alone (35). The use of repeated scanning after 1 week may therefore also depend on the technique used. If compression ultrasound alone is used, then repeated

32. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review. *BMJ*. 2004;329:821. [PMID: 15383452]

33. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med*. 2004;140:589-602. [PMID: 15096330]

34. Goodacre S, Sampson FC, Sutton AJ, et al. Variation in the diagnostic performance of D-dimer for suspected deep vein thrombosis. *QJM*. 2005;98:513-27. [PMID: 15955795]

35. Goodacre S, Sampson F, Thomas S, et al. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. *BMC Med Imaging*. 2005;5:6. [PMID: 16202135]

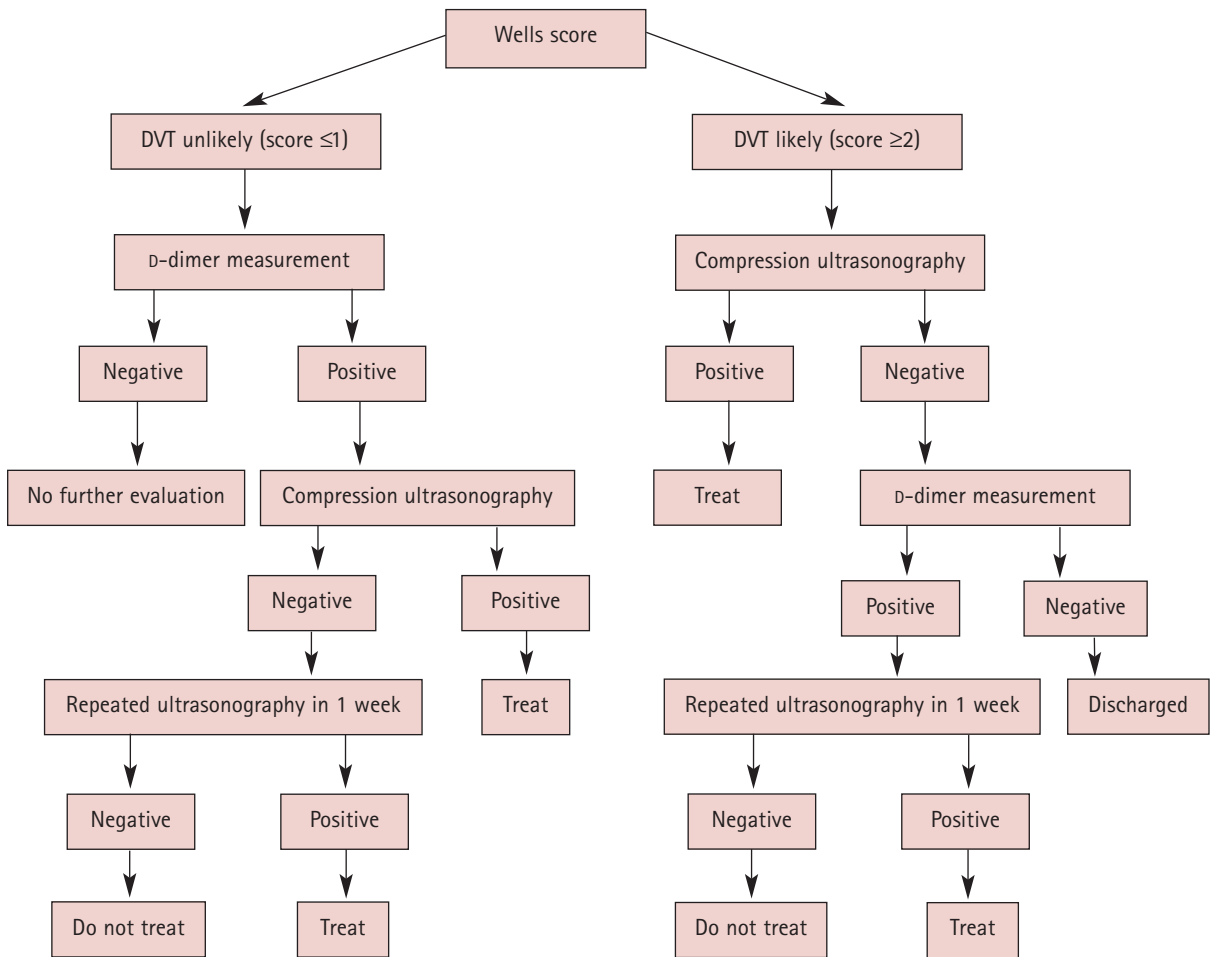


Figure. Deep Venous Thrombosis (DVT) treatment algorithm based on Wells score

scanning is likely to have greater value.

Magnetic resonance venography is an alternative to ultrasound and has equivalent accuracy (37). Impedance and strain-gauge plethysmography are alternatives that have lower accuracy and are now considered obsolete.

What other diagnoses should clinicians consider in patients with suspected DVT?

The differential diagnosis of suspected DVT is extensive. Table 2 outlines the main alternative considerations. Some of these, such as Baker cyst or superficial thrombophlebitis can be diagnosed by an experienced sonographer while investigating for DVT. Differentiation of DVT from muscle trauma

often requires ultrasound because muscle trauma may lead to elevated D-dimer levels, and DVT may complicate muscle trauma that results in immobilization. The patient with worsening pain or swelling after initially improving symptoms from muscle injury should be suspected of having DVT.

What underlying conditions and diagnostic studies should clinicians consider in patients with DVT who have no obvious inciting factor?

A number of acquired and hereditary hypercoagulability disorders can precipitate DVT in patients who are not immobilized and have no other obvious inciting factor. These include malignant conditions and thrombophilic disorders.

36. Goodacre S, Sampson F, Stevenson M, et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006;10:1-168, iii-iv. [PMID: 16707072]

37. Sampson FC, Goodacre SW, Thomas SM, et al. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. Eur Radiol. 2007;17:175-81. [PMID: 16628439]

38. Federman DG, Kirsner RS. An update on hypercoagulable disorders. Arch Intern Med. 2001;161:1051-6. [PMID: 11322838]

Table 2. Differential Diagnosis of DVT

Disease	Characteristics	Notes
Venous insufficiency (venous reflux)	Usually due to venous hypertension from such causes as venous reflux or obesity	Obtain ultrasonography of venous reflux
Superficial thrombophlebitis	Firm, tender, varicose vein	Superficial thrombosis is rarely associated with DVT
Muscle strain, tear, or trauma	Pain occurring with a range of motion more characteristic of orthopedic problem due to trauma; usually a history of leg injury	Order appropriate radiologic studies to evaluate for orthopedic problem
Leg swelling in a paralyzed limb	History of paraplegia	Patients with a paralyzed limb may develop edema without DVT
Baker cyst	Frequent pain localized to popliteal region of leg	Seen on ultrasonography
Cellulitis	Skin erythema and warmth	Consider antibiotic treatment
Lymphedema	Toe edema is more characteristic of lymphedema than of venous edema.	Lymphedema can occur in 1 or both legs

DVT = deep venous thrombosis.

Screening patients with a first episode of idiopathic DVT for thrombophilia is controversial. Testing is usually undertaken in patients who develop VTE before age 45 to 50 years, have a family history of VTE, have recurrent VTE thrombosis in an unusual site, or have life-threatening VTE (38).

Weight loss, general ill health, or specific symptoms might suggest a malignant condition. Clinicians should obtain a baseline complete

blood cell count, including platelets, prothrombin time and activated partial thromboplastin time, and a serum creatinine level in all patients with DVT before starting treatment. Choice of other investigations should be guided by clinical assessment. It is important that patients with unexplained DVT undergo age-appropriate cancer screening, even if the clinical picture does not suggest underlying malignant conditions.

Diagnosis... Clinicians should consider using such instruments as the Wells clinical probability score to stratify the risk for proximal DVT and guide further investigation. Patients with a low clinical probability score and negative D-dimer levels are unlikely to benefit from further investigation. Patients with high clinical probability or positive D-dimer levels should be investigated with ultrasonography. Patients with positive D-dimer levels and negative ultrasonography should undergo repeated ultrasonography investigation after 1 week to identify proximal propagation of possible distal DVT. Testing for underlying predisposing conditions in patients with idiopathic VTE should be done on the basis of clinical assessment.

CLINICAL BOTTOM LINE

Treatment

What criteria should clinicians use to decide whether to provide outpatient or hospital treatment for a patient with DVT?

Most patients with DVT can be safely treated as outpatients with LMWH unless they have suspected

PE. Patients with suspected PE usually receive hospital treatment, although outpatient management is currently being investigated.

A systematic review comparing patients with VTE treated with LMWH administered

39. Segal JB, Streiff MB, Hofmann LV, et al. Management of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med.* 2007;146:211-22. [PMID: 17261856]

at home with those treated with unfractionated heparin in the hospital found no difference in outcomes. Nine of 10 studies reporting treatment costs suggested cost savings with outpatient therapy when compared with inpatient therapy (39).

Patients with bilateral DVT, renal insufficiency, body weight below 70 kg, recent immobility, chronic heart failure, and cancer have an increased risk for adverse outcomes, such as symptomatic PE, recurrent DVT, major bleeding, or death and may benefit from hospital admission (40).

What local measures should clinicians recommend in patients with symptomatic DVT?

Clinicians should recommend compression stockings within 1 month of diagnosis of symptomatic proximal DVT to prevent the post-thrombotic syndrome and continued use for a minimum of 1 year. Graduated compression stockings provide venous support and reduce sequelae of the postthrombotic syndrome, such as debilitating edema.

Two randomized trials in which patients used compression stockings within 1

month (41) or 1 week (42) of diagnosis both showed significant reductions of about 50% in the postthrombotic syndrome compared with control participants. However, another trial that compared use of compression stockings with placebo showed no difference in incidence of the postphlebotic syndrome after 1 year (43).

What anticoagulant regimens should clinicians use to treat patients with DVT?

Table 3 outlines anticoagulant regimens that can be used for DVT. LMWH has largely replaced unfractionated heparin as initial treatment for DVT, but unfractionated heparin may be used in patients with severe renal impairment or to achieve rapid anticoagulation in massive DVT.

Of 11 systematic reviews of trials comparing LMWH with unfractionated heparin, all but 1 showed that LMWH significantly reduced mortality during the 3 to 6 months of follow-up compared with unfractionated heparin. None of the 11 showed unfractionated heparin to be superior in preventing recurrent DVT. Patients treated with LMWH had fewer episodes of major bleeding than those treated with unfractionated heparin (39).

40. RIETE Investigators. Predicting adverse outcome in outpatients with acute deep vein thrombosis: findings from the RIETE Registry. *J Vasc Surg.* 2006;44:789-93. [PMID: 16926081]
41. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet.* 1997;349:759-62. [PMID: 9074574]
42. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med.* 2004;141:249-56. [PMID: 15313740]
43. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of post-phlebotic syndrome: results of a 3-part study. *Arch Intern Med.* 2001;161:2105-9. [PMID: 11570939]

Table 3. Drug Treatment for DVT

Agent, Dosage	Mechanism of Action	Side Effects
LMWH Dalteparin, 200 IU/kg SC once daily Enoxaparin, 1 mg/kg SC every 12 h or 1.5 mg/kg SC every 24 h Tinzaparin, 175 IU/kg SC once daily	Inhibits thrombin generation by acting on factor Xa; also acts on antithrombin to inhibit factor IIa activity	Bleeding, thrombocytopenia, hypersensitivity, osteoporosis, HIT
Unfractionated heparin, IV infusion or intermittent SC doses to keep aPTT ≥ 1.5 times control value	Enhances antithrombin activity, thereby inhibiting thrombin activity	Bleeding, thrombocytopenia, hypersensitivity, HIT, osteoporosis, elevation of liver enzymes, and hyperkalemia
Direct thrombin inhibitors Lepirudin, 0.1 mg/kg per h Bivalirudin, 0.75 mg/kg IV loading; then 1.75 mg/kg per h Argatroban, 2 μ g/kg per min	Directly inhibits thrombin activity	Bleeding, hypersensitivity reactions, and injection-site reactions
Fondaparinux, 7.5 mg SC daily	Inhibits activated factor X	Bleeding, purpura, anemia
Coumarin derivatives (warfarin), give initial dose of 10 mg/d on day 1 of heparin, overlap for 4–5 d until INR becomes therapeutic for 2 consecutive days; adjust dose to keep INR between 2.0 and 3.0	Inhibits hepatic γ -carboxylation of glutamic acid residues of vitamin K–dependent coagulation factors II, VII, IX, and X. Inhibits production of antithrombotic proteins C and S	Hypercoagulability during first 24–36 h of therapy; bleeding; hypersensitivity; teratogenicity; many drug interactions; skin necrosis associated with malignancy and protein C and S deficiency; bleeding associated with malignancy

aPTT = activated partial thromboplastin time; DVT = deep venous thrombosis; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; SC = subcutaneous.

Warfarin Interactions with Different Drugs and Food

Decrease warfarin absorption

Cholestyramine
Colestipol

Enhance warfarin clearance

Phenytoin
Rifampin
Glutethimide
Griseofulvin

Potentiates warfarin action

Acetaminophen

Inhibit warfarin metabolism

Amiodarone
Disulfiram
Fluconazole
Cimetidine (but not other H₂-receptor blockers)
Omeprazole
Phenylbutazone and oxyphenylbutazone
Sulfinpyrazone
Sulfonamide antibiotics
Propafenone
Quinolone antibiotics
Tamoxifen
Disopyramide
Miconazole
Clofibrate

Warfarin should be started at the same time as heparin. Heparin should be continued concomitantly with warfarin until the therapeutic potential of warfarin is achieved. Although more expensive, long-term treatment with LMWH is a safe and effective alternative for patients in whom oral anticoagulation is not appropriate because of difficulty in titrating dose, poor patient adherence to monitoring, or adverse effects.

Fondaparinux at a subcutaneous dose of 7.5 mg subcutaneously daily seems to be as effective as LMWH for acute treatment of DVT.

A randomized trial comparing fondaparinux with enoxaparin in 2205 patients with acute symptomatic DVT found that 43 (3.9%) of 1098 patients receiving fondaparinux had recurrent thromboembolic events compared with 45 (4.1%) of 1107 patients receiving enoxaparin (absolute difference, -0.15% [CI, -1.8% to 1.5%]). Major bleeding occurred in 1.1% of patients receiving fondaparinux and 1.2% of patients receiving enoxaparin. Mortality rates were 3.8% and 3.0%, respectively (44).

Direct thrombin inhibitors (lepirudin, bivalirudin, and argatroban) are generally only used to treat DVT in patients with known heparin hypersensitivity or heparin-induced thrombocytopenia.

How should clinicians monitor patients on anticoagulation for DVT?

Clinicians should use the activated partial thromboplastin time to adjust the dose of unfractionated heparin, but it is not necessary to do so in patients treated with LMWH. They should monitor the international normalized ratio (INR) every 4 weeks for the duration of warfarin therapy once the level of anticoagulation is stable, aiming for an INR target between 2 and 3.

Randomized trials have shown that home monitoring of anticoagulation is safe and feasible for selected patients. The quality of

anticoagulant control seems to be equivalent and possibly superior to conventional management in an anticoagulation clinic (45–48).

What important drug and food interactions should clinicians consider in treating patients with warfarin?

Drugs and food may interact with warfarin in a number of ways to enhance or inhibit warfarin activity (see Box). Drugs that decrease warfarin absorption or enhance warfarin clearance may necessitate an increase in warfarin dose to avoid subtherapeutic INR levels, whereas those that potentiate warfarin action or inhibit warfarin metabolism may require a decrease in dose to avoid supratherapeutic levels. However, these effects are not always predictable. For example, cholestyramine and phenytoin can both enhance and reduce the effect of warfarin.

Foods with large amounts of vitamins A, E, K, and C can decrease the INR level in patients on warfarin. Green leafy vegetables contain the most vitamin K. Other examples include green and herbal teas, which can also alter the prothrombin time. Proteolytic enzymes, such as papain in fried or boiled onions, increase fibrinolytic activity.

What factors should clinicians consider in determining the duration of anticoagulation therapy for DVT?

Clinicians should consider inciting events and underlying conditions in determining the duration of anticoagulation therapy for DVT (Table 4). Patients with a major transient risk factor for DVT, such as major surgery, significant medical illness, or leg casting, are usually treated for 3 months. This may be extended if exposure to the risk factor is prolonged. Patients with persistent major risk factors, such as malignant conditions, may require long-term anticoagulation. Examples of minor risk factors

44. Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med.* 2004;140:867-73. [PMID: 15172900]

45. Sunderji R, Gin K, Shalansky K, et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Can J Cardiol.* 2004;20:1117-23. [PMID: 15457308]

46. Gardiner C, Williams K, Longair I, et al. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. *Br J Haematol.* 2006;132:598-603. [PMID: 16445833]

47. Fitzmaurice DA, Murray ET, McCahon D, et al. Self management of oral anticoagulation: randomised trial. *BMJ.* 2005;331:1057. [PMID: 16216821]

Table 4. Recommendations for the Duration of Anticoagulant Therapy for Patients with DVT

Characteristics of Patient	Risk for Recurrence in the Year After Discontinuation, %	Duration of Therapy
Major transient risk factor	3	3 mo
Minor risk factor; no thrombophilia:		
Risk factor avoided	<10 if risk factor avoided	6 mo
Risk factor persistent	>10 if risk factor persistent	Until factor resolves
Idiopathic event; no thrombophilia or low-risk thrombophilia	<10	6 mo
Idiopathic event; high-risk thrombophilia	>10	Indefinite
More than 1 idiopathic event	>10	Indefinite
Cancer; other ongoing risk factor	>10	Indefinite

Reprinted from (49) with permission. Data from (50–52).

include the use of an oral contraceptive and hormone-replacement therapy. Hormone therapy is contraindicated in patients who experience DVT and should be replaced by nonhormonal alternatives. When such a risk factor can be withdrawn, anticoagulation for 6 months is appropriate.

Patients without an identifiable risk factor are more likely to develop recurrent VTE and should be treated for a minimum of 6 months with oral anticoagulation. The duration of therapy may be influenced by detection of high- or low-risk thrombophilias. Examples of low-risk thrombophilias are heterozygosity for the factor V Leiden and G20210A prothrombin-gene mutations. Examples of high-risk thrombophilia are antithrombin, protein C, and protein S deficiencies; homozygosity for the factor V Leiden or prothrombin-gene mutation or heterozygosity for both; and the presence of antiphospholipid antibodies.

Determining the exact duration of therapy also involves weighing the risks of recurrent VTE against the risks of anticoagulant-related bleeding.

A meta-analysis showed a consistent reduction in the relative risk for recurrent events during prolonged treatment (odds ratio, 0.18 [CI, 0.13 to 0.26]) that was independent of the period elapsed since the

index event and a substantial increase in bleeding complications during the entire period after randomization (odds ratio, 2.62 [CI, 1.48 to 4.61]) (53).

D-dimer measurement may be helpful in determining treatment duration. One study showed that patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation for idiopathic thromboembolism have a significant incidence of recurrent thromboembolism, which is reduced by the resumption of anticoagulation (54).

What are the treatment options for patients who have contraindications to anticoagulation?

Inferior vena cava (IVC) filters may be used when anticoagulation is contraindicated in patients at high risk for proximal extension of DVT or embolization, such as those with bilateral or massive DVT, immobility, chronic heart failure, or cancer. However, IVC filters may not decrease the long-term incidence of recurrent proximal DVT.

IVC filters are often placed in patients with no contraindication to anticoagulation who experience recurrent VTE while on the drug, and anticoagulants are continued to prevent further recurrence. However, the efficacy of anticoagulants to do so is questionable.

A systematic review and meta-analysis of patients who received an IVC filter showed

48. Menéndez-Jándula B, Souto JC, Oliver A, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med.* 2005;142:1-10. [PMID: 15630104]
49. Bates SM, Ginsberg JS. Clinical practice. Treatment of deep-vein thrombosis. *N Engl J Med.* 2004;351:268-77. [PMID: 15254285]
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51. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest.* 1998;114:561S-578S. [PMID: 9822063]
52. Kearon C. Duration of anticoagulation for venous thromboembolism. *J Thromb Thrombolysis.* 2001;12:59-65. [PMID: 11711690]
53. Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. *Cochrane Database Syst Rev.* 2006; CD001367. [PMID: 16437432]

that anticoagulation did not significantly reduce the risk for recurrent VTE (odds ratio, 0.639 [CI, 0.35 to 1.16]) (55).

What are the complications of anticoagulation?

Clinicians should make patients aware that anticoagulation carries a small but important risk for bleeding.

A meta-analysis of patients taking anticoagulant therapy for VTE estimated that over the 3- to 6-month treatment period, there was a 0.34% probability of fatal bleeding, a 0.12% probability of nonfatal intracranial bleeding, and a 2.1% probability of other nonfatal major bleeding (56).

Other complications of heparin therapy include heparin-induced thrombocytopenia (HIT), hypersensitivity reactions, osteoporosis after long-term use, and elevation of liver enzymes. Hypersensitivity reactions include urticaria, angioedema, and anaphylaxis. Other complications of warfarin therapy include hypercoagulability during the first 24 to 36 hours of therapy, hypersensitivity reactions, teratogenicity, drug interactions, and skin necrosis associated with malignant conditions and protein C and S deficiency (51).

How should clinicians manage patients who develop HIT during DVT treatment?

HIT is an immune-mediated reaction that does not usually occur until 5 to 10 days after initiating treatment and is characterized by a 50% or greater reduction in platelet count. It may be associated with thrombosis but is more often detected in the process of monitoring the platelet count. When HIT is suspected, clinicians should avoid using all heparins, including LMWH, as well as warfarin, which can paradoxically worsen the thrombosis associated with HIT and cause venous limb gangrene and skin necrosis. Two alternative anticoagulants that can be used in HIT are the direct

thrombin inhibitors, argatroban (a synthetic molecule derived from L-arginine) and lepirudin (a recombinant protein derived from leech hirudin) (57, 58).

An analysis of 3 multicenter trials in patients with HIT showed that treatment with lepirudin was associated with a reduction in a combined end point of limb amputation, thromboembolic complications, and death when compared with control participants (19.8% vs. 29.9%; $P = 0.03$), primarily because of a reduction in new thromboembolic complications (4.4% vs. 14.9%; $P = 0.02$), and was not associated with any significant difference in major bleeding episodes (14.3% vs. 8.5%; $P = 0.54$) (57).

When should clinicians consider intravenous or catheter-directed thrombolysis to treat DVT?

Because severe postthrombotic syndrome is probably more common in patients with iliofemoral venous thrombosis, clinicians should consider intravenous or catheter-directed thrombolytic drug therapy in such patients in an attempt to reduce the risk for the postthrombotic syndrome. The potential benefit should be weighed against the risk for bleeding.

A randomized trial in 35 patients with iliofemoral DVT compared catheter-directed thrombolysis followed by anticoagulation with anticoagulation alone. At 6 months, the patency rate was higher (13 of 18 [72%] vs. 2 of 17 [12%]; $P < 0.001$) and venous reflux was lower (2 patients [11%] vs. 7 [41%]; $P = 0.04$) in patients treated with thrombolysis (59).

What modifications in treatment should clinicians consider in specific patient groups?

DVT during pregnancy requires special treatment and monitoring. Warfarin should not be given because of its teratogenic potential. Unfractionated heparin or LMWH therapy should be used instead throughout pregnancy. Heparin should be stopped before delivery, typically at induction of labor.

54. PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med*. 2006;355:1780-9. [PMID: 17065639]

55. Ray CE Jr, Prochazka A. The need for anticoagulation following inferior vena cava filter placement: systematic review. *Cardiovasc Intervent Radiol*. 2008;31:316-24. [PMID: 18080710]

56. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med*. 2003;139:893-900. [PMID: 14644891]

All patients with thrombophilia, both pregnant and nonpregnant, may have an increased risk for recurrent DVT and may require prolonged or even lifetime anticoagulation (38). The benefit of prolonged anticoagulation is likely to be determined by the increased risk for VTE associated with the specific thrombophilia and the number of thrombophilias identified. Thus, patients with antithrombin III deficiency, homozygous thrombophilic defect, or heterozygosity for 2 or more prothrombotic defects are most likely to benefit from lifelong anticoagulation, whereas 6 to 12 months of anticoagulation are probably appropriate for patients with a single thrombophilic defect, such as heterozygous factor V Leiden or PT G20210A (23). Clinicians should use warfarin for anticoagulation in nonpregnant patients unless contraindicated.

How should clinicians treat patients with the postthrombotic syndrome?

The postthrombotic syndrome is characterized by symptoms of recurrent pain and swelling and signs of stasis skin changes and

ulceration. Clinicians should advise patients with the syndrome to elevate their feet whenever possible and should prescribe graduated compression stockings with pressures ranging from 20 to 40 mm Hg, depending on severity of edema. Patients should be instructed to replace their stockings after 6 months of repeated use because the stockings lose the elasticity needed to maintain adequate pressure. Outpatient pneumatic compression is usually reserved for patients who do not respond to foot elevation and stockings. Recurrent DVT should also be considered in patients developing symptoms and signs of the postthrombotic syndrome.

When should clinicians consult a specialist for advice in treating patients with DVT?

Clinicians should consider consulting a specialist with expertise in vascular medicine and coagulation disorders for patients with recurrent idiopathic DVT or patients with suspected or proven hypercoagulability, for complications necessitating alternatives to anticoagulation, and for management of DVT in pregnant patients.

Treatment... Clinicians should initiate LMWH as first-line treatment for proximal DVT together with warfarin for ongoing anticoagulation. The INR should be monitored at least every 4 weeks for the duration of warfarin therapy. Once the level of anticoagulation is stable, aim for an INR target of between 2 and 3. Home monitoring may be used as an alternative to anticoagulant clinic monitoring for selected patients. Compression stockings should be used within 1 month of diagnosis of proximal DVT and continued for a minimum of 1 year. The duration of anticoagulation depends on identification of transient or persistent risk factors and weighing the risks for recurrent VTE against the risks for bleeding in each individual patient. IVC filters may be used when anticoagulation is contraindicated in patients at high risk for proximal DVT extension or embolization. An intravenous or catheter-directed thrombolytic drug may reduce the postthrombotic syndrome and should be considered for patients with iliofemoral DVT.

CLINICAL BOTTOM LINE

57. Lubenow N, Eichler P, Lietz T, et al. Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of 3 prospective studies. *Blood*. 2004;104:3072-7. [PMID: 15280202]
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Practice Improvement

60. American College of Physicians. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2007;146:204-10. [PMID: 17261857]
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Do U.S. stakeholders consider management of patients with DVT when evaluating the quality of care physicians deliver?

The Center for Medicare & Medicaid Services (CMS) has developed 119 measure of quality of care to use in the 2008 Physician Quality Reporting Initiative (PQRI), an initiative that will financially reward participating physicians who meet defined quality standards. Of these measures, one involves prophylaxis for VTE in surgical patients and relates to the percentage of patients age 18 years or older undergoing procedures for which VTE prophylaxis is indicated and who had an order for LMWH, low-dose unfractionated heparin, adjusted-dose warfarin, fondaparinux, or mechanical prophylaxis to be given within 24 hours before incision time or within 24 hours after surgery end time.

What do professional organizations recommend with regard to the management of patients with DVT?

The American College of Physicians and the American Academy

of Family Physicians published a clinical practice guideline for the management of VTE in 2007 specifically addressing use of LMWH and patient measurement, use of compression stockings, and duration of anticoagulations (60).

Recommendations issued by the American Society of Clinical Oncology VTE Guideline Panel in 2007 cover details of VTE thromboprophylaxis and preference for LMWH in treatment of cancer patients (61).

The National Comprehensive Cancer Network (NCCN) published clinical practice guidelines on venous thromboembolic disease in 2007, which outline strategies for improving VTE prophylaxis in hospitalized cancer patients (62).

In 2008, the American College of Chest Physicians (ACCP) issued its latest evidence-based clinical practice guidelines relating to a number of issues in VTE prevention and treatment. These include prevention of VTE (9), treatment of VTE (63), and treatment of HIT (64).

in the clinic Tool Kit Deep Venous Thrombosis

PIER Modules

pier.acponline.org

Access the following PIER modules: Deep Vein Thrombosis, Pulmonary Embolism, Venous Thromboembolism Prophylaxis in the Surgical Patient. PIER modules provide evidence-based, updated information on prevention, diagnosis, and treatment in an electronic format designed for rapid access of the point of care.

Patient Information

National Heart, Lung and Blood Institute

www.nhlbi.nih.gov/health/dci/Diseases/Dvt/DVT_WhatIs.html

Access "What is Deep Venous Thrombosis?", which provides information on all aspects of venous thromboembolic disease.

Other Useful Resources for Clinicians

www.annals.org/cgi/content/full/146/6/454

www.annals.org/cgi/content/full/146/3/204

Most recent evidence-based guidelines on diagnosis and treatment of VTE from ACP.

individual.utoronto.ca/mgreiver/dvt.htm

Wells score for deep venous thrombosis

www.acponline.org/running_practice/quality_improvement/projects/cfpi/doc_anticoag.pdf

Downloadable anticoagulation flow sheet from ACP.

in the clinic

WHAT YOU SHOULD KNOW ABOUT DEEP VEIN THROMBOSIS

Deep vein thrombosis (DVT) is a blood clot in the veins deep in the leg. It may cause pain and swelling in the leg. It is important to treat DVT so the clot does not get worse or move to the lungs. If it does, it can cause serious lung problems and even death.

What causes DVT?

DVT can happen:

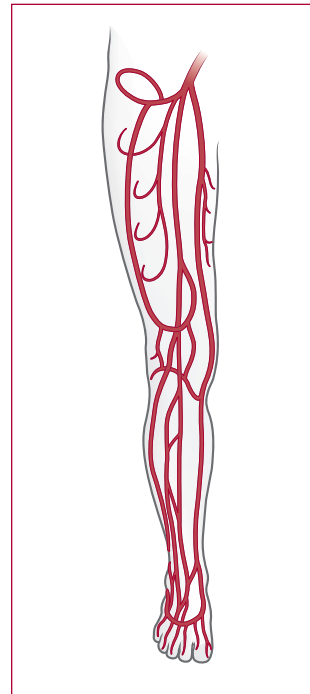
- If you don't move your legs after an injury
- In the hospital, when you are in bed for a long time
- After an operation
- During a long airplane trip
- In some people with cancer
- In people with blood that clots more easily
- For no clear reason

How can DVT be prevented?

- Keep moving your legs when you are laid up or on a long airplane trip.
- Take small doses of a blood thinner when in the hospital or after an operation.

How does your doctor diagnose DVT?

- When it is hard to tell if there is a clot in the leg, your doctor may order blood tests.
- An ultrasound scan using sound waves may help the doctor see a clot in the veins of the leg.
- Sometimes more tests are needed to look for the cause of the DVT.



Veins of the leg.

How is DVT treated?

- Most patients with DVT do not need to be in the hospital.
- Blood thinners are given to prevent more clots in the leg and to keep a clot from going to the lungs.
- People with DVT need to take blood thinners for many months and sometimes need to keep taking them.
- Special stockings can keep the leg from swelling while the clot is being treated.

What do patients need to know?

- Too much blood thinner can cause bleeding, and too little can cause another clot.
- It is important to get regular blood tests to be sure the dose of blood thinner is right.
- Some foods and other medicines can change how much blood thinner you need. It is important to tell your doctor what you eat and about changes in your medicines.

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1. A 23-year-old woman is evaluated for right-leg swelling and pain lasting 3 days. Her history is significant only for recent initiation of oral contraceptives 2 months ago.

On physical examination, there is swelling of the right leg from the ankle to the knee. A proximal deep venous thrombosis of the right leg is confirmed by compression ultrasound. Laboratory studies indicate the presence of a lupus anticoagulant; serum cardiolipin IgG and IgM antibody concentrations are within normal limits. The oral contraceptive is stopped, and she is treated with low-molecular-weight heparin followed by warfarin for 6 months. Laboratory studies 1 month after discontinuation of warfarin therapy are negative for lupus anticoagulant.

Which of the following is the most appropriate next step in management?

- A. Repeated lupus anticoagulant test in 1 month
 - B. Long-term warfarin therapy
 - C. No further therapy
 - D. Daily aspirin therapy
2. A 25-year-old pregnant woman is evaluated at the end of her first trimester. Three years ago, she sustained deep venous thrombosis while taking an oral contraceptive preparation. Her medical history is otherwise unremarkable and she is not currently taking anticoagulants or other medications. She recently underwent screening for thrombophilia, and no abnormalities were identified. There is no family history of venous thrombosis.

Which of the following is the best management recommendation?

- A. Monitor her pregnancy and initiate low-molecular-weight heparin at prophylactic doses after delivery and continue for 6 weeks
- B. Immediately initiate prophylactic doses of low-molecular-weight heparin and continue prophylaxis for 6 weeks after delivery

- C. Immediately initiate therapeutic doses of low-molecular-weight heparin and continue therapy for 6 weeks after delivery
- D. Do not administer anticoagulation before or after delivery unless she develops symptomatic venous thromboembolism

3. A previously healthy 65-year-old man is evaluated because of a 3-day history of swelling, warmth, and erythema in the left calf; compression ultrasound testing reveals deep venous thrombosis extending into the popliteal vein.

The patient is a heavy smoker. There is no history of recent surgery, travel, or immobilization. His mother had phlebitis in her 80s.

Rectal examination is unremarkable, and a stool specimen is negative for occult blood. Results of a complete blood count, prothrombin time, partial thromboplastin time, routine serum chemistry studies, and prostate-specific antigen are normal. Chest radiograph is within normal limits.

Which of the following is the next best step in the evaluation of this patient?

- A. No further evaluation is required
- B. CT scans of the chest, abdomen, and pelvis
- C. CT scan of the chest; upper and lower gastrointestinal endoscopy
- D. Evaluation for a hereditary thrombotic disorder

4. A 45-year-old man develops symptomatic deep venous thrombosis of the left leg 1 week after arthroscopic surgery. Doppler ultrasound examination shows a thrombus in the left posterior tibial vein extending to within 2 mm of the popliteal vein. The patient has mild hypertension but no other medical problems. There is no family history of thromboembolic disease.

Which of the following treatments is the most appropriate?

- A. Ibuprofen, 600 mg every 8 h, and repeat ultrasound in 1 week

- B. Warfarin, 10 mg for 2 nights; check the patient's INR the following day and adjust the dosage if necessary
- C. Enoxaparin, 1 mg/kg body weight subcutaneously every 12 hours, and warfarin, 5 mg/d, adjusted to an INR of 2 to 3
- D. Enoxaparin, 30 mg subcutaneously every 12 h, and warfarin, 5 mg/d, adjusted to an INR of 2 to 3

5. A 57-year-old man is referred by his orthopedist for recommendations regarding anticoagulation therapy before knee replacement surgery next month. He had an unprovoked deep venous thrombosis 6 months ago. He takes no medications except warfarin.

In addition to stopping the warfarin, which of the following anticoagulation regimens is most appropriate for this patient?

- A. Administer antithrombotic prophylaxis for 1 week after surgery
- B. Provide adequate antithrombotic prophylaxis after surgery and continue anticoagulation for a total of 6 weeks
- C. Hospitalize the patient for intravenous administration of heparin when his INR is less than 2; stop the heparin before surgery and administer anticoagulant prophylaxis for 1 week after surgery
- D. Begin therapeutic doses of low-molecular-weight heparin, and give a prophylactic dose the morning of surgery; resume therapeutic doses of low-molecular-weight heparin 12 hours after surgery

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.