MAYO
CLINIC

Succinct Review of the New VTE Prevention and Management Guidelines

Amy West Pollak, MD, MS, and Robert D. McBane II, MD

Abstract

Venous thromboembolism is a major source of morbidity and mortality in the United States. The American College of Chest Physicians Antithrombotic Guidelines, 9th edition, includes a large number of clinical practice recommendations regarding the diagnosis, treatment, and prevention of venous thromboembolism. This succinct clinical review of these guidelines specifically focuses on the evaluation, treatment, and prevention of venous thromboembolic disease.

© 2014 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2014;89(3):394-408

From the Division of Cardiovascular Medicine, Mayo Clinic, Rochester, MN.

Venous thromboembolism (VTE) represents a major cause of morbidity and mortality in the United States. The incidence of VTE exceeds 1 per 1000 with approximately 250,000 first lifetime cases diagnosed annually in the United States.[1] The 30-day mortality of patients suffering a thrombotic event exceeds 25%.[2] Of those individuals surviving the thrombotic event, 30% will develop recurrent VTE within 10 years. Furthermore, the risk of postthrombotic syndrome is approximately 30% at 10 years, with 10% of the patients suffering venous stasis ulceration.[3] Venous thromboembolism is typically a disease of older people, with the incidence of thrombotic events increasing substantially beyond the age of 60 years.[4] Despite advances in radiographic detection, expanded knowledge of risk factors, and anticoagulant development, the incidence of VTE has been relatively constant over the past several decades.[4]

The American College of Chest Physicians Antithrombotic Guidelines, 9th edition (AT9), were published in 2012 and include a large number of clinical practice recommendations encapsulated in an executive summary with 21 separate supporting articles that explore the available evidence used to formulate the guidelines.[5] Expert panelists reviewed the literature underlying each clinical question, evaluated the quality of evidence (A = high, B = moderate, and C = low), and provided a strength of the resulting recommendation (strong = grade 1 and weak = grade 2).

The intent of the article is to provide clinicians with a focused review of the AT9 VTE guidelines in a concise, easily digested format. Furthermore, controversial areas of clinical practice in which the guidelines are not straightforward are discussed. In particular, we endeavor to clarify issues surrounding debated treatment decisions and offer our current practice patterns for these situations.

VTE EVALUATION

Pretest Probability of Disease Assessment

The AT9 guidelines for the evaluation of patients with suspected VTE are based on several important considerations.[6] First, the clinical evaluation is an essential component to initial evaluation and must incorporate a pretest probability of disease assessment. The clinical assessment alone, however, is unreliable and must include further objective testing whereby only a minority of patients with suspected deep vein thrombosis (DVT) actually have the diagnosis (20%).[6] Moreover, the consequences of misdiagnosis are serious. Patients may be placed at an unnecessary risk of major hemorrhage if anticoagulation therapy is initiated for a thrombotic event that is not present. In contrast, patients with VTE who were left untreated may suffer thrombus propagation, embolization, or death. According to the AT9 guidelines, diagnostic strategies are deemed acceptable if 2% or less of the patients with VTE are missed during the evaluation process including the ensuing 3 to 6 months.[6]

The Wells criteria for the clinical pretest probability assessment of DVT classify patients into low, moderate, or high probability categories depending on the underlying risk,

physical findings on examination, and the probability of a more likely alternate diagnosis.[7,8] On the basis of this tool, the prevalence of DVT ranges from 5% (low), 17% (moderate), to 53% (high) pretest probability of disease. Similar tools are available for pulmonary embolism (PE) prediction.[8,9] For patients with suspected VTE, the AT9 guidelines recommend performing a thorough clinical assessment to determine the pretest probability of disease to guide further evaluation (grade 2B; Figures 1 and 2).[6]

Fibrin D-Dimer

Fibrin D-dimer provides a measure of ongoing fibrinolysis.[6] When combined with clinical pretest probability of disease assessment, fibrin D-dimer can be useful in the diagnostic evaluation of patients suspected to have VTE (Figure 1). These assays can be generally classified as quantitative or qualitative. The quantitative assays use ELISA, enzyme-linked or latex platforms for plasma-based testing, and take longer to perform but are highly sensitive for circulating fibrin D-dimer. The qualitative assays are typically performed on whole blood samples and are available at point of care. With the use of the highly sensitive quantitative assays, a negative test result when combined with low or moderate pretest probability of disease clinical assessment excludes the diagnosis of venous thrombosis with 99% negative predictive value.[10] The high sensitivity fibrin D-dimer assay is therefore the first line of testing for patients with low-to-moderate pretest likelihood of disease (grade 2B).[6] Similar negative predictive values can be achieved with the moderate sensitivity qualitative assays, however, only for patients at low pretest probability of disease. The moderate sensitivity assay is the first line of testing for patients with low pretest likelihood of disease only (grade 2C).[6] For either type of assay, a positive test result is not helpful and carries a low positive predictive value. For patients likely to have a positive assay result owing to comorbid conditions such as recent surgery or major trauma, fibrin D-dimer assessment would have little utility.
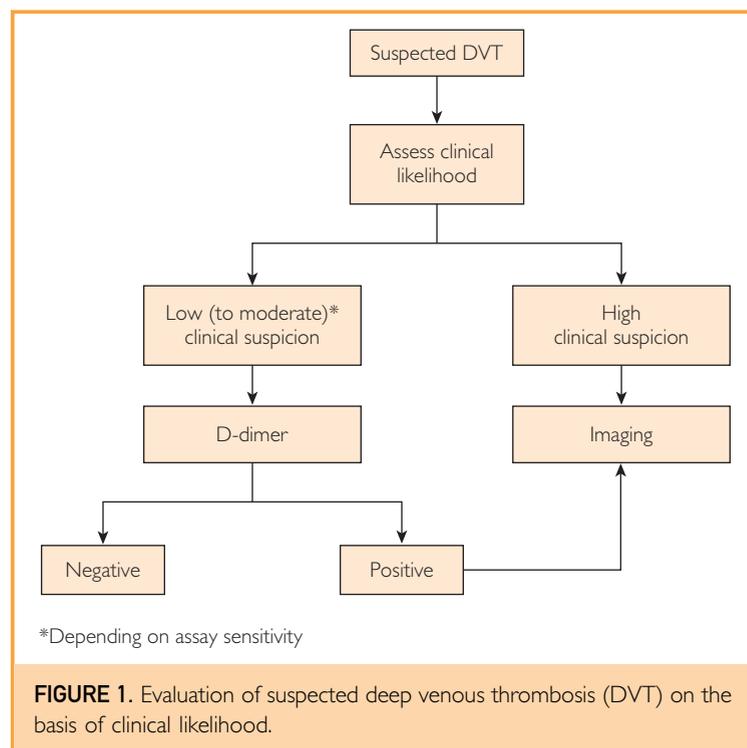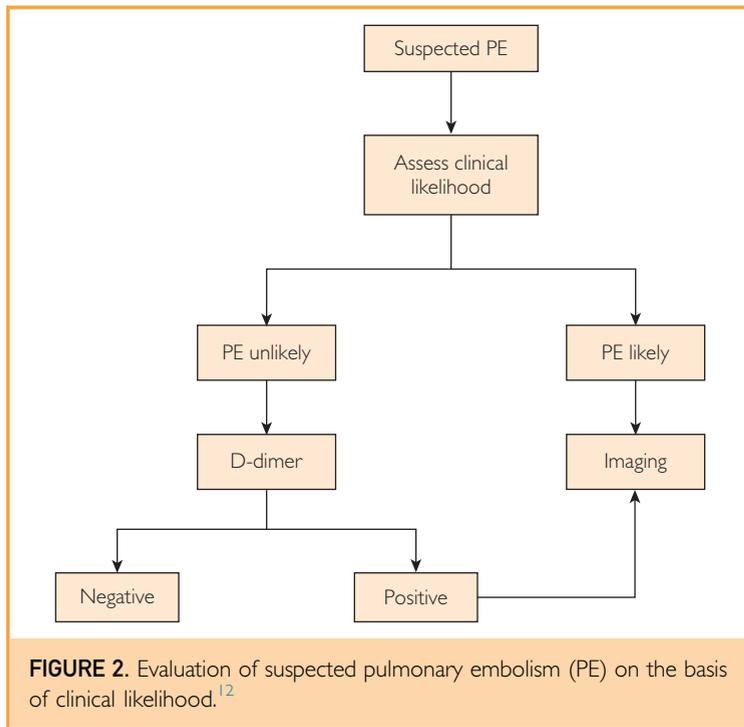
Compression Duplex Ultrasound

Imaging with compression duplex ultrasound is warranted for patients with a high pretest probability of DVT, for patients with a moderate

pretest probability of disease in which the available fibrin D-dimer assay has moderate sensitivity, or for patients with a positive fibrin D-dimer test result (Figure 1).[6] Compression ultrasound testing of the lower extremity for venous thrombosis assessment is defined as "proximal," where the popliteal, femoral, and common femoral veins are imaged, or as "whole leg," which includes an assessment of venous segments of the calf. Whole leg compression ultrasound is useful in the assessment of symptomatic patients with an overall specificity of 96% and a 3-month VTE rate of 0.57% with a

FIGURE 1. Evaluation of suspected deep venous thrombosis (DVT) on the basis of clinical likelihood.

FIGURE 2. Evaluation of suspected pulmonary embolism (PE) on the basis of clinical likelihood.[12]

negative study result.[6] When an ultrasound assessment is limited to proximal veins, a negative study result does not adequately exclude DVT. For patients with high pretest probability of disease and a negative "proximal" ultrasound, the AT9 guidelines recommend further testing to include either a high sensitivity fibrin D-dimer, whole leg ultrasound, or repeat proximal ultrasound in 1 week (all grade 1B) or venography (grade 2B).[6]

Computed Tomography and Magnetic Resonance Venography

Neither computed tomography venography nor magnetic resonance venography is recommended for routine use in the evaluation of DVT.[6]

Specific Evaluation for PE

Signs and symptoms of PE are often nonspecific[11]; therefore, a well-structured evaluation is needed when the diagnosis of PE is considered. The Wells[8] and Geneva[9] criteria provide a framework for risk-stratifying individuals on the basis of the pretest probability of disease . The Christopher study[12] categorized patients into "PE unlikely" for a Wells score of 4 or less or "PE likely" for a Wells score of more than 4, with subsequent evaluation dependent

on the likelihood of disease (Figure 2). Online calculators are readily available to calculate the Wells score for DVT (http://www.mdcalc.com/wells-criteria-for-dvt/) and PE (http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/). Additional imaging is necessary for patients with "PE likely" or an abnormal D-dimer test result. Computed tomography pulmonary angiography is the most common imaging modality used to diagnose PE with a high specificity and sensitivity.[13] With high pretest probability of disease, a negative study result is associated with a 3-month cumulative VTE rate of 1.5%. If a negative fibrin D-dimer test result is added to the testing algorithm, the 3 months event rate is 0.5% or less. The use of iodinated contrast dye is problematic for individuals with advanced renal disease, substantial risk factors for contrast-induced nephropathy, or allergic reactions. For these individuals, a ventilation-perfusion scan can be useful if interpreted as showing either definitely "positive" or definitely "negative" test results.[13] However, a substantive proportion of ventilation-perfusion scans are "indeterminate" and require additional testing. The gold standard diagnostic tool for PE, invasive pulmonary angiography, has largely been supplanted by using computed tomography pulmonary angiography.

VTE TREATMENT

Medications for Acute VTE

In patients with acute DVT or PE, initial therapy can include either parenteral anticoagulation (grade 1B) or oral rivaroxaban.[14] For patients bridged to warfarin, the use of either low-molecular-weight heparin (LMWH) or fondaparinux is preferred to unfractionated heparin (UFH) (grade 2C).[14]

Unfractionated Heparin

Unfractionated heparin is typically given intravenously by using a weight-based dosing algorithm (80 U/kg bolus followed by 18 U/kg per hour).[15,16] Dose adjustment nomograms using the activated partial thromboplastin time should be validated at one's institution, with an activated partial thromboplastin time ratio of 1.5 to 2.5 approximating heparin levels of 0.3 to 0.7 IU/mL measured by using an anti—factor Xa assay.[15,17] Weight-based unmonitored subcutaneous UFH has been found to provide an

TABLE 1. VTE Treatment Options (Presently FDA Approved)

Medication	Dosing	Considerations
Unfractionated heparin	Intravenous: 80 U/kg bolus and then 18 U/kg per hour infusion Subcutaneous: 333 U/kg and then 250 U/kg twice daily	• HIT monitoring • Nomogram aPTT ratio of 1.5-2.5 with anti–factor Xa level (0.3-0.7 IU/mL)
Enoxaparin	Subcutaneous: 1 mg/kg twice daily or 1.5 mg/kg once daily	• If CrCl < 30 mL/min, caution is advised because of LMWH accumulation
Dalteparin	Subcutaneous: 200 U/kg once daily	• If CrCl < 30 mL/min, caution is advised because of LMWH accumulation

Fondaparinux	Subcutaneous: Based on weight:
	  <50 kg = 5 mg once daily
	  50-100 kg = 7.5 mg once daily
	  >100 kg = 10 mg once daily
		• Contraindicated if CrCl < 30 mL/min

Warfarin	Oral: Initial dosing typically 5 mg once daily titrated for a goal of INR 2-3	• Lower starting dose in elderly patients, poor nutritional status, concurrent medications affecting metabolism, or underlying liver disease
Rivaroxaban	Oral: 15 mg twice daily for 21 days and then 20 mg once daily	• Avoid if CrCl < 30 mL/min • Avoid if moderate-to-severe liver disease or hepatic coagulopathy • Avoid for pregnant or nursing patients

aPTT = activated partial thromboplastin time; FDA = Food and Drug Administration; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism.

effective treatment of acute VTE (Table 1). In the FIDO trial,[18] subcutaneous heparin (333 U/kg followed by 250 U/kg twice daily) was as safe and effective as weight-based low-molecular-weight UFH for the treatment of VTE.

An important complication of heparin therapy is heparin-induced thrombocytopenia (HIT), which may be associated with both arterial and venous thrombosis.[19] With UFH, the risk of HIT may be as high as 5%, depending on the patient population studied. The development of HIT appears to be particularly high in patients recuperating from orthopedic surgery and receiving UFH.[19] Immune-mediated HIT is associated with a decline of 50% or more in platelet count typically within 5 to 10 days after beginning heparin (earlier with previous exposure). In patients with a risk of HIT of 1% or more, the AT9 guidelines recommend platelet count monitoring every 2 to 3 days from day 4 to day 14 while receiving heparin to proactively screen for thrombocytopenia (grade 2C).[19]

Low–Molecular-Weight Heparin

Food and Drug Administration (FDA)-approved LMWHs include enoxaparin and dalteparin. For patients with acute lower extremity DVT with or without PE, the AT9 guidelines prefer LMWH over intravenous (grade 2C) or subcutaneous (grade 2B) UFH.[14] Low-molecular-weight heparin should overlap warfarin initiation for a minimum of 5 days or until the international normalized ratio (INR) exceeds 2.0 for at least 24 hours (grade 1B).[14]

Once daily injection is preferred to twice daily injections (grade 2C).[14] For once daily dosing, however, the AT9 guidelines recommend using the full anticoagulant LMWH dose of enoxaparin (2 mg/kg once daily) or dalteparin (200 IU/kg once daily) (no grading provided).[14] Many clinicians however, use enoxaparin 1.5 mg/kg once daily on the basis of a single randomized trial.[20] This trial compared intravenous UFH with enoxaparin 1 mg/kg twice daily or enoxaparin 1.5 mg/kg once daily in 900 patients with symptomatic leg DVT, including approximately one-third with PE.[20] In this study, neither symptomatic VTE recurrence nor major bleeding differed by treatment arm. On the basis of this study, enoxaparin 1.5 mg/kg once daily has therefore become the clinical standard for outpatient treatment of DVT. It is our practice to treat patients with either acute DVT or small PE with enoxaparin 1.5 mg/kg once daily. For

patients with large PE, we recommend enoxaparin 1 mg/kg twice daily.

Owing to the more neutral charge of LMWHs, there is a lower risk of HIT such that platelet count monitoring is not indicated for most patients (grade 2C).[19]

Fondaparinux

Fondaparinux, a synthetic pentasaccharide, binds antithrombin with high affinity and has a greater specificity for factor Xa inhibition.[14] Given once daily weight-based dosing, it has excellent bioavailability after subcutaneous injection with a long half-life ($\sim$17 hours). Fondaparinux is contraindicated in severe renal insufficiency (CrCl < 30 mL/min). For patients with acute VTE, the AT9 guidelines prefer fondaparinux over intravenous heparin (grade 2C) or subcutaneous UFH (grade 2C).[14] There is insufficient data for use in pregnancy.

The risk of HIT with fondaparinux is insignificantly low such that platelet count monitoring is not indicated (grade 2C).[19]

Vitamin K Antagonist

The warfarin-specific AT9[21] guidelines include the following: (1) early initiation is preferred to delayed initiation (grade 1B); (2) stable outpatients begun on warfarin at a dose of 10 mg for the first 2 days followed by anticipated maintenance dosing, monitored with INR measurements (grade 2C); (3) for patients with consistently stable INRs, INR testing intervals may be lengthened to 12 weeks instead of a month (grade 2B); (4) for patients with previously stable INRs who have a single out of range result ±0.5, continue the present dose and recheck the INR within 1 to 2 weeks (grade 2C); (5) home INR monitoring may be implemented for patients who demonstrate competency in self-testing and who have stable INR measurements (grade 2B); and (6) nonsteroidal anti-inflammatory drugs and/or antiplatelet drugs should be avoided unless specifically indicated (eg, mechanical heart valves and acute coronary syndrome; grade 2C). Of these guidelines, we have not adopted the practice of extending INR interval testing beyond 4 weeks. Our initiation dose of warfarin is more conservative than outlined especially for elderly patients and those with confounding medications and coexisting comorbidities known to increase warfarin sensitivity.

The use of vitamin K for lowering excessive INR values depends on both the hemostatic assessment of the patient and the level of INR excess.[21] For INR values 4.5 to 10 with no bleeding, the routine use of vitamin K is not recommended (grade 2B).[21] In such patients, it is our practice to reassess the INR the following day to ensure patient safety and determine the INR trend. For INR values greater than 10 and no bleeding, vitamin K may be orally administered (grade 2C).[21] Typically 1 to 2 mg administered orally will result in INR reduction within 18 to 24 hours. With major bleeding, prothrombin complex concentrates are recommended (instead of plasma) in addition to parenteral vitamin K (grade 2C).[21] It has been our experience that parenteral vitamin K is typically well tolerated.[22] When indicated, we suggest 1 mg aliquots adequately diluted and administered intravenously (using an infusion pump) over 20 to 30 minutes followed by serial INR assessment.

For patients not receiving warfarin therapy, an increased INR in the setting of liver dysfunction (so-called auto-anticoagulation) is insufficient to prevent thromboembolism.[23]

Warfarin is metabolized by the highly polymorphic hepatic cytochrome p450 CYP2C9 system, which affects the rapidity of warfarin elimination. Enzymes responsible for vitamin K metabolism are also polymorphic, an important example being vitamin K epoxide reductase complex subunit 1.[24,25] There are presently insufficient randomized controlled trial data to warrant universal pharmacogenetic testing before warfarin initiation. The AT9 guidelines do not endorse pharmacogenomic-guided warfarin dosing (grade 1B).[21]

Direct Thrombin Inhibitor

Dabigatran, an oral direct thrombin inhibitor, was assessed in the RECOVER trial which randomized 2539 patients with acute VTE to receive either dabigatran 150 mg twice daily or warfarin[26] after a median of 9 days of the initial parenteral anticoagulant therapy. In this trial, dabigatran was found to be noninferior to warfarin from a safety and efficacy standpoint. The REMEDY and RESONATE trials[27] assessed dabigatran 150 mg twice daily compared with either warfarin or placebo for the secondary prevention of VTE in patients already completing at least 3 months of anticoagulant therapy. Venous

thromboembolism recurrence rates were similarly improved with either dabigatran or warfarin. Bleeding rates were lower in patients treated with dabigatran compared with warfarin. At present, dabigatran is not FDA approved for either the treatment or the prevention of VTE.

Direct Factor Xa Inhibitors

Rivaroxaban, an oral direct factor Xa inhibitor, has a time to peak concentration of 2 to 4 hours with an elimination half-life of 7 to 11 hours. Metabolized in the liver and excreted by the kidneys, rivaroxaban is contraindicated in patients with severe liver disease, any degree of hepatic coagulopathy, or severe renal insufficiency (CrCl < 30 mL/min) for the VTE indication.[21]

Rivaroxaban is FDA approved for thromboembolic prevention in atrial fibrillation, VTE prophylaxis after knee or hip replacement surgery, and VTE treatment. The RECORD trials[28] compared rivaroxaban 10 mg once daily with enoxaparin (40 mg once daily or 30 mg twice daily) for VTE prophylaxis in patients undergoing hip (RECORD 1 and 2) or knee (RECORD 3 and 4) replacement surgery.[28-31] Treatment duration was 35 days for hip arthroplasty and 10 to 15 days for knee arthroplasty. RECORD 1, 3, and 4 found that rivaroxaban therapy reduced DVT, PE, or death without increased bleeding rates. RECORD 2 reported that extended duration rivaroxaban (31-39 days) after hip arthroplasty was more effective than enoxaparin (10-14 days) without increased bleeding complications.

The EINSTEIN Investigators[32] randomized 3449 patients with symptomatic DVT to oral rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or enoxaparin followed by warfarin (or acenocoumarol).[32] The EINSTEIN-PE Investigators[33] randomized 4832 patients with acute PE to either rivaroxaban or enoxaparin/warfarin. In both trials, rivaroxaban was initiated without parenteral anticoagulant bridging or monitoring and was noninferior to enoxaparin/warfarin for safety and efficacy. After completing the initial treatment phase, 1196 patients were re-randomized to either continued rivaroxaban 20 mg once daily or placebo (EINSTEIN-EXTEND).[32] Continued rivaroxaban reduced recurrent thrombotic events compared with placebo (1.3% vs 7.1%) yet with similar bleeding rates (0.7% vs 0%). Despite these data, the AT9 guidelines prefer warfarin or LMWH

over rivaroxaban for VTE treatment (grade 2B).[14] In our practice, the use of rivaroxaban for the treatment of VTE is steadily increasing.

Apixaban, an oral factor Xa inhibitor, has a 12-hour half-life and is eliminated through renal, hepatic, and enteral routes. The AMPLIFY Investigators[34] randomized 5395 patients with acute VTE to either apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) or enoxaparin/warfarin. From an efficacy standpoint, apixaban was deemed noninferior to standard anticoagulant therapy. Both major bleeding and the composite of major plus nonmajor yet clinically relevant bleeding were significantly lower for patients receiving apixaban. The AMPLIFY-EXTEND Investigators[35] randomized 2486 patients with VTE who had recently completed 6 to 12 months of anticoagulation to receive 1 of 2 doses of apixaban (2.5 mg or 5 mg twice daily) or placebo for an additional 12 months. Both apixaban doses reduced recurrent VTE without increasing major bleeding. Apixaban is not yet FDA approved for the VTE indication.

Antiplatelet Agents

Although aspirin is the cornerstone antiplatelet therapy for the prevention and treatment of coronary and cerebral atherothrombotic events, recent attention has focused on its role in VTE. The WARFASA trial[36] found that aspirin 100 mg once daily reduced the risk of recurrence (6.6% vs 11.2% per year) in patients with unprovoked VTE after an initial treatment period of 6 to 18 months with a vitamin K antagonist. In the similarly designed ASPIRE trial,[37] low-dose aspirin resulted in a trend toward reduced VTE recurrence rates (hazard ratio, 0.74; 95% CI, 0.52-1.05; P=.09). With regard to VTE secondary prevention, the AT9 guidelines make no specific recommendations.[14] A recent study[38] found that aspirin was noninferior to LMWH for extended VTE prophylaxis for patients after total hip arthroplasty who were initially treated with 10 days of LMWH.

Outpatient vs Inpatient Treatment

The decision to treat suspected VTE while awaiting confirmatory testing depends on the pretest probability of finding an acute DVT or PE and the anticipated delay to acquiring test results.[14] If the pretest probability is high, prompt parenteral anticoagulation is recommended while

awaiting test results (grade 2C).[14] For those at moderate pretest probability, early treatment is recommended if there is an anticipated delay in test results exceeding 4 hours (grade 2C).[14] With a low clinical suspicion of DVT or PE using the Wells criteria, empiric therapy is not recommended, provided that confirmatory testing is available within 24 hours (grade 2C).[14]

For stable patients without significant risk of bleeding, outpatient therapy is acceptable for acute DVT treatment (grade 1B).[14] A number of studies have compared outpatient LMWH with inpatient intravenous UFH for the initial treatment of DVT.[39,40] One study assessed the importance of hospitalization by randomizing 201 patients with DVT to outpatient vs inpatient LMWH for this initial therapy. The rates of thrombus extension (1% vs 2%), major bleeding (2% vs 2%), and mortality (0% vs 2%) were almost identical for outpatient vs inpatient LMWH delivery.[40] For patients with DVT, threatened venous gangrene, or extensive iliofemoral involvement, inpatient admission for mechanical and pharmacologic thrombolytic therapy should be considered.[14]

For appropriately selected patients with PE, outpatient treatment may also be acceptable. Criteria include hemodynamic and clinical stability, strong social support and access to medical care, and good adherence to medically recommended treatment. The simplified PE Severity Index (PESI) is an easy-to-use risk stratification tool to help discern which patients with PE may be treated as outpatients.[41] This tool assigns 1 point each for age greater than 80 years, history of cancer, history of chronic lung disease or heart failure, pulse exceeding 110 per minute, systolic blood pressure less than 100 mm Hg, and oxygen saturation less than 90%. Risk is classified as low (0 points) or high ($\geq$1 point) risk. In both the derivation and validation cohorts, nearly one-third of the patients who were deemed "low risk" by these criteria had a very low 30-day mortality rate of 1.1% or less. This result is comparable to a 30-day mortality rate approaching 10% for high-risk patients.

Duration of Anticoagulation

For a DVT or PE that is provoked by either surgery or a transient risk factor, the recommended duration of treatment is 3 months (grade 1B).[14] In the setting of an unprovoked proximal DVT or PE, the duration of anticoagulation depends on the risk of bleeding for the individual patient. For patients at low-to-moderate risk for bleeding, extended therapy is recommended (grade 2B).[14] For those with high risk of bleeding, treatment may be discontinued after 3 months (grade 1B).[14]

Bleeding risk assessment may be complicated, relies on the summation of a number of variables, and risk calculation tools have not been well validated. Factors used in this prediction may vary by extent and severity (eg, thrombocytopenia extent), temporal relation to a specific provocation (eg, major trauma or surgery), and the extent to which previous causes have been modified.[14] In general, bleeding rates vary from low (0.8%/y) to moderate (1.6%/y) to high ($\geq$6.5%/y) risk. A number of bleeding prediction tools have been proposed,[42-45] including online calculators.[46,47]

Factors deemed inadequate to affect anticoagulation duration include fibrin D-dimer assessment after the initial treatment of VTE, antiphospholipid antibodies, hereditary thrombophilias, male sex, and the presence of residual thrombus on follow-up ultrasound imaging (no grade provided).[14] It is our practice to provide prolonged secondary prophylaxis to patients with high-risk hereditary (homozygous or compound heterozygous factor V Leiden, prothrombin G20210A sequence variations, or congenital deficiencies of protein C, protein S, or antithrombin) or acquired (antiphospholipid antibody syndrome) thrombophilias.

VTE in the Setting of Underlying Malignant Disease

For patients with VTE in the setting of an active malignant disease, extended anticoagulation is recommended regardless of the bleeding risk (grade 2B) and LMWH is the preferred anticoagulant (grade 2B).[14] Anticoagulants are continued until there is no evidence of active malignant disease defined as any evidence of cancer on cross-sectional imaging or any cancer-related treatment (surgery, radiation, or chemotherapy) within the past 6 months.[14]

The CLOT Investigators[48] randomized 672 patients with active cancer and acute VTE to receive either LMWH (dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for 5 months) or adjusted dose warfarin. At the end of the 6-month study

period, recurrent thromboembolism was 17% in the oral anticoagulant group and 9% in the dalteparin group (hazard ratio, 0.48; P=.002). There was no significant difference between groups in the rate of major bleeding (dalteparin 6% vs warfarin 4%). Enoxaparin is likely a reasonable alternative LMWH.[49-51]

For patients with cancer who have suffered recurrent VTE despite LMWH, "LMWH failure," there are several entities to consider. First, it is helpful to obtain a heparin level by using anti—factor Xa assay, which should be performed before additional heparin is added. This finding can help determine whether LMWH was within the therapeutic range as well as whether the patient adhered to therapy. Second, it is important to exclude HIT as a potential therapeutic adverse reaction. Third, it is important to determine whether cancer recurrence or progression has occurred as a contributing factor. Augmenting the LMWH dose and transitioning to twice daily dosing may be helpful. In general, however, LMWH failure in the setting of cancer portends a poor prognosis.

Acute Isolated Distal DVT

Distal DVT is defined as DVT confined to the deep veins of the calf (posterior or anterior tibial, peroneal, soleal, or gastrocnemius veins). Initial anticoagulation is recommended for acute isolated distal leg DVT if patients have risk factors for extension or severe symptoms (grade 2C).[14] Risk factors for extension include thrombus length greater than 5 cm, multiple veins involved, unprovoked event, cancer, previous VTE, hospitalization, or recent surgery.[14] In addition, in the discussion section of the AT9 guidelines, D-dimer is noted as a possible risk factor for extension; however, there are no recommendations for how this is to be used clinically. In the absence of risk factors or severe symptoms, serial imaging can be performed at 1 and 2 weeks while withholding anticoagulation (grade 1B).[14] Most of the thrombus propagation occurs within the first 2 weeks. If there is thrombus propagation, then anticoagulation should be initiated (grade 1B).[14] It is our practice to offer anticoagulation for patients with calf DVT unless there is an obvious contraindication such as major bleeding. Even with an unprovoked calf DVT, 3 months of anticoagulation is recommended over extended therapy (grade 1B).[14]

VTE in Pregnant Patients

Anticoagulation in pregnancy must take both the fetus and the mother into consideration.[52] Low-molecular-weight heparin is recommended over warfarin for both prevention and treatment of VTE in pregnant patients (grade 1A).[52] If acute VTE is diagnosed during pregnancy, anticoagulation should be continued until delivery and reinitiated for at least 6 weeks postpartum with a total duration of at least 3 months (grade 2C).[52] The use of fondaparinux or parenteral direct thrombin inhibitors should be reserved for women with HIT (grade 2C).[52] The oral direct thrombin inhibitors and factor Xa inhibitors should also be avoided in pregnancy owing to the lack of safety data (grade 1C).[52]

Antepartum prophylaxis is suggested for pregnant women at increased risk: previous unprovoked VTE, pregnancy or estrogen-related VTE, homozygous factor V Leiden or prothrombin G20210A, or antiphospholipid antibody syndrome (grade 2C).[52] For these patients, prophylactic or intermediate dose LMWH (enoxaparin 40 mg once daily, dalteparin 5000 U once daily, or LMWH with dose-adjusted anti—factor Xa levels 0.2-0.6 U/mL) is recommended. For pregnant women with single previous VTE associated with a transient risk factor (not pregnancy or estrogen related), no antepartum prophylaxis is recommended (grade 2C).[52] Pregnant women with previous VTE should receive postpartum prophylaxis for 6 weeks with prophylactic dose LMWH or warfarin with a goal INR of 2.0 to 3.0 (grade 2B).[52] Neither LMWH nor warfarin is secreted in breast milk.

Catheter–Related Upper Extremity DVT

For patients with a catheter-related upper extremity DVT, therapeutic anticoagulation is indicated, typically for 3 months.[14] Catheter retrieval is not necessary as long as it remains functional and required for clinical care (grade 2C).[14] Anticoagulation for upper extremity DVT in the setting of a central venous catheter should be continued as long as the catheter is in place (grade 1C).[14] The deep veins of the upper extremity include the brachial, axillary, subclavian, and innominate veins. Superficial thrombosis of the cephalic and basilic veins does not require anticoagulant therapy. It is not our practice to provide primary prophylaxis

to patients with indwelling central venous catheters.

Splanchnic and Hepatic Vein Thrombosis

The splanchnic venous system includes the portal, hepatic, splenic, superior, and inferior mesenteric veins. Depending on the extent and rapidity of thrombus propagation, complications may include bowel or splenic infarction or portal hypertension. Anticoagulation initiation depends on symptoms, extent, and acuity of thrombus formation. With symptoms or extensive and acute appearing thrombosis, anticoagulation therapy should be considered (grade 1B).[14] For incidentally found asymptomatic splanchnic vein thrombosis, the AT9 guidelines suggest no anticoagulation (grade 2C).[14] It is our clinical practice to treat acute splanchnic vein thrombosis irrespective of symptoms to prevent thrombus propagation. In the absence of randomized trial data, it has been our practice to treat splanchnic vein thrombosis for 6 months.[53]

Superficial Venous Thrombosis

Superficial "phlebitis" is common, with an incidence of approximately 125,000 annually. Whereas approximately 25% of the patients will have an underlying DVT, ultrasound imaging both to confirm the diagnosis and to exclude subclinical DVT is warranted.[54] Most events can be treated conservatively without anticoagulant therapy owing to the low risk of PE (1.3%).[55] For superficial phlebitis exceeding 5 cm in length, prophylactic dose fondaparinux or LMWH is recommended for 45 days (grade 2B).[14] Fondaparinux (2.5 mg daily) is preferred to LMWH (grade 2C).[14] It is our practice to reserve parental anticoagulation for those patients with severe pain, extensive venous involvement, or evidence of thrombus propagation.

Preventing Postthrombotic Syndrome

Compression stockings (30-40 mm Hg knee high) worn for 2 years have been found to reduce the risk of postthrombotic syndrome by 50%[56,57] (grade 2B).[14]

Mechanical Thrombectomy or Catheter-Directed Lysis for Acute DVT

In patients with proximal DVT, approximately half will develop postthrombotic syndrome despite anticoagulant therapy.[58] Approximately 50% will have disabling venous claudication and will be unable to walk more than 240 m because of severe pain.[59,60] Moreover, iliac vein involvement is relatively common, affecting 25% of all patients with leg DVT.[60] At present, mechanical thrombectomy and catheter-directed thrombolysis are considered for patients with iliofemoral DVT in whom the risk of postthrombotic syndrome is relatively high as well as for the rare patients with threatened venous gangrene despite treatment with anticoagulant therapy.[14] The CaVenT study[61] compared catheter-directed thrombolysis and anticoagulant therapy in 103 patients with acute proximal venous thrombosis. Eighty-eight percent of the patients treated with catheter-directed therapy achieved either complete or partial (50%-90%) lysis. At 6 months, iliofemoral patency was twice as frequent in the invasive treatment arm as in the conservative arm. At 2 years, iliofemoral patency was significantly increased and postthrombotic syndrome was significantly reduced in the active treatment arm.[62] The risk of major bleeding did not differ between the 2 groups. The AT9 guidelines state that anticoagulant therapy is recommended over catheter-directed thrombolysis (grade 2C).[14] However, for patients at reasonable risk for bleeding who place a high value on preventing postthrombotic syndrome and a low value on treatment complexity, cost, and risk of bleeding, catheter-directed thrombolysis is reasonable. It is our practice to assess all patients with iliac vein thrombosis for thrombolysis and mechanical thrombectomy candidacy.

Thrombolytic Therapy in the Setting of PE

For patients with PE and hypotension (systolic blood pressure <90 mm Hg or abrupt decrease by >40 mm Hg persisting for >15 minutes) who are not at high risk for bleeding, systemic thrombolytic therapy is reasonable (grade 1B).[14] Specific recommendations include a short infusion time (2 hours instead of 24 hours) delivered systemically as opposed to directed with a pulmonary artery catheter (grade 2C).[14] Catheter-directed or surgical pulmonary thrombectomy may be pursued for hypotensive patients who have failed thrombolytic therapy, have a contraindication to their use, or are likely to die of shock before realizing any benefit from systemic thrombolytic therapy (grade 2C).[14] The decision to use catheter-directed or surgical thrombectomy depends on available expertise and resources.

Role of Inferior Vena Cava Filters

In general, there is a marked overuse of inferior vena cava (IVC) filters (both temporary and permanent) in the United States.[63] Inferior vena cava filters are recommended for patients with acute proximal lower extremity DVT or PE who have a contraindication to anticoagulation (grade 1B).[14] Preference is given for a temporary IVC filter that can be removed when the bleeding risk has resolved. Although IVC filters have been associated with an increased DVT recurrence rate,[64] this is not an indication for extended secondary prophylaxis with anticoagulants. The duration of anticoagulant therapy is based on patient-specific risk, nature of the VTE event (provoked vs unprovoked), and perceived bleeding risk regardless of whether an IVC filter remains in place.

Perioperative Management of Anticoagulation

For the perioperative management of anticoagulation, the decision to use bridging therapy depends on the risk of thromboembolism as well as the potential for bleeding complications.[65] For patients at moderate-to-high risk for thromboembolism, bridging anticoagulation should be considered in the periprocedural period (grade 2C).[65] In our experience, this would include patients with a recent VTE diagnosis (<3 months) or those with active cancer.[66] If possible, elective procedures should be delayed until the acute anticoagulation treatment period (3 months) can be completed. For patients requiring more urgent procedures, warfarin is discontinued 5 days before the anticipated procedure and bridging therapy with LMWH is initiated when the INR is less than 2.0 (grade 2C).[65] The last dose of LMWH is provided on the morning of the day before the surgery. Warfarin is resumed the evening after surgery, assuming that hemostasis has been achieved. Resumption of therapeutic LMWH postoperatively should be at 48 hours once hemostasis is assured. Prophylactic dose LMWH can be initiated 12 hours after surgery. If individuals are at low risk for thromboembolism, anticoagulation can be discontinued 5 days before the procedure without bridging therapy (grade 2C).[65]

PREVENTION OF VTE

Whereby the adverse consequences of VTE result in considerable morbidity and mortality, prevention of this disease is a high priority. The Agency for Healthcare Research and Quality has deemed VTE prophylaxis as one of the top priorities of improved patient safety practices.[67,68] Moreover, the National Quality Forum has endorsed VTE prophylaxis standards and outcomes measures.[69] Despite a large volume of high-quality randomized controlled trial data demonstrating safety and efficacy, many hospitalized surgical and nonsurgical patients with an indication fail to receive VTE prophylaxis. For example, the ENDORSE study[70] of 358 hospitals in 32 countries enrolling 68,183 patients found that only 58.5% of at-risk surgical patients and 39.5% of at-risk medical patients received American College of Chest Physicians-recommended VTE prophylaxis. Similar results have been reported for US hospitals. In the DVT FREE prospective registry,[71] of 2726 hospital inpatients with ultrasound-confirmed DVT, only 42% received prophylaxis within the 30 days before diagnosis. Improving best practices for ensuring appropriate delivery of VTE prophylaxis can be challenging. Information technology using computerized clinical decision support with informed order sets and "opt-in" strategies may improve this delivery.[72]

General Medical Patients

For patients who are acutely ill and hospitalized, a strategy for VTE prevention may include prophylactic dose LMWH, low-dose UFH (twice or thrice daily), or fondaparinux (Table 2) continued throughout the hospitalization (grade 1B).[73] For patients at high risk for bleeding, mechanical thromboprophylaxis with graduated compression stockings and/or intermittent pneumatic compression (IPC) is recommended (grade 2C).[73] The AT9 guidelines do not recommend rivaroxaban for VTE prevention in acutely ill general medical patients. The recent MAGELLAN trial[74] evaluated the extended use of rivaroxaban (35±4 days) vs enoxaparin (10±4 days) or placebo. Rivaroxaban was associated with fewer VTE events, but at the cost of higher risk of bleeding. Overall, rivaroxaban was noninferior to the standard prevention with enoxaparin.

When determining the likelihood of VTE for general medical patients, the Padua Prediction

TABLE 2. VTE Prophylaxis Strategies.

Treatment	Acutely Ill General Medical Patients	Patients Who Undergo Nonorthopedic Surgery	Patients Who Undergo Orthopedic Surgery (THA or TKA)
Enoxaparin	Subcutaneous: 40 mg once daily	Subcutaneous: 40 mg once daily	Subcutaneous: 30 mg twice daily • ≥12 h before or after surgery • Continued for ≥10-14 d • Consider up to 35 d
Dalteparin	Subcutaneous: 5000 IU once daily	Subcutaneous: • Low risk: 2500 IU once daily • High risk: 2500 IU for 12 h after surgery and then 5000 IU once daily	Subcutaneous: 2500 IU • ≥12 h after surgery and then 5000 IU once daily • Continue for ≥10-14 d • Consider up to 35 d
Fondaparinux	Subcutaneous: 2.5 mg once daily	Subcutaneous: 2.5 mg once daily continued for up to 10 d	Subcutaneous: 2.5 mg once daily • Continue for ≥10-14 d • Consider up to 35 d • CrCl 30-50 mL/min: 1.5 mg once daily
Warfarin	Not recommended	Not recommended	Adjusted dose warfarin for a goal INR of 2.0 to 3.0 for ≥10-14 d • Consider up to 35 d
Rivaroxaban	Noninferior to LMWH at a dose of 10 mg once daily (see text discussion)	Not studied	10 mg once daily for ≥6-10 h after surgery • Continue ≥10-14 d • Consider up to 35 d
Unfractionated heparin	Subcutaneous: 5000 U thrice daily in cancer patients	Subcutaneous: 5000 U twice daily or thrice daily until fully ambulatory	Subcutaneous: 5000 U twice daily or thrice daily until fully ambulatory • Continue for ≥10-14 d • Consider up to 35 d

THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

Score can help stratify patients into low or high risk.[75] This scoring system requires further validation; however, it is poised to be a useful clinical tool. It is important to identify those general medical patients who will benefit most from pharmacologic thromboprophylaxis.

Nonorthopedic Surgery Patients

The greatest risk of VTE in nonorthopedic surgery includes general and abdominal pelvic surgery, particularly in the setting of an underlying malignant disease.[76] Decisions regarding pharmacologic (Table 2) or mechanical prophylaxis depend on the patient-specific VTE risk and bleeding propensity (Figure 3). Venous thromboembolism risk assessment can be accomplished by using the Caprini score, which stratifies patient risk into 4 categories of thrombosis risk: very low (0 points; ≤0.5%), low (1-2 points; 1.5%), moderate (3-4 points; 3%), and high (>5 points; 6%) (Figure 2 and Table 3).[77] For patients at very low risk, early and frequent ambulation is recommended only over

pharmacologic (grade 1B) or mechanical (grade 2C) interventions.[76]

Patients who undergo cardiac surgery and have an uncomplicated postoperative course can be treated with IPC (grade 2C).[76] With any nonhemorrhagic complications (ie, electromechanical, infectious, pulmonary, neurologic, or renal dysfunction that may prolong hospital stay), LMWH or UFH should be added (grade 2C).[76] For patients who undergo thoracic surgery and have moderate-to-high risk of VTE as assessed by using the Caprini method, without significant risk of bleeding, either LMWH or low-dose UFH should be combined with mechanical prophylaxis (grade 2B).[76] For patients at high risk for bleeding, mechanical prophylaxis should be used until the risk of significant hemorrhage decreases and pharmacologic treatment can be initiated. In the setting of spinal surgery in which a patient is at high risk for VTE, once hemostasis is achieved and the bleeding risk decreases, the addition of pharmacologic prophylaxis is recommended in addition to the use of IPC
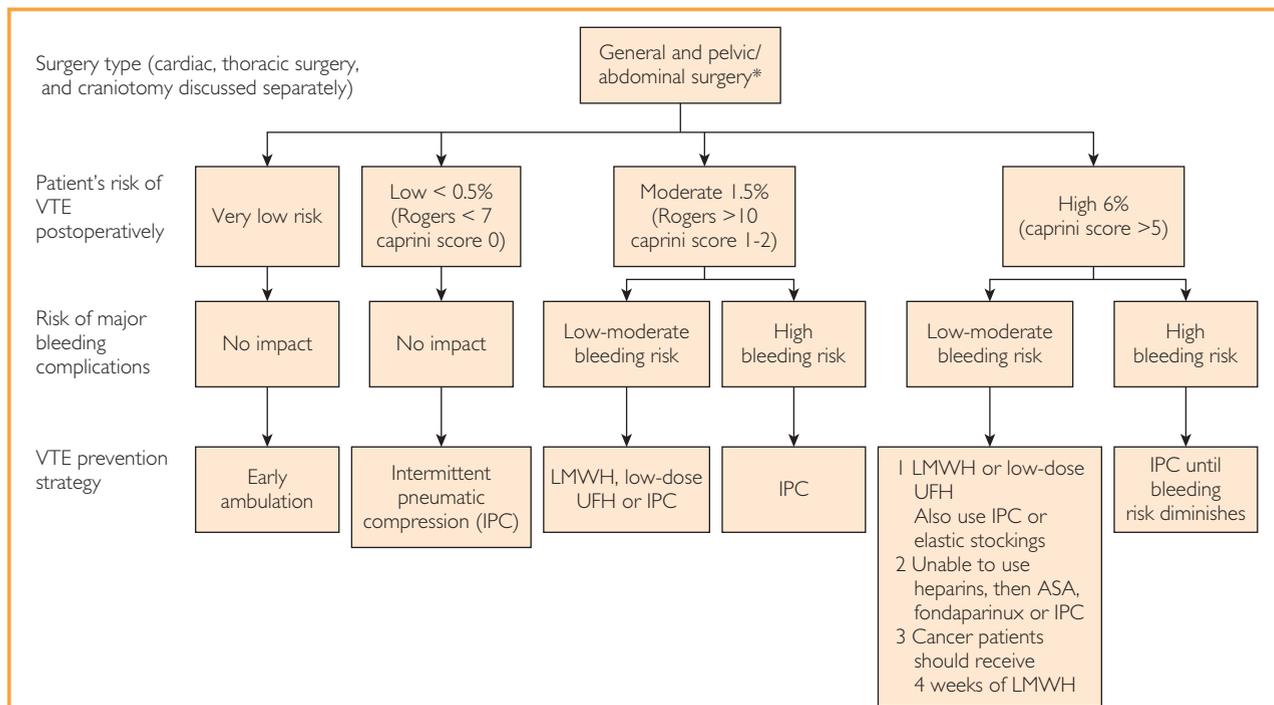
Surgery type (cardiac, thoracic surgery, and craniotomy discussed separately) → General and pelvic/abdominal surgery*

Patient's risk of VTE postoperatively:
- Very low risk
- Low < 0.5% (Rogers < 7 caprini score 0)
- Moderate 1.5% (Rogers >10 caprini score 1-2)
- High 6% (caprini score >5)

Risk of major bleeding complications:
- No impact (Very low risk)
- No impact (Low risk)
- Low-moderate bleeding risk / High bleeding risk (Moderate)
- Low-moderate bleeding risk / High bleeding risk (High)

VTE prevention strategy:
- Early ambulation
- Intermittent pneumatic compression (IPC)
- LMWH, low-dose UFH or IPC
- IPC
- 1 LMWH or low-dose UFH. Also use IPC or elastic stockings. 2 Unable to use heparins, then ASA, fondaparinux or IPC. 3 Cancer patients should receive 4 weeks of LMWH
- IPC until bleeding risk diminishes

FIGURE 3. Choosing strategies for venous thromboembolism (VTE) prevention in patients who undergo nonorthopedic surgery.[76] LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

(grade 2C).[76] Patients with major trauma should be treated with both mechanical and pharmacologic prophylaxis unless contraindicated (grade 2C).[76] Inferior vena cava filters are not routinely recommended for primary VTE prevention in patients with major trauma (grade 2C).[76]

Orthopedic Surgery Patients
For major orthopedic surgery, there are many options for VTE prevention including LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban, low-dose UFH, adjusted-dose vitamin K, and aspirin (Table 3; grade 1B).[78]

TABLE 3. Caprini Risk Assessment Model[77]			
1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age >75 y	Stroke <1 mo
Minor surgery	Arthroscopic surgery	History of VTE	Elective lower extremity arthroplasty
Body mass index >25 kg/m^2	Major open surgery >45 min	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery >45 min	Any thrombophilia	Acute spinal cord injury <1 mo
Varicose veins	Bed rest >72 h	Elevated serum homocysteine	
Pregnant or postpartum	Immobilizing plaster cast	Heparin-induced thrombocytopenia	
History of miscarriage	Central venous access		
Oral contraceptives or hormone replacement therapy			
Sepsis <1 mo			
Serious lung disease <1 mo			
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure <1 mo			
History of inflammatory bowel disease			
Medical patient on bed rest			
VTE = venous thromboembolism.			

Low-molecular-weight heparin is preferred with the first dose given at least 12 hours from the time of surgery (either pre- or postoperatively; grade 2C).[78] Rivaroxaban is the only new oral anticoagulant with FDA approval for VTE prophylaxis in orthopedic surgery. Intermittent pneumatic compression for a goal of 18 hours daily is recommended in addition to anticoagulant therapy.[78] When patients have a significant risk of bleeding, IPC may be used alone. A minimum duration of 10 to 14 days of thromboprophylaxis is recommended, with consideration of up to 35 days for patients at higher risk for VTE (grade 2B).[78]

CONCLUSION

Data from an increasing number of published randomized controlled trials exist for VTE prevention and treatment with new and conventional anticoagulants, including mechanical devices. Incorporating a guideline-based approach to VTE evaluation, prevention, and treatment is anticipated to improve patient safety and outcomes, improve satisfaction of health care professionals knowing they have adhered to the latest and highest standards, and reduce health care delivery costs by reducing outcome events.

This is a review for clinicians based on the American College of Chest Physicians Clinical Practice Guidelines 2012 for Antithrombotic Therapy and Prevention of Thrombosis.

Abbreviations and Acronyms: AT9 = American College of Chest Physicians Antithrombotic Guidelines, 9th edition; **DVT =** deep vein thrombosis; **FDA =** Food and Drug Administration; **HIT =** heparin-induced thrombocytopenia; **INR =** international normalized ratio; **IPC =** intermittent pneumatic compression; **IVC =** inferior vena cava; **LMWH =** low-molecular-weight heparin; **PE =** pulmonary embolism; **UFH =** unfractionated heparin; **VTE =** venous thromboembolism

Correspondence: Address to Robert D. McBane II, MD, Gonda Vascular Center, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (mcbane.robert@mayo.edu).

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2013;127(1):doi:10.1161/CIR. 0b013e31828124ad and *Circulation*. 2013;127(23):e841]. *Circulation*. 2013;127(1):e6-e245.
2. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med*. 1999;159(5):445-453.
3. Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc*. 2000;75(12):1249-1256.
4. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.
5. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schüünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published corrections appear in *Chest*. 2012;142(6):1698 and *Chest*. 2012; 141(4):1129]. *Chest*. 2012;141(2, suppl):7S-47S.
6. Bates SM, Jaeschke R, Stevens SM, et al; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, suppl):e351S-e418S.
7. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798.
8. Gibson NS, Sohne M, Kruip MJ, et al; Christopher Study Investigators. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. *Thromb Haemost*. 2008;99(1):229-234.
9. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med*. 2006;144(3):165-171.
10. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA*. 2006;295(2): 199-207.
11. Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med*. 2011;155(7):448-460.
12. van Belle A, Büller HR, Huisman MV, et al; Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295(2):172-179.
13. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990; 263(20):2753-2759.
14. Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in *Chest*. 2012;142(6):1698-1704]. *Chest*. 2012;141(2, suppl):e419S-e494S.
15. Garcia DA, Baglin TP, Weitz JI, Samama MM; American College of Chest Physicians. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in *Chest*. 2012; 141(5):1369]. *Chest*. 2012;141(2, suppl):e24S-e43S.
16. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med*. 1993;119(9):874-881.
17. Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med*. 1972;287(7):324-327.
18. Kearon C, Ginsberg JS, Julian JA, et al; Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296(8):935-942.

19. Linkins LA, Dans LA, Moores LK, et al; American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia treatment of HIT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2, suppl):e495S-e530S.

20. Merli G, Spiro TE, Olsson CG, et al; Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001;134(3):191-202.

21. Ageno W, Gallus AS, Wittkowsky A, et al; American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2, suppl):e44S-e88S.

22. Shields RC, McBane RD, Kuiper JD, Li H, Heit JA. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc. 2001; 76(3):260-266.

23. Dabbagh O, Oza A, Prakash S, Sunna R, Saettele TM. Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease. Chest. 2010; 137(5):1145-1149.

24. Jonas DE, Evans JP, McLeod HL, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. Pharmacogenomics. 2013;14(13):1593-1603.

25. Kimmel SE, French B, Anderson JL, et al. Rationale and design of the Clarification of optimal anticoagulation through genetics trial. Am Heart J. 2013;166(3):435-441.

26. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-2352.

27. Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709-718.

28. Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358(26):2765-2775.

29. Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-39.

30. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-2786.

31. Turpie AG, Lassen MR, Davidson BL, et al; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-1680.

32. EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-2510.

33. EINSTEIN-PE Investigators; Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-1297.

34. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.

35. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699-708.

36. Becattini C, Agnelli G, Schenone A, et al; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism [published correction appears in N Engl J Med. 2012; 367(16):1573]. N Engl J Med. 2012;366(21):1959-1967.

37. Brighton TA, Eikelboom JW, Mann K, et al; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012;367(21):1979-1987.

38. Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med. 2013;158(11):800-806.

39. Koopman MM, Prandoni P, Piovella F, et al; The Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home [published correction appears in N Engl J Med. 1997; 337(17):1251]. N Engl J Med. 1996;334(11):682-687.

40. Boccalon H, Elias A, Chalé JJ, Cadène A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Arch Intern Med. 2000; 160(12):1769-1773.

41. Jiménez D, Aujesky D, Moores L, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-1389.

42. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol. 2011;57(2):173-180.

43. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713-719.

44. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105(2):91-99.

45. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. Chest. 2006;130(5): 1390-1396.

46. Hemorr2hages Bleeding Risk Score. http://www.globalrph.com/hemorr2hages-bleeding-risk.htm. Accessed January 13, 2014.

47. Has Bled Score. http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/. Accessed January 13, 2014.

48. Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-153.

49. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J; ONCENOX Investigators. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost. 2006;12(4): 389-396.

50. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162(15): 1729-1735.

51. Hull RD, Pineo GF, Brant RF, et al; LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119(12):1062-1072.

52. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2, suppl):e691S-e736S.

53. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. *Clin Gastroenterol Hepatol*. 2010;8(2):200-205.

54. Jorgensen JO, Hanel KC, Morgan AM, Hunt JM. The incidence of deep venous thrombosis in patients with superficial thrombophlebitis of the lower limbs. *J Vasc Surg*. 1993;18(1):70-73.

55. Decousus H, Prandoni P, Mismetti P, et al; CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363(13):1222-1232.

56. 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(9054):759-762.

57. 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(4):249-256.

58. Baldwin MJ, Moore HM, Rudarakanchana N, Gohel M, Davies AH. Post-thrombotic syndrome: a clinical review. *J Thromb Haemost*. 2013;11(5):795-805.

59. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. *Ann Surg*. 2004; 239(1):118-126.

60. Wysokinska EM, Sobande F, Wysokinski WE, Bjarnason H, McBane RD II. Iliac vein thrombosis: feasibility assessment of randomized controlled trials of endovascular pharmacomechanical thrombolysis. *J Thromb Haemost*. 2010;8(9):1943-1949.

61. Enden T, Kløw NE, Sandvik L, et al; CaVenT Study Group. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. *J Thromb Haemost*. 2009;7(8):1268-1275.

62. Enden T, Haig Y, Kløw NE, et al; CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.

63. Kinney TB. Update on inferior vena cava filters. *J Vasc Interv Radiol*. 2003;14(4):425-440.

64. Decousus H, Leizorovicz A, Parent F, et al; Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med*. 1998;338(7):409-415.

65. Douketis JD, Spyropoulos AC, Spencer FA, et al; American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [pubished correction appears in *Chest*. 2012;141(4):1129.]. *Chest*. 2012; 141(2, suppl):e326S-e350S.

66. McBane RD, Wysokinski WE, Daniels PR, et al. Periprocedural anticoagulation management of patients with venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2010;30: 442-448.

67. Shekelle PG. Nurse-patient ratios as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5, Pt 2):404-409.

68. Shekelle PG, Pronovost PJ, Wachter RM, et al. The top patient safety strategies that can be encouraged for adoption now. *Ann Intern Med*. 2013;158(5, Pt 2):365-368.

69. National Quality Forum. NQF-Endorsed Standards; 2012. Washington, DC: National Quality Forum. http://www.qualityforum.org/QPS/QPSTool.aspx. Accessed January 14, 2014.

70. Cohen AT, Tapson VF, Bergmann JF, et al; ENDORSE Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study [published correction appears in *Lancet*. 2008;371(9628):1914]. *Lancet*. 2008;371(9610):387-394.

71. Goldhaber SZ, Tapson VF, DVT FREE Steering Committee. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol*. 2004;93(2):259-262.

72. Zeidan AM, Streiff MB, Lau BD, et al. Impact of a venous thromboembolism prophylaxis "smart order set": improved compliance, fewer events. *Am J Hematol*. 2013;88:545-549.

73. Kahn SR, Lim W, Dunn AS, et al; American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, suppl):e195S-e226S.

74. Cohen AT, Spiro TE, Büller HR, et al; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(6):513-523.

75. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8(11):2450-2457.

76. Gould MK, Garcia DA, Wren SM, et al; American College of Chest Physicians. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, suppl): e227S-e277S.

77. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. *Ann Surg*. 2010;251(2):344-350.

78. Falck-Ytter Y, Francis CW, Johanson NA, et al; American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2, suppl):e278S-e325S.