CONT. blood product (erythrocytes or platelets) engraft in an immunocompromised recipient and cause toxic effects in the bone marrow, skin, liver, and gastrointestinal tract. Patients at risk include those receiving chemotherapy for autoimmune disorders or malignancy, recipients of blood components from first-degree relatives, and premature infants. Prevention involves γ irradiation of cellular blood components intended for recipients at risk. Patients who have undergone stem cell transplantation typically require irradiated blood components indefinitely; this should be communicated from the transplant center at the time of discharge from the transplant program.

KEY POINT

- Patients who have undergone stem cell transplantation typically require γ-irradiated blood products to prevent transfusion-associated graft-versus-host disease.

Transfusion in Special Circumstances

Massive transfusion refers to the transfusion of one total blood volume, which is equivalent to 8 to 10 units of blood, within a 24-hour period. Conditions requiring massive transfusion include trauma, ruptured aortic aneurysm, and severe gastrointestinal bleeding. When whole blood is lost and replaced with crystalloid and PRBCs, a dilutional coagulopathy develops that is often exacerbated by hypothermia, acidosis, and liver injury as well as concomitant disseminated intravascular coagulation. Contemporary practice is to transfuse plasma and platelets concurrently with PRBCs to avert the development of dilutional coagulopathy. During resuscitation, patients must be monitored for electrolyte disturbances such as hypocalcemia (because the citrate in the anticoagulant used for all blood components binds free calcium, which lowers the serum calcium concentration), hyperkalemia or hypokalemia, and metabolic alkalosis (from citrate metabolism).

Autoimmune hemolytic anemia presents a unique transfusion challenge. Warm reactive autoantibodies are usually polyclonal IgG antibodies directed against erythrocytes (the patient's own, reagent, and donor erythrocytes). The clinical significance of warm autoantibodies derives from their hemolytic potential and their interference with routine pretransfusion compatibility testing, specifically the detection of alloantibodies and the provision of crossmatch-compatible blood. The urgency of the transfusion, particularly the presence of acute cardiopulmonary or central nervous system symptoms, must be considered along with the risk for hidden alloantibodies, which are rare in patients without previous pregnancy or transfusion. Transfused units should be matched for ABO and Rh. Care of these patients should be closely coordinated between the hospitalist, hematologist, and blood bank specialist.

KEY POINTS

- As patients requiring massive transfusion are resuscitated, they must be monitored for electrolyte disturbances such as hypocalcemia, hyperkalemia or hypokalemia, and metabolic alkalosis.
- Patients with warm autoimmune hemolytic anemia have autoantibodies that react against all erythrocytes, including donor erythrocytes, so a completely crossmatch-compatible unit may be impossible to find; these patients should be transfused with ABO and Rh type-specific, crossmatch-incompatible blood.

Therapeutic Apheresis

Apheresis procedures use an automated blood cell separator to collect whole blood, separate it into the plasma and cellular components, remove the component contributing to disease, and return the other blood components to the patient combined with replacement fluids. Plasmapheresis for patients suspected of having Guillain-Barré syndrome is a classic example. Crystalloid and colloid fluids are used for replacement, and plasma components are typically avoided. Therapy for thrombotic thrombocytopenic purpura is more appropriately characterized as plasma exchange because fresh frozen plasma is provided as the replacement fluid. The same cell separators can be used to perform plateletpheresis, erythrocyte exchange transfusion, and other procedures in patients with specific indications (**Table 26**).

Thrombotic Disorders

The burden of venous thromboembolic disease continues to increase despite increased awareness of risk factors and prevention options. The incidence of a first episode of venous thromboembolism (VTE) is approximately 1 to 2 per 1000 person/years.

VTE most commonly manifests as lower extremity deep venous thrombosis (DVT) or pulmonary embolism (PE). Many nosocomial VTEs are preventable, although thromboprophylaxis continues to be underused. D-dimer testing and imaging for VTE diagnosis should be used within the context of appropriate clinical algorithms.

Opinions differ regarding the relevance of thrombophilia testing, and results usually do not affect the length of anticoagulation. The landscape of treatment options continues to evolve.

Pathophysiology of Thrombosis

Alterations in three primary mechanisms of thrombosis predispose persons to VTE. Described by the German pathologist Rudolph Virchow more than 150 years ago, reduced or otherwise turbulent blood flow, alterations or injury to the vessel

TABLE 26. Indications for Therapeutic Apheresis[a]

Plasmapheresis/Plasma Exchange
Thrombotic thrombocytopenic purpura
Hyperviscosity syndrome (Waldenström macroglobulinemia and multiple myeloma)
Paraproteinemic polyneuropathies
Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)
Chronic inflammatory demyelinating polyradiculoneuropathy
Myasthenia gravis
ANCA-associated rapidly progressive glomerulonephritis
Anti-glomerular basement membrane disease
Recurrent focal segmental glomerulosclerosis
Severe, symptomatic cryoglobulinemia
Antibody-mediated renal allograft rejection
Fulminant Wilson disease
Erythrocyte Exchange
Severe babesiosis[b]
Sickle cell disease with acute cerebral infarct
Sickle cell disease with severe acute chest syndrome[c]
Leukapheresis
Hyperleukocytosis syndrome
Plateletpheresis
Symptomatic extreme thrombocytosis[d]
Extracorporeal Photopheresis
Cardiac allograft rejection, prophylaxis
Erythrodermic cutaneous T-cell lymphoma/Sézary syndrome
Selective Blood Component Removal
LDL cholesterol for familial hypercholesterolemia

[a]This list includes diseases for which apheresis is an accepted part of front-line therapy for a particular indication, either as the sole therapeutic modality or in combination with other therapy. It is not an all-inclusive list.

[b]Erythrocyte exchange for severe malaria is a category II indication (accepted second-line therapy).

[c]Erythrocyte exchange for acute chest syndrome is a category II indication but recommended by many as first-line therapy for those severely affected.

[d]The use of plateletpheresis is a category II indication for patients with life-threatening thrombosis or hemorrhage associated with thrombocytosis (for example, in a patient with essential thrombocytosis).

Data from Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, et al; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25:83-177. [PMID: 20568098] doi:10.1002/jca.20240

H CONT. wall, and changes in blood components that are prothrombotic or that inhibit fibrinolysis (or both) compose the Virchow triad. VTE usually develops as a result of the synergistic effect of multiple risk factors, which may be inherited, acquired, or a combination of both.

Thrombophilia

Thrombophilia Testing

One aspect of the Virchow triad is blood hypercoagulability, or thrombophilia. Thrombophilia can be inherited or acquired. Thrombophilia testing should not be routinely pursued in all patients presenting with DVT or PE. Although guidelines differ, most experts agree that thrombophilia evaluation should be considered only in certain populations, including patients with thromboses at unusual sites or recurrent idiopathic thrombosis, patients younger than 45 years with unprovoked thrombosis, patients with a clear family history of thrombosis in one or more first-degree relatives, and patients with warfarin-induced skin necrosis.

Additionally, many variables can affect outcomes of thrombophilia testing, including acute thrombosis and anticoagulant use, which may lead to false-positive test results. For this reason, and because a known thrombophilia will not change immediate management, testing should not be pursued in the acute setting. Asymptomatic patients with a family history of thrombosis should not undergo thrombophilia testing. H

KEY POINTS

- Thrombophilia evaluation should not be performed in most patients with acute venous thromboembolism. HVC
- Thrombophilia testing should be considered in patients with thromboses at unusual sites or recurrent idiopathic thrombosis, patients younger than 45 years with unprovoked thrombosis, patients with a clear family history of thrombosis in one or more first-degree relatives, and patients with warfarin-induced skin necrosis.
- Thrombophilia testing is less accurate during episodes of acute venous thromboembolism, and test results would not change immediate management; if indicated, testing should be performed after anticoagulation has been discontinued. HVC

Inherited Thrombophilias H

Inherited thrombophilias typically affect components of the coagulation cascade (see Figure 2 in Bleeding Disorders) that keep the hemostatic system in balance, either causing the prothrombotic system to continue unsuppressed or inhibiting clot lysis. All known inherited thrombophilias are autosomal dominant, meaning that most affected patients are heterozygous for the disorder. The two most common inherited causes are factor V Leiden and prothrombin *G20210A* gene mutation. Less common mutations involve antithrombin deficiency and protein C and S deficiency, although these latter disorders seem to be more significant risk factors for VTE.

Failure to identify a thrombophilia does not mean a thrombophilia does not exist. Studies have shown that even when an inherited disorder is not identified, a family history of thrombosis remains an independent risk factor for VTE. It is also possible for two thrombophilic defects to coexist, such as protein S deficiency and factor V Leiden.

H CONT.

Although identification of the inherited thrombophilias has advanced our understanding of the pathophysiology of VTE, it has had less influence on clinical management. The acute management of patients with VTE does not differ based on the presence of an inherited thrombophilia. Management duration is typically determined by whether the VTE event was provoked by a reversible or self-limited insult and is not often influenced by the presence of an underlying inherited thrombophilia, especially the more common disorders. Even if a patient with VTE is found to have an inherited thrombophilia, no evidence indicates asymptomatic family members should be screened to determine whether they also have the mutation.

Factor V Leiden

Factor V Leiden is the most common inherited thrombophilia. When factor V is activated, it combines with factor X to produce thrombin, which leads to clot formation. This process is regulated by activated protein C, which inactivates factor V to stop the process of ongoing clot formation. Factor V Leiden is resistant to cleavage by activated protein C, leading to predisposition of thrombus formation. Although persons who are heterozygous are at a fourfold to eightfold increased risk for developing a first VTE, most remain asymptomatic. Heterozygous factor V Leiden is found in about 5% of whites, whereas the homozygous form is found in less than 1%. Factor V Leiden is rare in Asian, African, African American, and Native American populations. It does not appear to be associated with arterial thrombosis. Factor V Leiden genetic testing or activated protein C resistance testing can be used to diagnose this condition.

Prothrombin *G20210A* Gene Mutation

The prothrombin *G20210A* gene mutation occurs in approximately 2% of whites and 0.5% of blacks and causes increased production of prothrombin (factor II) through a mutation at nucleotide 20210 from guanine to adenine. Persons with this mutation are at a twofold to fourfold increased risk for developing a first VTE, although, as with factor V Leiden, most patients with this mutation do not experience VTE events. Data are unclear regarding risks with the homozygous state, which is rare.

Antithrombin Deficiency

Antithrombin III (ATIII) and proteins C and S serve as natural anticoagulants in the body. Mutations that lead to loss of function of these components contribute to a tendency to develop VTE.

ATIII deficiency, although rare, with a prevalence of 1 in 3000 to 5000 persons, is a more significant thrombophilic risk factor than factor V Leiden or the prothrombin *G20210A* gene mutation. The main role of ATIII is to inhibit thrombin and activated factors IX and X (IXa and Xa). VTE-related pregnancy loss and pregnancy morbidity is common. Acquired ATIII deficiency is much more common than the congenital version (**Table 27**), and repeat testing is typically required to determine whether the deficiency is persistent.

TABLE 27. Conditions Associated with Acquired Decreased Coagulation Factor Levels

Coagulation Factor	Acquired Condition
Protein C	Acute thrombosis
	Warfarin therapy
	Liver disease
	Protein-losing enteropathy
Protein S	Acute thrombosis
	Warfarin therapy
	Liver disease
	Inflammatory states
	Estrogens (contraceptives, pregnancy, postpartum state, hormone replacement therapy)
	Protein-losing enteropathy
Antithrombin	Acute thrombosis
	Heparin therapy
	Liver disease
	Nephrotic syndrome
	Protein-losing enteropathy

For patients in whom heparin is initiated and titration to a therapeutic range is difficult, ATIII deficiency should be considered because heparin requires ATIII to be effective. ATIII concentrate can be used to treat this condition.

Protein C Deficiency

Protein C is a vitamin K–dependent protein that degrades activated factors V and VIII. Heterozygous protein C deficiency is uncommon, with a prevalence of 2 to 5 per 1000 persons. Many persons with this deficiency will experience a thrombotic event or pregnancy morbidity before 50 years of age, with a strong family history of thrombosis. Patients can also develop warfarin-induced skin necrosis because of further rapid depletion of protein C, which proceeds more rapidly than depletion of the coagulation factors. Homozygous deficiency is rare and causes neonatal purpura fulminans. If protein C deficiency is found, acquired causes should be ruled out (see Table 27). Repeat testing is often necessary to confirm a hereditary deficiency. Patients should not be tested during acute VTE events or while receiving warfarin. Protein C functional testing can be ordered to evaluate for evidence of deficiency.

Protein S Deficiency

Protein S is a cofactor for protein C to degrade activated factors V and VIII. Deficiency is uncommon and bears many similarities to protein C deficiency. Patients who are heterozygous for protein S deficiency typically experience VTE at a younger age

(<50 years). Protein S is a vitamin K–dependent factor synthesized by the liver; it circulates in a free form and bound to a complement-binding protein. Although rare case reports show patients with a functional protein S deficiency, immunoassay of the free form of protein S is usually sufficient to make the diagnosis. Protein S deficiency is likely the most difficult hereditary thrombophilia to confirm because multiple laboratory assays for protein S are available, with cutoffs between normal and deficient that may be imprecise.

Other Inherited Disorders

Methylene tetrahydrofolate reductase (*MTHFR*) gene polymorphisms cause mild elevations in homocysteine levels, which are associated with a mildly increased risk of cardiovascular and thrombotic disease. The heterozygous mutation is found in 20% of whites and 2% of blacks. Vitamin B_6 and B_{12} supplementation can lower homocysteine levels without lowering thrombotic risk, which suggests the mutation may be a marker of thrombotic risk rather than a cause of thrombosis. Testing for the *MTHFR* mutation and measuring homocysteine levels should not be done in the evaluation of thrombophilia.

Factor VIII levels and plasminogen activator inhibitor activity should not be part of the standard thrombophilia evaluation because clinical trials regarding their importance have been inconclusive and results do not influence management.

KEY POINTS

- Although the risk of venous thromboembolism is increased in patients who are heterozygous for factor V Leiden or prothrombin *G20210A* gene mutation, most patients are asymptomatic.
- HVC Methylene tetrahydrofolate reductase (*MTHFR*) gene mutations are associated with an elevated homocysteine level and a modest increased risk of venous thrombosis; no treatment is available, and *MTHFR* mutation testing and homocysteine level measurement should not be performed.
- HVC Measurement of homocysteine, factor VIII levels, and plasminogen activator inhibitor activity should not be part of the standard thrombophilia evaluation because results do not influence management.

Acquired Thrombophilias

VTE is more likely to occur in the setting of an acquired rather than an inherited thrombophilia. Many conditions predispose patients to the development of thrombosis.

Surgery, Trauma, Hospitalization, and Immobility

Surgery, trauma, hospitalization, and immobilization are some of the most significant risk factors for VTE. VTE occurs frequently in medical and surgical patients. Approximately half of all new VTEs are diagnosed during or within 3 months of a hospital stay or surgical procedure. If prophylaxis is not used, the risk of DVT in the general surgical patient is 15% to 30%. In the orthopedic patient, the risk of DVT is approximately 60% after hip fracture surgery. Patients with cancer who undergo surgery and those undergoing orthopedic procedures, including knee arthroplasty, hip fracture repair, or hip replacement, are at particularly high risk. Nosocomial VTE risk is also increased for nonsurgical hospitalized patients, more so for immobilized patients, patients with acute neurologic illness, and patients in the medical ICU.

Certain medical conditions, including inflammatory conditions, nephrotic syndrome, and inflammatory bowel disease, have also been associated with increased thrombotic risk. In nephrotic syndrome, this risk is attributed to loss of antithrombin and proteins C and S in the urine. Obesity is also associated with increased thrombotic risk.

Cancer

Thrombosis remains a leading cause of death in patients with cancer and is a significant source of morbidity. Increased thrombotic risk has been associated with numerous malignancies, including prostate and breast cancer.

Cancer is diagnosed in 10% of patients within 1 year of an unprovoked VTE occurrence. Cancer of the ovary, pancreas, and liver are most often found. The only randomized controlled clinical trial that compared routine age- and gender-indicated screening with extensive malignancy screening using CT of the thorax, abdomen, and pelvis showed that extensive malignancy screening provided no survival benefit. Extensive cancer screening should not be performed beyond recommendations for gender and age, independent of the VTE event.

In addition, other factors, such as hormonal therapy, can further increase risk.

Medication

Hormones used in oral contraceptives and in the treatment of menopause increase the risk of VTE. The risk in women using oral contraceptives is increased approximately threefold, but the absolute number of patients affected in this young healthy population remains small. VTE risk correlates with the specific progestin agent and is somewhat higher in oral contraceptives containing desogestrel and gestodene and somewhat lower with levonorgestrel. Injectable progestin agents do not increase the risk. Regardless of the type of contraceptive, VTE risk tends to be greater in obese women and those who are older than 39 years. Women with a previous VTE event and a known inherited thrombophilia should not take oral contraceptives because the thrombotic risk is further increased. However, experts do not recommend routine thrombophilia screening before beginning contraceptive therapy because many women would need to be screened to prevent one adverse event from pulmonary embolism (PE). VTE risk is also increased by approximately twofold in menopausal women taking conjugated estrogen-medroxyprogesterone hormone replacement therapy, but the absolute risk remains small. The VTE risk in

CONT. menopausal women seems lower in those taking estrogen only and in those using transdermal hormone replacement.

The antiestrogen, tamoxifen, also increases VTE risk in women with estrogen receptor-positive breast cancer, and the risk increases further, approximately three times baseline, in women receiving tamoxifen with systemic chemotherapy. The risk for VTE with aromatase inhibitors, such as anastrozole, is lower than that seen with tamoxifen.

Patients with multiple myeloma receiving thalidomide and its analogs as part of combination chemotherapy have a significant risk of VTE that warrants prophylaxis. The vascular endothelial growth factor inhibitor bevacizumab and newer multitargeted tyrosine kinase inhibitors, such as sunitinib and sorafenib, also increase VTE risk.

Glucocorticoid therapy has also been identified to increase the risk for VTE.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is an autoimmune disorder in which thrombosis and fetal demise (in pregnancy) may occur. Patients with antiphospholipid antibody syndrome are at risk for arterial and venous thrombosis.

Antiphospholipid antibodies are the anticardiolipin antibodies and the lupus anticoagulant. The diagnosis of antiphospholipid antibody syndrome is based on the clinical criteria of thromboembolism or pregnancy morbidity and laboratory findings of medium or high titer antiphospholipid antibodies present on two or more occasions at least 12 weeks apart (**Table 28**). A clue to the presence of the lupus anticoagulant is activated partial thromboplastin time prolongation.

Typically, patients who are diagnosed with antiphospholipid antibody syndrome require long-term anticoagulation owing to the risk of recurrent thrombosis.

Other Acquired Thrombophilic Conditions

The myeloproliferative neoplasms have been found to carry a particularly increased risk of thrombosis; although these thromboses include PE and DVT, portal vein thrombosis and Budd-Chiari syndrome (hepatic venous outflow obstruction) (see MKSAP 18 Gastroenterology and Hepatology) are often found. Evidence of a myeloproliferative neoplasm is found in approximately 50% of patients with Budd-Chiari syndrome, even when the complete blood count is normal. In the setting of splanchnic vein thrombosis (which includes Budd-Chiari syndrome and portal vein thrombosis), evaluation for evidence of a myeloproliferative neoplasm should be considered, including evaluation for the *JAK2* tyrosine kinase mutation.

Paroxysmal nocturnal hemoglobinuria is another acquired stem cell disorder associated with hemolytic anemia, bone marrow failure, and thrombosis (see Erythrocyte Disorders).

A previous VTE event is one of the most powerful predictors of a subsequent VTE, regardless of whether an additional inherited or acquired thrombophilic risk factor is identified.

KEY POINTS

- Approximately half of all new VTEs are diagnosed during or within 3 months of a hospital stay or surgical procedure.
- Patients with cancer undergoing extensive surgery and those undergoing knee arthroplasty, hip fracture repair, or hip replacement surgery are at especially high risk for postoperative venous thromboembolism.
- The diagnosis of antiphospholipid antibody syndrome is based on the clinical criteria of thromboembolism or pregnancy morbidity and laboratory findings of medium or high titer antiphospholipid antibodies present on two or more occasions at least 12 weeks apart.
- Evidence of a myeloproliferative neoplasm is found in approximately 50% of patients with Budd-Chiari syndrome, and *JAK2* tyrosine kinase mutation testing should be performed even if blood counts are normal.

TABLE 28. Diagnosis of Antiphospholipid Antibody Syndrome[a]

Vascular Thrombosis	Pregnancy Morbidity	Laboratory Criteria
One or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ	One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or	Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
	One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia, or placental insufficiency; or	Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater than the 99th percentile), measured by a standardized ELISA
	Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation	Anti-β_2-glycoprotein-1 antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by a standardized ELISA

ELISA = enzyme-linked immunosorbent assay; GPL = specificity for IgG phospholipid antigens; MPL = specificity for IgM phospholipid antigens.

[a]Diagnosis is based on the presence of vascular thrombosis OR pregnancy morbidity PLUS relevant laboratory criteria.

Deep Venous Thrombosis and Pulmonary Embolism

Prevention

All hospitalized patients should be assessed for the risk of developing a VTE and treated with appropriate prophylaxis (see MKSAP 18 General Internal Medicine) because VTE is a major preventable cause of hospital morbidity and mortality. Generally, unless a clear contraindication to prophylaxis exists, pharmacologic treatment is indicated as opposed to mechanical prophylaxis. In acutely ill patients with risk for thrombosis, low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux is advised for prophylaxis. Patients with cancer or stroke and those in the ICU have a particularly high risk for VTE. Despite the well-recognized risks of VTE, the rate of appropriate prophylaxis remains low in general hospitalized patients. Most patients do not require continued pharmacologic VTE prevention after discharge. However, patients with cancer who are undergoing major surgical procedures, patients undergoing knee arthroplasty, and those with hip fracture repair or hip replacement require VTE prophylaxis for as long as 4 weeks after discharge.

Diagnosis

DVT and PE cause significant morbidity and require efficient evaluation and diagnosis. Previous VTE, immobilization, and other thrombophilia risk factors, especially cancer, should be assessed. History pertinent to other potential causes of leg or respiratory symptoms should be elicited. The typical clinical presentation of DVT involves unilateral swelling, pain, warmth, and erythema of the extremity. Patients with PE may present with chest pain, dyspnea, and tachypnea. Less commonly, symptoms may include cough, fever, cyanosis, syncope, or shock.

CT angiography has significantly improved the accuracy of evaluating PE, generally replacing ventilation-perfusion scanning, which lacks specificity, and avoiding the need for more invasive pulmonary arteriography. However, the overuse of CT angiography and D-dimer measurement in patients at low risk for PE has needlessly exposed patients to the additional radiation and expense of these procedures. For patients who present with symptoms suspicious for an acute VTE, validated prediction rules have been developed that use D-dimer testing to help effectively evaluate this condition. The Wells criteria for diagnosis of DVT (**Table 29**) and PE (**Table 30**) and the Geneva Score (**Table 31**) for diagnosis of PE are well-studied tools in this setting. Based on these criteria, patients with low pretest probability and low D-dimer levels do not require imaging because a VTE diagnosis is unlikely. Recent studies suggest that a subset of patients at very low risk can be identified using the Pulmonary Embolism Rule-Out Criteria (PERC) (**Table 32**); these patients do not require D-dimer testing to eliminate the need for additional imaging. American College of Physicians guidelines published in 2015 recommend using the PERC as the initial step in evaluating patients at low risk. If the PERC score is zero, no D-dimer testing is needed, and no CT angiography should be performed. In a recent meta-analysis of 12 studies, it was found that if the PERC were applied, only 0.3% of PEs

TABLE 29. Wells Criteria for Deep Venous Thrombosis

Variables	Points
Leg Symptoms and Findings	
Calf swelling ≥3 cm	+1
Swollen unilateral superficial veins (nonvaricose)	+1
Unilateral pitting edema	+1
Swelling of the entire leg	+1
Localized tenderness along the deep venous system	+1
History	
Previously documented DVT	+1
Active cancer or treatment in previous 6 months	+1
Paralysis, paresis, recent cast immobilization of legs	+1
Recently bedridden for ≥3 days; major surgery	+1
Alternative explanation for leg symptoms at least as likely	−2

DVT = deep venous thrombosis.

0-1 points = DVT unlikely; obtain D-dimer assay. If the result is negative, no further evaluation; if the result is positive, obtain Doppler ultrasonography.

>1 point = DVT likely; obtain Doppler ultrasonography.

From Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349:1227-35. [PMID: 14507948] Reprinted with permission from Massachusetts Medical Society.

TABLE 30. Wells Criteria for Pulmonary Embolism

Variables	Points
Symptoms and Signs	
Hemoptysis	1
Heart rate >100/min	1.5
Clinical signs and symptoms of DVT	3
History	
Previously documented DVT or PE	1.5
Active cancer	1
Bedridden ≥3 days or major surgery in previous 4 weeks	1.5
Other	
PE is most likely diagnosis	3

DVT = deep venous thrombosis; PE = pulmonary embolism.

≤4 points = PE unlikely; obtain D-dimer.

4-6 points = moderate possibility of PE.

>6 points = high probability of PE.

Republished with permission of Schattauer, from Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-20. [PMID: 10744147]

TABLE 31. Revised Geneva Score

Clinical Characteristic	Score
Age >65 y	1
Previous PE or DVT	1
Heart rate 75-94/min	1
Heart rate ≥94/min	2
Active cancer	1
Unilateral lower limb pain	1
Hemoptysis	1
Surgery or fracture within last month	1
Pain on lower limb deep venous palpation	1

DVT = deep venous thrombosis; PE = pulmonary embolism.

<2 points: low probability of PE.

2-4 points: intermediate probability.

≥5 points: high probability.

TABLE 32. Pulmonary Embolism Rule-Out Criteria for Predicting Probability of Pulmonary Embolism in Patients with Low Pretest Probability

Clinical Characteristic	Meets Criterion	Does Not Meet Criterion
Age <50 y	0	1
Initial heart rate <100 beats/min	0	1
Initial oxygen saturation >94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 wk	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1

Pretest probability with score of 0 is <1%.

H CONT. would have been missed, and 22% of D-dimer testing would have been safely avoided. PERC will help eliminate unnecessary D-dimer testing in patients at low risk.

In patients at low risk but who have a PERC score greater than zero, D-dimer testing should be pursued. If the result is negative, no imaging is warranted. If the result is positive, further evaluation is merited. If a patient has a moderate or high pretest probability, imaging studies are indicated. D-dimer testing should not be pursued in patients with moderate or high pretest probability because results would not change the need for imaging.

Duplex ultrasonography is the imaging modality of choice for suspected DVT. Lower extremity DVT is considered proximal if the popliteal veins are involved and is considered distal if only the calf veins are involved. CT angiography is the study of choice for suspected PE.

In patients with kidney disease or in whom intravenous contrast is contraindicated, a ventilation-perfusion lung scan can be pursued. A normal ventilation-perfusion scan result effectively rules out PE, and a high probability study result in a patient with a high likelihood of disease has a strong positive predictive value. The sensitivity and specificity of low probability or intermediate probability study results may not be accurate enough to establish or rule out the diagnosis. MRI can visualize intraluminal filling defects in the pulmonary vasculature, but not as well as CT, and avoids the ionizing radiation of CT. New MRI techniques are being evaluated that may enhance its role in diagnosis. CT is still considered standard of care for evaluation of PE.

Patients with study results that establish the diagnosis of PE do not require routine duplex imaging of the lower extremities, and patients with acute DVT in the absence of respiratory symptoms do not require CT angiography. Patients with established PE should undergo cardiac ultrasonography to evaluate acute pulmonary artery hypertension and right ventricular strain that may signify a more massive PE. Serum troponin and B-type natriuretic peptide measurements also help stratify risk in patients with PE. An elevated serum troponin level is associated with increased mortality. H

KEY POINTS

- Patients with a Pulmonary Embolism Rule-Out Criteria score of zero do not require further testing with D-dimer or imaging. HVC
- Patients with a low probability Wells criteria score for DVT or PE should undergo D-dimer testing; if the results are normal, no further imaging is necessary. HVC
- Patients with moderate or high probability Wells criteria do not require D-dimer testing but should undergo duplex imaging of the lower extremities for symptoms suggesting deep venous thrombosis or CT angiography for symptoms suggesting pulmonary embolism.

Treatment H

Most patients with DVT can be efficiently and safely diagnosed and treated without hospitalization. More recent literature has shown a subset of patients with PE with an excellent prognosis who can also avoid inpatient care. Clinical predication models have been developed to help determine the outcome of patients with acute PE, such as the Pulmonary Embolism Severity Index (PESI), which predicts clinical severity and outcome of patients with PE using 11 clinical criteria. In a multicenter, prospective, open-label, randomized trial of patients with low-risk PE as determined by the PESI score, no difference was found between outpatient and inpatient management

H CONT.

in recurrent VTE, major bleeding, or 90-day mortality. A simplified version of the PESI defines patients who are younger than 80 years, who are without significant comorbidity, and who have a pulse rate less than 110/min, systolic blood pressure greater than 100 mm Hg, and oxygen saturation greater than 90% breathing ambient air as low risk for adverse outcomes.

For most patients, anticoagulation is the primary treatment for VTE. Anticoagulant options for acute VTE include unfractionated heparin, which usually requires hospitalization, low-molecular-weight heparin (LMWH), fondaparinux, or one of the non-vitamin K oral anticoagulants, all of which are safe and effective for immediate outpatient management, although patients must learn injection technique for LMWH and fondaparinux. Traditional vitamin K antagonists are not effective without at least 5 days of concomitant parenteral heparin therapy, and dabigatran and edoxaban have not been evaluated in acute VTE without previous parenteral heparin therapy. Apixaban and rivaroxaban are safe and effective as monotherapy. Patients who require hospitalization should avoid initial treatment with unfractionated heparin because of its unpredictable bioavailability compared with LMWH; however, unfractionated heparin, with a short half-life of residual anticoagulation after the infusion is stopped, may be preferred in patients who are not stable and who may need emergent surgery or transition to thrombolytic therapy.

Duration of therapy varies based on the clinical scenario surrounding the event (**Table 33**). In provoked thrombosis with reversible risk factors, 3 months of anticoagulation is adequate. Extended therapy should be considered in patients at low bleeding risk with unprovoked VTE or with irreversible risk factors for recurrent VTE, such as underlying heart failure or stroke with long-term ambulatory dysfunction. If extended therapy is chosen, the risks, benefits, and choice of anticoagulant should be re-evaluated yearly.

In patients with unprovoked VTE in whom anticoagulation is discontinued, initiating aspirin is associated with approximately a 30% to 40% risk reduction in recurrent VTE. The American College of Chest Physicians (ACCP) guidelines published in 2016 recommend aspirin if a patient with unprovoked VTE does not continue long-term anticoagulation.

In patients with malignancy, LMWH remains preferable to warfarin; the CLOT trial, in which patients were randomly assigned to LMWH or warfarin, found that 15% of patients treated with warfarin developed recurrent VTE compared with 7.9% of patients treated with LMWH. Anticoagulation should be continued as long as the cancer is active.

The role of non-vitamin K antagonist oral anticoagulants compared with LMWH has not been studied in patients with cancer. Although 6 months of anticoagulation was studied in clinical trials, anticoagulation is recommended for the duration of cancer activity.

Thrombolytic therapy is necessary to treat patients with massive PE and shock from low cardiac output. Growing data, including meta-analyses, support thrombolytic therapy as superior to traditional anticoagulation in select patients with submassive PE who remain normotensive but have poor prognostic features on cardiac ultrasonography and elevated serum troponin and B-type natriuretic peptide levels. For acute DVT, thrombolysis is indicated for massive thrombus leading to impaired venous drainage, severe edema, and acute limb

TABLE 33. Duration of Anticoagulant Therapy for Venous Thromboembolism[a]

Type of Thrombotic Event	Duration of Anticoagulant Therapy
Distal leg DVT	
Provoked or unprovoked, mild symptoms	No anticoagulation suggested, but monitor with serial duplex ultrasonography for 2 weeks
Provoked or unprovoked, moderate-severe symptoms	3 months
Proximal leg DVT or PE	
Provoked (by surgery, trauma, immobility)	3 months
Unprovoked	Extended[b]
Recurrent	Duration of therapy depends on whether VTE events were provoked or unprovoked
Upper extremity DVT, proximal	At least 3 months
Cancer-associated DVT or PE	As long as the cancer is active or being treated LMWH is the preferred anticoagulant
Chronic thromboembolic pulmonary hypertension	Extended[b]

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

[a]Decisions regarding duration of anticoagulation must always weigh the risk of VTE recurrence, risk of bleeding, and patient preference.

[b]Indicates long-term anticoagulation therapy with periodic (such as once per year) re-evaluation of the risks, benefits, and burdens of long-term therapy and discussion of new clinical study results and new anticoagulant drugs.

Data from Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-52. [PMID: 26867832] doi:10.1016/j.chest.2015.11.026

CONT. ischemia. The main function of an inferior vena cava (IVC) filter is to prevent death from PE. In 2012, the ACCP recommended IVC filters for those with a contraindication to anticoagulation who either have acute PE or acute proximal (above the knee) DVT. If an IVC filter is placed, a temporary filter should be used.

Distal DVT does not usually require anticoagulation. Isolated distal DVT can be monitored with serial Doppler ultrasonography performed 5 to 7 days after the initial event in otherwise healthy, asymptomatic patients. According to ACCP guidelines, anticoagulation similar to that for proximal DVT is suggested in patients with certain risk factors for extension, including a positive D-dimer test result, extensive thrombosis or proximity to proximal veins, no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status.

KEY POINTS

HVC
- Most patients with deep venous thrombosis and those with pulmonary embolism who have a good prognosis (defined as age <80 years, no significant comorbidity, and stable vital signs) can be safely managed without hospitalization.
- If patients with deep venous thrombosis or pulmonary embolism require hospitalization, they should be treated initially with low-molecular-weight heparin, fondaparinux, or the non-vitamin K antagonist oral anticoagulants (apixaban or rivaroxaban) instead of unfractionated heparin, unless they are unstable and at risk for requiring emergent surgery or thrombolytic therapy.
- In patients with a provoked thrombosis with reversible risk factors, 3 months of anticoagulation is adequate, but in patients at low bleeding risk with unprovoked VTE or with irreversible risk factors, extended therapy should be considered.

Long-term Complications

Patients with DVT or PE can develop long-term complications affecting function and quality of life. Approximately 25% to 40% of patients with symptomatic DVT can develop aspects of postthrombotic syndrome (PTS) and chronic venous insufficiency, which often develop within 2 years of diagnosis. Symptoms of postthrombotic syndrome include pain in the affected limb, heaviness, swelling, stasis dermatitis, and ulceration. It often leads to poor quality of life and contributes to work disability. Treatment includes leg exercises, avoiding dependent positions for lengthy periods, and using compression stockings. Skin moisturizers and a low-moderate potency topical glucocorticoid may be used for stasis dermatitis (see MKSAP 18 Dermatology).

Patients with PE can also develop chronic thromboembolic pulmonary hypertension (see Pulmonary and Critical Care Medicine), cardiopulmonary dysfunction, or decreased exercise tolerance.

Other Sites of Thrombosis

Superficial Vein Thrombosis and Thrombophlebitis

Superficial thrombophlebitis describes thrombus in a vein located near the skin's surface; it is a common inflammatory-thrombotic disorder that does not usually cause significant morbidity or progress to PE. It typically is treated with supportive care, analgesia, warm compresses, and NSAIDs. Imaging is indicated if symptoms progress or swelling occurs. Cannulated veins of the hands and arms often thrombose after infusions and intravenous catheter placement; this condition does not require anticoagulant therapy.

Superficial vein thrombosis (SVT) often affects the lower extremities and is thought to account for 10% of lower extremity thromboses. When affecting the great saphenous vein (also referred to as the greater or long saphenous vein), SVT may progress into the deep venous system. In a randomized trial of fondaparinux versus placebo for lower extremity SVT, it was found that fondaparinux was safe and effective in preventing PE. In patients with lower extremity SVT of at least 5 cm in length or close to the deep venous system, fondaparinux or an alternate anticoagulant is recommended. Anticoagulation may also be indicated for patients with SVT and other thrombophilic risk factors, including cancer or previous DVT. Patients with lower extremity SVT who are not treated initially with anticoagulants should undergo follow-up evaluation in 1 week to assess signs of thrombus progression. Imaging is necessary for persistent or worsening symptoms.

KEY POINTS

- Patients with lower extremity superficial vein thrombosis managed conservatively with warm compresses, analgesics, and NSAIDs require follow-up evaluation after 1 week to determine whether symptoms have resolved; duplex imaging is indicated for symptoms that persist or worsen.
- In patients with lower extremity superficial vein thrombosis of at least 5 cm in length or close to the deep venous system, or in patients with other thrombophilic risk factors, including cancer or previous venous thromboembolism, therapy with fondaparinux or an alternate anticoagulant is recommended.

Unexplained Arterial Thrombosis

Thrombophilias do not play a significant role in arterial thrombosis. The primary causes of arterial thrombosis are arteriosclerosis and atrial fibrillation with systemic arterial embolism. Patients with arterial thrombosis due to arteriosclerosis are typically treated with antiplatelet therapy. It is unknown whether patients with arterial clots in whom a strong thrombophilia is found are more effectively treated with antiplatelet therapy or anticoagulants.

KEY POINT

- Patients with arterial thrombosis due to arteriosclerosis are typically treated with antiplatelet therapy.

Upper Extremity Deep Venous Thrombosis

Upper extremity DVT accounts for 10% all DVT occurrences. Secondary DVT of the upper extremity is much more common than primary (two thirds versus one third). Secondary upper extremity DVT usually occurs with central venous catheter use or malignancy; treatment consists of 3 months of anticoagulation. However, if the catheter will not be removed in the setting of a proximal DVT, anticoagulation should continue as long as the catheter remains in place.

Primary upper extremity DVT is uncommon and usually caused by anatomic abnormalities of the thoracic outlet system leading to axillosubclavian compression and thrombosis (venous thoracic outlet syndrome). Patients are usually young, and thrombus occurs with strenuous upper extremity activity. Expert recommendations vary regarding the use of thrombolysis or thoracic outlet decompression surgery in addition to anticoagulation. ACCP guidelines recommend that treatment of primary and secondary upper extremity DVT follow similar guidelines as lower extremity DVT. Provoked upper extremity DVT should be treated for 3 months.

KEY POINT

- Provoked upper extremity deep venous thrombosis (DVT) should be managed with 3 months of anticoagulation; however, in patients with catheter-associated DVT in whom the catheter will not be removed, anticoagulation should continue for as long as the catheter remains in place.

Anticoagulants

Unfractionated Heparin

Unfractionated heparin works by binding to antithrombin, which leads to activation and potentiation of its action, resulting in inactivation of thrombin and factor Xa.

The activated partial thromboplastin time (aPTT) is used in monitoring patients receiving heparin therapy. In the setting of lupus anticoagulant (which prolongs the aPTT), heparin resistance, or markedly elevated factor VIII, antifactor Xa monitoring can be used. Although ideal dosing has been controversial, a weight-based nomogram is usually used, and most hospitals follow a specific heparin dosing algorithm. Typically, an initial bolus dose of 80 to 100 U/kg is given.

Heparin is available in intravenous and subcutaneous preparations for the treatment of VTE, although the intravenous form is typically used. A parenteral agent should be overlapped with warfarin for 5 days and until the INR is 2 or greater for at least 24 hours.

The rate of heparin-associated major bleeding is approximately 3%. Failure to follow a dosage adjustment algorithm is associated with increased bleeding risk. When major bleeding occurs, protamine sulfate can be administered to reverse anticoagulation. A dose of 1 mg of protamine per 100 units of heparin is recommended. Protamine has its own significant adverse effects, which include allergic reactions, hypotension, bradycardia, and respiratory toxicity.

Although weight-based nomograms for instituting heparin therapy and specific algorithms for adjusting dose based on aPTT results have enhanced the safety and efficacy of unfractionated heparin, variations in bioavailability and potential delay in arriving at a therapeutic dose are still more likely than in patients treated with LMWH. Unfractionated heparin should generally be reserved for patients for whom LMWH is contraindicated or in those who require anticoagulation that can be stopped quickly, generally in anticipation of an invasive procedure or surgery.

Heparin-induced thrombocytopenia is a paradoxical adverse effect of heparin that can result in life-threatening thrombosis (see Platelet Disorders).

KEY POINTS

- A weight-based nomogram is usually used to determine the initial dose of unfractionated heparin, and algorithms are used to calculate subsequent dose modifications based on the activated partial thromboplastin time.
- Protamine sulfate can be administered to reverse the anticoagulant effects of unfractionated heparin.
- Variations in bioavailability of unfractionated heparin lead to an increased likelihood of delay in achieving a steady-state therapeutic dose compared with treatment with low-molecular-weight heparin.

Low-Molecular-Weight Heparin

LMWH is derived from unfractionated heparin through a chemical depolymerization producing smaller fragments that are one third the size of heparin.

LMWH does not affect the aPTT because the smaller fragment size does not bind as readily to thrombin but retains the ability to inactivate factor Xa. Dosing is more predictable and laboratory testing is generally unnecessary. LMWH is cleared through the kidney, and the biological half-life is increased in patients with kidney disease. In obese patients, twice daily dosing is suggested. Although laboratory monitoring is typically unnecessary, it is required when treating patients with stage V chronic kidney disease or severe obesity; anti-Xa levels should be obtained 3 to 4 hours after dosing.

LMWH is preferred to unfractionated heparin. In a meta-analysis of DVT treatment comparing LMWH with unfractionated heparin, LMWH was associated with less major bleeding, decreased mortality, and decreased thrombotic recurrence.

Protamine does not fully reverse the anti-Xa effect of LMWH but provides some benefit in restoring hemostasis; it should be given at a dose of 0.5 to 1 mg of protamine per 1 mg of enoxaparin.

KEY POINTS

- Low-molecular-weight heparin typically does not require laboratory monitoring and is associated with less bleeding, decreased recurrent thrombosis, and improved mortality compared with unfractionated heparin.
- Patients with severe obesity or stage V chronic kidney disease who are treated with low-molecular-weight heparin should have factor Xa levels measured 3 to 4 hours after a dose is administered to assess the adequacy of anticoagulation.

Fondaparinux

In a clinical trial, fondaparinux, dose adjusted based on patients' weights, was noninferior to enoxaparin with respect to the primary endpoint of recurrent VTE at 3 months (3.9% vs. 4.1%). Fondaparinux is also cleared through the kidney and should be avoided in patients with creatinine clearance less than 30 mL/min. As with LMWH or unfractionated heparin, treatment with fondaparinux and warfarin should overlap for 5 days.

Fondaparinux has no reversal agent. Caution should be used in patients at risk for bleeding because the half-life is 17 hours. Prothrombin complex concentrates (PCCs) and fresh frozen plasma (FFP) have been administered with positive outcomes in patients experiencing bleeding.

KEY POINT

- Because fondaparinux is cleared through the kidney, it should be avoided in patients with a creatinine clearance less than 30 mL/min.

Warfarin

Warfarin is a vitamin K antagonist. It inhibits vitamin K epoxide reductase, which leads to inhibition of γ carboxylation of precursor coagulation factors II, VII, IX, and X and proteins C and S. Laboratory monitoring involves the prothrombin time and INR.

Because warfarin lowers protein C levels before inducing its anticoagulant effect, it can initially cause a prothrombotic state. For this reason, for the treatment of acute VTE, it must be administered initially with a parenteral anticoagulant. Warfarin should be initiated as soon as possible after diagnosis of VTE. Typically, unfractionated heparin or LMWH is used with warfarin. As noted previously, the parenteral agent should be given for at least 5 days, and the INR can be measured on day 3; heparin is continued until the INR is 2 or greater for at least 24 hours.

Although non–vitamin K antagonist oral anticoagulants have changed the landscape of treatment for patients with VTE, warfarin remains a reasonable anticoagulant for some patients. This may include patients with known kidney disease and obesity or patients with a mechanical heart valve, for whom alternate oral anticoagulants have not been approved.

Patients must have access to continued outpatient INR monitoring. Studies evaluating the use of cytochrome 2C9 and vitamin K epoxide reductase (VKORC1) pharmacogenetics to guide warfarin therapy have not shown benefit. Common reasons for fluctuations in INR include changes in vitamin K intake, medications, and nonadherence. Studies attempting to decrease INR variability with low-dose daily vitamin K supplementation were unsuccessful, so this supplementation is not indicated.

Bleeding is the most significant complication in patients treated with warfarin, occurring in 1% to 3% of patients per year. The risk is higher when warfarin therapy is initiated and during episodes of concurrent acute illness. Bleeding risk increases further in patients with an INR greater than 5. Independent of INR, bleeding risk is increased in patients older than 75 years or in those with previous stroke, gastrointestinal bleeding, or most other chronic comorbidities. Concomitant aspirin, clopidogrel, and NSAID use increases the bleeding risk. The indication for antiplatelet agents for patients taking warfarin should be carefully reviewed, and dual antiplatelet therapy avoided if possible. Acetaminophen should be used instead of NSAIDs when feasible.

Concern is often expressed when older adults begin oral anticoagulation, often for atrial fibrillation, because age is an important risk factor for stroke and bleeding complications associated with warfarin. Oral anticoagulation may be prematurely excluded as a therapeutic option in these patients because of concerns regarding a "falls risk." The true risk of serious bleeding related to a fall while taking an anticoagulant is unclear, although small studies have not shown an increased risk of major bleeding in patients taking oral anticoagulants who were considered at high risk for falls. Risk factors for falls should be thoroughly evaluated and appropriate steps employed for prevention (see MKSAP 18 General Internal Medicine). Recommendations suggest that neither age nor a risk of falls is reason to withhold warfarin anticoagulation from a patient who has clinical criteria warranting such therapy for VTE or stroke prevention.

Patients with asymptomatic INR elevation between 4.5 and 10 can often be managed by simply withholding warfarin. For INRs greater than 10 in patients without bleeding, oral vitamin K, 2.5 mg, should be given. In patients experiencing bleeding, in addition to vitamin K, three- or four-factor PCCs should be given rather than FFP. Although FFP contains the appropriate clotting factors, it requires thawing and large volumes to correct the INR. Three- and four-factor PCCs contain proteins C and S and factors II, IX, and X; four-factor PCC also contains factor VII. In a clinical trial of vitamin K antagonist–related bleeding, four-factor PCC was found to be noninferior to FFP for hemostatic efficacy. Four-factor PCC is preferred because of its rapid reversal of INR, rapid infusion and administration, and lack of volume overload. Recombinant factor VIIa is not recommended for warfarin reversal.

Bridging therapy, which uses heparin or LMWH for patients in whom warfarin has been stopped for an invasive

H CONT. procedure and will be resumed, is not necessary for most patients and is associated with more bleeding complications without additional anticoagulant benefit. The exception to this may be patients with recent VTE (within the past 4 weeks), history of VTE during anticoagulant interruption for surgery, or a procedure with very high VTE risk, such as orthopedic surgery. Bridging is also indicated in patients with atrial fibrillation who have had a stroke or transient ischemic attack in the preceding year, in patients who have multiple risk factors for stroke ($CHADS_2$ score of 5-6), and in most patients with a mechanical heart valve. H

KEY POINTS

- Warfarin must be administered initially with at least 5 days of a parenteral anticoagulant (usually unfractionated or low-molecular-weight heparin) for the treatment of venous thromboembolism.

HVC

- Bridging therapy, which uses unfractionated heparin or low-molecular-weight heparin during warfarin discontinuation before an invasive procedure, is not indicated for most patients because it is associated with more bleeding complications without any reduction in thrombotic events.

H Non-Vitamin K Antagonist Oral Anticoagulants

The non–vitamin K antagonist oral anticoagulants (NOACs) have emerged as a safe and effective treatment for certain patients with VTE. In the 2016 CHEST guidelines for DVT and PE treatment, NOACs are suggested as the treatment of choice for anticoagulation in patients without cancer. The NOACs available for use in the United States are dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. In clinical trials of patients with VTE, patients were initially treated with a parenteral agent and transitioned to dabigatran or edoxaban. Rivaroxaban and apixaban were studied without concomitant parenteral therapy and were approved as monotherapy for DVT and PE. Dabigatran functions as a direct thrombin inhibitor, whereas the other agents are factor Xa inhibitors. Betrixaban is only approved for DVT prophylaxis (**Table 34**).

Routine coagulation studies do not reliably measure the degree of coagulation activity. However, the thrombin time is quite sensitive to the presence of dabigatran and, if normal, indicates that the anticoagulant effect of dabigatran is no longer significant.

Advantages of the NOACs include no need for routine monitoring, rapid onset of action and short half-life, fixed dosing, and fewer drug-drug interactions. These drugs are as effective as warfarin in the prevention of VTE; although the overall bleeding risk was comparable, less central nervous system bleeding, fatal bleeding, and use of blood product support among patients taking NOACs was seen than with warfarin. The bleeding risk is higher in patients taking aspirin or clopidogrel with a NOAC and is further increased in patients taking dual antiplatelet drugs plus NOACs. These qualities must be considered when choosing the appropriate patient for these therapies. No head-to-head trials have been performed comparing the various NOACs. It must be noted that certain patient groups were excluded from the major trials of the NOACs, including patients with severe obesity (BMI >40), pregnant patients, and those with mechanical heart valves. Nonadherent patients should not be treated with NOACs, and the additional cost of these drugs compared with warfarin may be a barrier for some patients. Few patients with cancer were included in clinical trials, and LMWH is still considered standard of care for VTE in these patients. In patients with antiphospholipid antibody syndrome, the role of NOACs remains unclear, although clinical trials are ongoing. Treatment failures with the use of NOACs in patients with antiphospholipid antibody syndrome have been reported. Dyspepsia and gastrointestinal bleeding were seen more frequently with dabigatran compared with warfarin in clinical trials. In patients with concern for gastrointestinal bleeding, dabigatran may not be the preferred option.

All of the NOACs are at least partially eliminated through the kidney (see Table 34), and the dose must be reduced in patients with advanced chronic kidney disease. Apixaban has the lowest renal elimination, so it is approved for patients undergoing dialysis; however, many physicians still prefer warfarin in patients with kidney disease, and caution should be used.

Bridging therapy is typically unnecessary in patients taking NOACs. Discontinuation of the NOAC depends on the half-life of the drug, the type of procedure, and the patient's kidney function. NOACs should be stopped 24 to 48 hours before surgery with moderate bleeding risk and 72 hours before surgery with higher bleeding risk. In patients with impaired kidney function, NOACs should be stopped earlier. For procedures with low bleeding risk, NOACs can be resumed promptly when effective hemostasis is secured. For procedures with higher rates of bleeding, reinstitution is usually delayed 2 to 3 days.

The standard approach to patients experiencing bleeding involves hemodynamic monitoring and resuscitation with fluid and blood products. Activated charcoal can be considered if the NOAC was ingested recently (<6 hours). Hemodialysis can be considered with dabigatran therapy if new kidney disease is found. No specific antidote is available for bleeding associated with rivaroxaban, apixaban, or edoxaban. For patients experiencing major bleeding while taking these agents, fibrinolytic agents such as tranexamic acid or ε-aminocaproic acid may be used. Although three- and four-factor PCCs and recombinant factor VIIa have been used in NOAC-associated bleeding, their benefit has not been confirmed in randomized trials, and the data remain unclear. Idarucizumab, a monoclonal antibody fragment, binds free and thrombin-bound dabigatran and neutralizes its activity. In a phase 3, multicenter, prospective, cohort trial, idarucizumab was found to be safe and effective in reversing the anticoagulant effects of dabigatran in patients who either experienced serious, overt, life-threatening bleeding determined to require

TABLE 34. Key Features of the Non-Vitamin K Antagonist Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Class of anticoagulant	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
T_{max} (h)	2	3	3	1-2	3-4
Half-life (h)	12-17	7-11	9-14	9-11	20
Protein binding	35%	95%	87%	54%	60%
Renal elimination	80%	66% (33% as active metabolite)	25%	35%	5%
FDA-approved indications	Atrial fibrillation VTE treatment	Atrial fibrillation VTE treatment[a] VTE prevention	Atrial fibrillation VTE treatment[a] VTE prevention	Atrial fibrillation VTE treatment	Extended VTE prophylaxis
Reversal agent	Idarucizumab	No	No	No	No
Dosing					
Atrial fibrillation	CrCl >30 mL/min: 150 mg twice daily CrCl 15-30 mL/min: 75 mg twice daily CrCl ≤15 mL/min: do not use	CrCl >50 mL/min: 20 mg once daily CrCl 15-50 mL/min: 15 mg once daily CrCl ≤15 mL/min: do not use	5 mg twice daily 2.5 mg twice daily if ≥2 criteria present: (a) ≥80 years of age (b) Weight ≤60 kg (132 lb) (c) Creatinine ≥1.5 mg/dL (133 µmol/L)	60 mg once daily CrCl 15-50 mL/min: 30 mg once daily CrCl >95 mL/min: do not use	NA
VTE prevention	NA	10 mg once daily	2.5 mg twice daily	NA	160 mg day 1; 80 mg/d for 35-42 days
VTE treatment	CrCl >30 mL/min: 150 mg twice daily CrCl <30 mL/min: do not use	CrCl >30 mL/min: 15 mg twice daily × 3 wk, then 20 mg once daily CrCl ≤30 mL/min: do not use	VTE treatment: 10 mg twice daily × 1 wk, then 5 mg twice daily Reduction in VTE recurrence: 2.5 mg twice daily	60 mg once daily 30 mg once daily with the following criteria: CrCl 30-50 mL/min Weight ≤60 kg (132 lb) Concomitant p-glycoprotein inhibitor use	NA

CrCl = creatinine clearance; h = hour; NA = not applicable; T_{max} = time to maximum concentration; VTE = venous thromboembolism.

[a]Approved as monotherapy for VTE.

H CONT. a reversal agent or who required an urgent invasive procedure that could not be delayed. Idarucizumab was FDA approved for this indication in October 2015. Specific antidotes for this class of agents continue to be developed. H

KEY POINTS

- The non-vitamin K antagonist oral anticoagulants dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban have a rapid onset of activity, no need for laboratory monitoring, and therapeutic effect that is less likely than warfarin to be influenced by changes in diet or medications.

(Continued)

KEY POINTS *(continued)*

- Non-vitamin K antagonist oral anticoagulants (NOACs) are as effective as warfarin in preventing and treating venous thromboembolism; although the overall rate of bleeding is comparable, patients taking a NOAC have less central nervous system bleeding and less fatal bleeding.
- The non-vitamin K antagonist oral anticoagulants should not be used in patients with valvular heart disease or severe obesity, or in those who are pregnant or nonadherent; patients with active cancer are better treated with low-molecular-weight or unfractionated heparin.

CONT. left atrial appendage thrombus and facilitate urgent cardioversion. Regardless of the duration or nature of atrial fibrillation, all patients who undergo cardioversion must receive anticoagulation therapy for at least 4 weeks following the procedure owing to an increased risk for thromboembolic events after sinus rhythm is restored.

Cardioversion and Rate Control

Pharmacologic or electrical cardioversion should be pursued in patients with significant symptoms despite rate control. In patients without structural heart disease, class IC agents or ibutilide can be considered for pharmacologic cardioversion. Patients treated with ibutilide should be monitored on telemetry for a minimum of 6 hours or until the QTc returns to baseline, owing to a small risk for torsade de pointes.

Heart rate control is necessary in patients with rapid ventricular rates to improve cardiac function and alleviate symptoms. Acutely, the goal heart rate should be between 60/min and 110/min. Commonly used medications include AV nodal blockers, such as metoprolol or diltiazem. Intravenous or oral administration may be appropriate depending on a patient's symptoms. In patients with left ventricular dysfunction, calcium channel blockers should be avoided. Digoxin can be used as adjunctive therapy to improve rate control, especially in patients with heart failure.

Long-Term Management

Anticoagulation

Arterial thromboembolic events are the most serious complication of atrial fibrillation. In nonvalvular atrial fibrillation patients, the absolute risk for stroke is approximately 4% per year; however, the presence of comorbidities (such as heart failure, hypertension, diabetes, or vascular disease) can increase the risk 15- to 20-fold. Hypertension is associated with an increased risk for both atrial fibrillation and stroke; therefore, blood pressure control is critical in the management of atrial fibrillation.

Stroke prevention with antithrombotic therapies is dependent on the patient's risk for stroke and risk for bleeding. Although several risk stratification scores are available, current guidelines recommend the use of the CHA_2DS_2-VASc score in patients with nonvalvular atrial fibrillation. Adjusted stroke rates and recommendations for antithrombotic therapy based on the CHA_2DS_2-VASc score are shown in Table 18. Patients with nonvalvular atrial fibrillation who have a CHA_2DS_2-VASc score of 2 or higher should be treated with anticoagulation to prevent stroke. Patients with valvular atrial fibrillation (rheumatic heart disease, mitral stenosis, and valve replacement) should receive warfarin. Non vitamin K antagonist oral anticoagulants (NOACs) are not approved for use in valvular atrial fibrillation. However, patients with atrial fibrillation and other valvular lesions (aortic valve disease, mitral regurgitation, and tricuspid regurgitation) are eligible for NOAC therapy.

Bleeding scores, such as the ATRIA, HAS-BLED, and ORBIT scores, may be used to identify patients with significant bleeding risk based on patient characteristics, including anemia, hypertension, labile INR, older age, kidney insufficiency, and treatment with antiplatelet medications. Reversible risk factors for bleeding should be addressed in patients receiving anticoagulants. Concomitant antiplatelet therapy should be avoided unless the patient has recent active coronary artery disease (acute coronary syndrome or revascularization within the past year).

Several oral anticoagulants are available for stroke prevention in patients with atrial fibrillation. Vitamin K antagonism with dose-adjusted warfarin is an effective, low cost therapy; however, warfarin has limitations, including the need for frequent monitoring and adjustment and numerous food and drug interactions. The safety and efficacy of warfarin therapy depend on the time the patient is in the therapeutic range (INR 2–3).

Four NOACs are approved for the prevention of stroke in atrial fibrillation (Table 19). Dabigatran, an oral direct thrombin inhibitor, is superior to warfarin for the prevention of ischemic stroke and results in less intracranial bleeding. Patients taking dabigatran have a higher risk for gastrointestinal bleeding relative to warfarin and may experience dyspepsia. Rivaroxaban, a direct factor Xa inhibitor, is noninferior to warfarin in the prevention of stroke or systemic embolism and is associated with less intracranial and fatal bleeding. As with dabigatran, patients taking rivaroxaban have a higher risk for gastrointestinal bleeding compared with those taking warfarin. Apixaban, another oral factor Xa inhibitor, is superior to warfarin for the prevention of stroke and confers less risk for major bleeding, including intracranial bleeding. Edoxaban is noninferior to warfarin for stroke prevention and is associated with less major bleeding. All of the NOACs have shorter half lives than warfarin; however, there are no quick, readily available serum assays to accurately determine anticoagulant activity. Reversal agents and antidotes continue to be developed for these agents. Andexanet alfa is being evaluated for reversal of factor Xa inhibition, for use in patients treated with rivaroxaban, apixaban, or edoxaban. Idarucizumab is a dabigatran reversal agent available for emergency invasive or surgical procedures or in cases of uncontrolled or life-threatening bleeding.

Approximately 10% to 25% of patients with atrial fibrillation have contraindications to oral anticoagulation or discontinue therapy for various reasons, including bleeding events. In patients who are at moderate to high risk for stroke (CHA_2DS_2-VASc score ≥3), left atrial appendage occlusion to prevent stroke and systemic thromboembolism can be considered. Occlusion of the left atrial appendage can be achieved percutaneously with a self-expanding device that is implanted in the left atrial appendage or with surgical closure. Left atrial

TABLE 19. Anticoagulants Approved for Stroke Prevention in Atrial Fibrillation

Medication	Frequency	Type of AF	Cautions and Dosing
Warfarin (vitamin K antagonist)	Dosing adjusted to INR	Valvular[a] or nonvalvular	Avoid in pregnancy Caution with idiopathic thrombocytopenic purpura, heparin-induced thrombocytopenia, liver disease, protein C or S deficiency Many drug interactions
Dabigatran (direct thrombin inhibitor)	Twice daily	Nonvalvular	Caution with P-glycoprotein inhibitors Reduce dose with CrCl 15-30 mL/min/1.73 m^2
Rivaroxaban (factor Xa inhibitor)	Once daily	Nonvalvular	Avoid with CrCl <30 mL/min/1.73 m^2, moderate liver impairment, strong P-glycoprotein inhibitors, and strong cytochrome P-450 inducers and inhibitors Reduce dose with CrCl 30-50 mL/min/1.73 m^2
Apixaban (factor Xa inhibitor)	Twice daily	Nonvalvular	Avoid with strong P-glycoprotein inhibitors or strong cytochrome P-450 inducers and inhibitors Reduce dose with two of the following criteria: creatinine ≥1.5 mg/dL (133 [μmol/L]), age ≥80 years, or weight ≤60 kg (132 lb)
Edoxaban (factor Xa inhibitor)	Once daily	Nonvalvular	Avoid with strong cytochrome P-450 inducers and inhibitors Reduce dose with CrCl 30-50 mL/min/1.73 m^2, weight ≤60 kg (132 lb), or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors)

AF = atrial fibrillation; CrCl = creatinine clearance.

[a]Valvular atrial fibrillation refers to atrial fibrillation in the presence of a mechanical heart valve, rheumatic mitral valve disease, and/or mitral stenosis.

CONT.

appendage occlusion has a lower risk for intracranial bleeding compared with dose-adjusted warfarin.

Rate Versus Rhythm Control

Studies have not demonstrated that sinus rhythm restoration is superior to rate control alone. Consequently, the decision to initiate a rate or rhythm control strategy is predominantly based on symptoms, patient age, and patient preference. Rate control can be used to manage asymptomatic patients, with a resting heart rate goal of less than 80/min. A goal of less than 110/min may be considered in select patients without left ventricular dysfunction. β-Blockers, calcium channel blockers, and digoxin can be used to control the ventricular rate in patients with atrial fibrillation. Combination therapy may be needed to adequately control heart rate. Aside from resting heart rate assessment, evaluation of the heart rate with activity, such as with a 6 minute walk test, stress test, or 24-hour ambulatory ECG monitoring, should be performed.

A rhythm control strategy can improve quality of life in patients who continue to have symptoms despite adequate rate control. Because the long term effects of rate control are unknown, rhythm control is often pursued in younger patients (aged <50 years) with minimal symptoms. Rhythm control may require cardioversion in addition to antiarrhythmic therapy. Antiarrhythmic drug selection is guided by the patient's comorbid conditions and safety considerations. Patients with infrequent atrial fibrillation who have no structural heart disease or conduction disease often benefit from a "pill in the pocket" approach. With this strategy, patients take a class IC drug (flecainide or propafenone) at the onset of an episode of atrial fibrillation. These patients should be receiving β-blocker or calcium channel blocker therapy or should take one of these medications before taking the "pill in the pocket." Pill-in-the-pocket therapy should be initiated in a monitored setting to ensure patient safety.

Nonpharmacologic Strategies

Catheter ablation with pulmonary vein isolation is an effective rhythm control therapy in patients with recurrent symptomatic atrial fibrillation despite antiarrhythmic drug therapy. Catheter ablation is most effective in patients without significant left atrial enlargement and multiple comorbid conditions. Seventy percent to 90% of patients with paroxysmal atrial fibrillation are symptom-free 1 year after the procedure; however, success rates vary. Complications include thromboembolism (0.5%-1% risk), tamponade, and vascular complications (such as insertion hematoma, pseudoaneurysm, arteriovenous fistula, and retroperitoneal bleeding). Longer term complications, such as pulmonary vein stenosis, are uncommon.

AV node ablation is an option in patients with atrial fibrillation who have continued symptomatic tachycardia despite rate and rhythm control therapy. Therapeutic ablation of the

syndrome, and medication use (for example, the ergot agents pergolide or cabergoline). Symptoms of tricuspid stenosis (fatigue, cold skin) are typically overshadowed by those caused by the left-sided abnormalities of coexistent rheumatic mitral disease. Findings on physical examination include those of right-sided congestion (elevated jugular venous pulse, hepatic congestion, peripheral edema) and a diastolic rumble. Surgery for tricuspid stenosis is typically performed in concert with therapy for rheumatic mitral disease.

KEY POINTS

- Loop diuretics and aldosterone antagonists can improve symptoms of right-sided congestion in patients with significant tricuspid regurgitation.
- Tricuspid valve surgery is recommended for patients with severe tricuspid regurgitation undergoing left-sided valve surgery and may be considered in select cases of severe tricuspid regurgitation that are refractory to medical therapy.

Prosthetic Valves

The choice of prosthesis for a patient undergoing surgical valve replacement is complex. Factors to consider are the patient's age, the expected durability of the prosthesis, the surgical risk for reoperation in the event of degeneration, and the ability and willingness of the patient to take warfarin for anticoagulation. The American College of Cardiology/American Heart Association VHD guideline recommends a mechanical valve prosthesis in patients younger than 50 years, bioprosthesis in patients older than 70 years, and either a bioprosthesis or mechanical valve prosthesis in those age 50 to 70 years. However, the final decision on valve type should be reached through a shared decision-making process between the care provider and patient. The patient should thoroughly understand the risks and benefits as well as have decision-making capacity. Additional considerations include the expected durability of bioprostheses (15 years) and that structural deterioration of the valve is more common in younger patients. In those younger than 60 years, approximately 40% of valves have evidence of clinically severe deterioration by 15 years.

Immediately after implantation, all patients should undergo echocardiography to document the baseline hemodynamic performance of the valve, and repeat evaluations should be performed for signs or symptoms of prosthetic dysfunction. Annual evaluation is recommended for all patients with a bioprosthesis beginning at 10 years after surgery. Data on long-term durability of TAVR prostheses are currently limited to a follow-up of 5 years; however, thus far, valve durability is not different from surgical prostheses.

Lifelong warfarin anticoagulation is indicated in all patients with a mechanical valve prosthesis. In recent VHD guidelines, the goal INR for warfarin anticoagulation in patients with a mechanical prosthesis has shifted from a range to a single value. This change was made to minimize the time the patient spends at the low and high ends of a target range because drifting above and below the range can be deleterious. The use of a single-value INR target can pose logistic challenges for testing and warfarin adjustments, and in those instances, recommendations to improve processes and enhance patient understanding and motivation should be considered.

In patients with a mechanical aortic valve prosthesis (bileaflet or current-generation single-tilting disc) with no additional risk factors for thromboembolism (history of embolization, hypercoagulable disorder, LV dysfunction, atrial fibrillation), the goal INR for warfarin anticoagulation is 2.5. In patients with a mechanical aortic valve prosthesis with risk factors for thromboembolism, an older-generation aortic valve prosthesis (ball-in-cage), or any mitral prosthesis, the target INR is 3.0. Because of the risk for valve thrombosis, direct thrombin inhibitors and factor Xa inhibitors should not be used for anticoagulation therapy in patients with a mechanical valve prosthesis. Oral anticoagulation with warfarin should be considered for at least 3 months and as long as 6 months after implantation of a mitral or aortic bioprosthesis. An INR of 2.5 should be targeted in these patients.

Aspirin (75–100 mg/d) is highly recommended in addition to warfarin therapy for patients with a mechanical prosthesis based on the results of randomized trials, which showed reduction in the risk for embolic events, including stroke (1.3% per year versus 4.2% per year, $P < 0.027$) and death (2.8% per year versus 7.4% per year; $P < 0.01$). For all patients with a bioprosthesis, low-dose aspirin is generally recommended.

KEY POINTS

- A shared decision-making process should guide the choice of prosthetic valve type.
- Echocardiographic evaluation of prosthetic valve function is recommended at baseline and in patients with symptoms or signs suggesting prosthetic dysfunction.
- Annual echocardiographic evaluation is recommended for all patients with a bioprosthesis beginning at 10 years after surgery.
- Lifelong warfarin anticoagulation is indicated in all patients with a mechanical valve prosthesis.
- Antiplatelet therapy with low-dose aspirin is strongly recommended for patients with a mechanical prosthesis and is reasonable for patients with a bioprosthesis.

Infective Endocarditis

Diagnosis and Management

Infective endocarditis is a life-threatening disorder that involves native valvular structures or implanted cardiovascular devices. Such devices include cardiac valve prostheses, permanent pacemakers, implanted cardioverter-defibrillators, and occluders for repair of congenital lesions (such as atrial septal defect and ventricular septal defect occluders). Risk factors for