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Diagnosis and Treatment of Lower Extremity Venous Thromboembolism
A Review

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IMPORTANCE Incidence rates for lower extremity deep vein thrombosis (DVT) range from 88 to 112 per 100 000 person-years and increase with age. Rates of recurrent VTE range from 20% to 36% during the 10 years after an initial event.

OBSERVATIONS PubMed and Cochrane databases were searched for English-language studies published from January 2015 through June 2020 for randomized clinical trials, meta-analyses, systematic reviews, and observational studies. Risk factors for venous thromboembolism (VTE), such as older age, malignancy (cumulative incidence of 7.4% after a median of 19 months), inflammatory disorders (VTE risk is 4.7% in patients with rheumatoid arthritis and 2.5% in those without), and inherited thrombophilia (factor V Leiden carriers with a 10-year cumulative incidence of 10.9%), are associated with higher risk of VTE. Patients with signs or symptoms of lower extremity DVT, such as swelling (71%) or a cramping or pulling discomfort in the thigh or calf (53%), should undergo assessment of pretest probability followed by D-dimer testing and imaging with venous ultrasonography. A normal D-dimer level (ie, D-dimer <500 ng/mL) excludes acute VTE when combined with a low pretest probability (ie, Wells DVT score ≤1). In patients with a high pretest probability, the negative predictive value of a D-dimer less than 500 ng/mL is 92%. Consequently, D-dimer cannot be used to exclude DVT without an assessment of pretest probability. Postthrombotic syndrome, defined as persistent symptoms, signs of chronic venous insufficiency, or both, occurs in 25% to 50% of patients 3 to 6 months after DVT diagnosis. Catheter-directed fibrinolysis with or without mechanical thrombectomy is appropriate in those with iliofemoral obstruction, severe symptoms, and a low risk of bleeding. The efficacy of direct oral anticoagulants—rivaroxaban, apixaban, dabigatran, and edoxaban—is noninferior to warfarin (absolute rate of recurrent VTE or VTE-related death, 2.0% vs 2.2%). Major bleeding occurs in 1.1% of patients treated with direct oral anticoagulants vs 1.8% treated with warfarin.

CONCLUSIONS AND RELEVANCE Greater recognition of VTE risk factors and advances in anticoagulation have facilitated the clinical evaluation and treatment of patients with DVT. Direct oral anticoagulants are noninferior to warfarin with regard to efficacy and are associated with lower rates of bleeding, but costs limit use for some patients.

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Supplemental content

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Lower extremity venous thromboembolism (VTE), including deep vein thrombosis (DVT) of the leg, is common.[1] The incidence rate for DVT ranges from 88 to 112 per 100 000 person-years.[2] Rates of recurrent VTE range from 20% to 36% during the 10 years after an initial event.[3,4] Isolated distal DVT, defined as thrombosis involving 1 or more of the deep calf veins without reaching the popliteal vein, is associated with a 1-year all-cause mortality rate of 4.6 per 100 person-years (95% CI, 3.8-5.7).[5] This review provides an evidence-based update of the diagnosis and therapy of lower extremity DVT.

Methods

We searched PubMed and the Cochrane databases for English-language studies published from January 2015 through June 2020 for randomized clinical trials, meta-analyses, systematic reviews, and observational studies, resulting in 2125 retrieved articles (see eAppendix in the Supplement for search terms). We manually searched references of selected articles, reviews, meta-analyses, and practice guidelines. Selected articles were mutually agreed on by the authors. A total of 86 articles (20 randomized clinical trials, 20 systematic reviews and meta-analyses, 33 observational cohort studies, 7 reviews, and 6 guideline documents) were included in the final review. Randomized clinical trials and meta-analyses and information of interest to a general medical readership were prioritized.

Risk Factors for VTE

Most patients with VTE have multiple risk factors for VTE (**Table 1**). Risk factors include demographic factors (eg, older age,

Table 1. Risk Factors for Venous Thromboembolism (VTE)

Risk factor	Data on study participants	Absolute risk estimates[a]
Demographic		
Age and sex Young age: female sex at greater risk Older age: male sex at greater risk		Not available
Genetic		
Inherited thrombophilia	Community-based sample of 3424 southeastern Minnesota residents identified within the Mayo Clinic community: 230 (6.7%) factor V Leiden carriers; 220 carriers (mean age, 68 y) matched to a noncarrier	Cumulative incidence for VTE over 14 722 person-years for factor V Leiden carriers, 10.9%[6]
Sickle cell disease	6237 Patients with sickle cell disease in the Patient Discharge Database from California (52.6% women)	Cumulative incidence of VTE by age 40 years, 17.1% for patients with severe sickle cell disease (hospitalized ≥3 times/y) vs 8.0% for matched asthma control patients[7]
Non-O blood type		Not available
Lifestyle-related		
Smoking		Not available
Obesity		Not available
Acquired		
Malignancy	Included results from the Vienna Cancer and Thrombosis Study (CATS), a large prospective observational study: 1544 patients with cancer (median age, 62 y; 45% women)	Cumulative incidence of VTE among patients with cancer (median, 19 mo), 7.4%[8]
Infection	Olmsted County, Minnesota, residents with objectively diagnosed incident DVT or PE: time period of 1988-2000; cases (n = 1303; mean [SD] age, 65.2 [18.9] y) matched with control patients (n = 1494; mean [SD] age, 64.9 [18.8] y)	513 (39.4%) cases and 189 (12.7%) control patients had an infection in the previous 92 d[9]
Inflammatory disorders	Cohort study conducted in a primary care medical record database in the UK with data from 1994-2014: patients with rheumatoid arthritis (mean [SD] age, 62.5 [16.5] y; 70% women)	VTE risk (mean follow-up, 6.3 y): 4.7% for patients with rheumatoid arthritis vs 2.5% for control patients[2]
Atherosclerotic cardiovascular disease	The TRA2P-TIMI 50 trial randomized 26 449 stable outpatients with a history of myocardial infarction, ischemic stroke, or peripheral artery disease (median age, 68 y for patients with VTE and 32 y for patients without VTE; 75% of patients with VTE were men and 76% of patients without VTE were men)	3-year rates of VTE: 0.76% for 1 symptomatic vascular territory, 1.53% for 2, and 2.45% for 3[10]
Major surgery		Not available
Chronic kidney disease		Not available
Diabetes	Data from the National Health Insurance Research Database of Taiwan: 4967 patients with type 1 diabetes and 19 868 controls (mean [SD] age, 27 [15] y in both groups; 53.5% women)	During a mean follow-up of 8.61 years, 45 participants developed VTE in the nondiabetes group (0.3%) and 80 developed VTE in the diabetes group (1.6%)[11]
Heart failure	Population-based cohort study of 2330 Danish patients with heart failure (15 238 [47%] women; mean [SD] age, 78.9 [12.4] y; mean age of men, 72.3 [13.3] y)	After 3 years of follow-up, cumulative incidence of 1.5% for men and 2.0% for women[12]
Chronic pulmonary disease	Population-based retrospective cohort study using information from the National Health Insurance Research Database of Taiwan: 15 478 patients with nonchronic pulmonary disease and 7739 with chronic pulmonary disease (mean age, 72 y; 67% men)	During 11 y follow-up: 137 DVT events (0.89%) in the nonchronic pulmonary disease group and 94 DVT events (1.21%) in the chronic pulmonary disease group[13]
Pregnancy/puerperium	Review and meta-analysis of 27 articles	Pregnancy-associated VTE: 1.4% (95% CI, 1.0%-1.8%) for VTE, 1.1% (95% CI, 1.0%-1.3%) for DVT, and 0.3% (95% CI, 0.2%-0.4%) for PE[14]
Hormonal contraception/ replacement therapy		Not available
Immobilization		Not available
Acquired hypercoagulable states (eg, antiphospholipid antibodies)	Cohort of 104 patients with triple-positive antiphospholipid tests prospectively followed up in Italian thrombosis centers (mean age, 45 y; 79% women)	Cumulative incidence after 10 y: 37.1% (95% CI, 19.9%-54.3%)[15]

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] The estimates presented do not originate from the same study. They represent different cohorts and should not be directly compared.

sex), intrinsic characteristics of blood (eg, factor V Leiden, non-O blood type, sickle cell disease), lifestyle (eg, current smoking, obesity), and acquired risk factors (eg, malignancy, hormonal therapies, acute infection).[7,16-20] The association of sex and VTE depends on age; female sex is associated with the highest risk in a younger age (<50 years), whereas male sex is associated with the highest risk among older adults (≥65 years).[21]

Genetic Risk Factors

Inherited thrombophilias, the most common of which are factor V Leiden, prothrombin gene polymorphism, and methylenetetrahydrofolate reductase (*MTHFR*) gene polymorphism, increase the risk of VTE, especially in people who are homozygous carriers.[19] Factor V Leiden carriers have a cumulative incidence for VTE over 14 722 person-years of 10.9%, corresponding to a cumulative VTE incidence at age 65 years of 6.3% (95% CI, 2.7%-9.7%) among carriers and 5.2% (95% CI, 2.0%-8.4%) among noncarriers.[6] Factor V Leiden is more common in people of northern European descent. In a registry of 5451 patients with ultrasonography-confirmed DVT, thrombophilia, an imbalance of blood clotting factors that predisposes to thrombosis, was observed in only 5% of patients, compared with cancer in 32% of patients, immobility in 34% of patients, and obesity in 27% of patients, all of which are more traditional VTE risk factors.[22]

Testing for inherited thrombophilia is the most helpful when the results will inform decision-making for preventing or managing VTE, such as when deficiency of protein C or antithrombin would influence a decision to prescribe extended-duration antithrombotic therapy. Thrombophilia should be suspected in patients with VTE at a young age (ie, <50 years); disease in first-degree relatives (at least 1 parent or sibling); venous thrombosis in unusual locations, such as the cerebral venous sinuses or splanchnic veins; idiopathic or recurrent VTE; or a history of recurrent miscarriage.

Lifestyle-Related Risk Factors

Lifestyle-related risk factors for VTE are often modifiable and include some risk factors for atherosclerosis, such as cigarette smoking and obesity.[20] In addition to the VTE risk associated with higher body mass index (BMI), childhood obesity was associated with increased risk in adulthood independent of BMI in adulthood.[23] An association has been observed between atherosclerosis and VTE. A greater number of symptomatic arterial locations affected by atherosclerotic disease correlated with a graded increase in 3-year rates of VTE (0.8% for 1 territory, 1.5% for 2, and 2.5% for 3) after adjustment for other thromboembolic risk factors.[10] In a cohort study from Taiwan of 4967 patients with type 1 diabetes and 19 868 control individuals without diabetes, 45 participants developed VTE in the control group (0.3%) vs 80 patients in the diabetes group (1.6%) during a mean follow-up of 8.61 years.[11]

Acquired Risk Factors

Both acute infection and cancer are risk factors for VTE.[8,9,24-27] For cancer, there is a cumulative VTE incidence of 7.4% at a median of 19 months after cancer diagnosis.[8] In a cohort study from Olmsted County, Minnesota, that investigated the association of infection with VTE, 1303 patients with incident VTE were compared with 1494 control individuals without VTE. Among the patients with VTE, 39.4% were diagnosed with infection in the previous 92 days vs 12.7% among the control individuals.[9] Inflammation is associated with increased risk of venous thrombosis,[28] supported by a high prevalence of VTE in individuals with chronic inflammatory diseases, such as rheumatoid arthritis (absolute risk, 4.7% vs 2.5% in control individuals),[29] and in patients with chronic obstructive lung disease (absolute risk, 1.2% vs 0.9% in control individuals).[13] Key elements of the systemic inflammatory response, including platelets and neutrophils, have been identified in the pathogenesis of VTE.[28,30] Other acquired risk factors include chronic kidney disease, dehydration, immobilization, major surgery, and trauma.[31,32] Increased titers of a specific antiphospholipid antibody identified on 2 separate occasions (such as an increased anticardiolipin antibody detected on initial evaluation and confirmed 12 weeks later) are associated with increased risk of VTE, especially for VTE recurrence (16.2% recurrence vs 8.0% for those not meeting this criterion).[33]

Women are at increased risk for VTE during pregnancy and the puerperium, with a pooled pregnancy-associated VTE rate of 1.4%.[14] Furthermore, VTE risk increases with hormone replacement therapy and combination oral contraceptives in an estrogen dose–dependent manner.[14,16,34]

Clinical Presentation

Patients with lower extremity DVT commonly describe swelling (71%) or a cramping or pulling discomfort in the thigh or calf (53%) that may worsen with ambulation (10%).[35] Other symptoms and signs include warmth, rubor, a palpable cord, and prominent venous collaterals.

Diagnosis

Because the prevalence of DVT in patients with suspected DVT and no prior history of VTE is less than 20%,[36] a diagnostic strategy that includes assessment of the pretest probability, followed by D-dimer testing and imaging, is required (**Figure 1**; **Box**).[37,38]

Assessing Pretest Probability

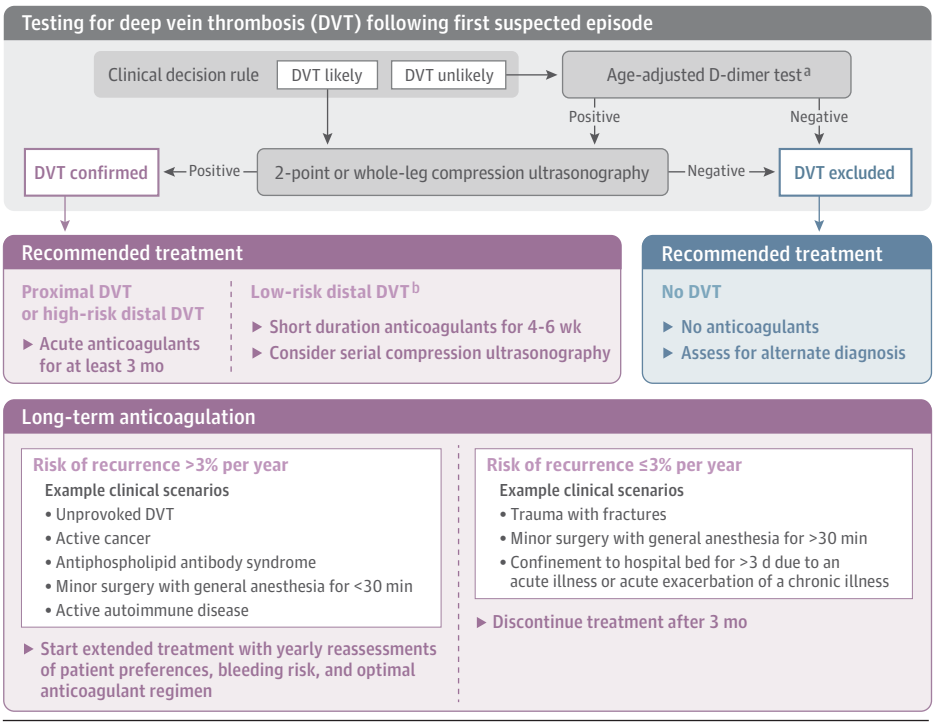
Determining pretest probability is the first step in the outpatient diagnosis of DVT. The Wells DVT score is the most widely used and validated clinical decision rule. It assigns points for 10 variables to yield a total score ranging from −2 to 9 points, with a score of 3 or higher suggesting a high likelihood of DVT (eTable 1 in the Supplement).[39] However, in patients with the lowest Wells score of −2, the prevalence of DVT is approximately 5%, underscoring that DVT cannot be excluded using the Wells score alone.[39]

Clinical decision rules perform more poorly among inpatients. In a cohort study of 1135 inpatients, the discriminatory accuracy of the Wells score for DVT risk prediction was low (area under curve = 0.60).[40] Therefore, inpatients with suspected DVT require direct imaging.

D-Dimer Testing

Because clinical decision rules alone do not exclude the presence of DVT, they should be used with D-dimer testing and, when

Figure 1. A Proposed Diagnosis and Treatment Algorithm for Patients With Suspected Deep Vein Thrombosis (DVT)



This algorithm has not been validated in clinical trials but represents a synthesis of evidence-based approaches to DVT diagnosis and management.
[a]Age-adjusted D-dimer threshold, calculated as the patient's age multiplied by 10 ng/mL for patients older than 50 years with suspected venous thromboembolism.
[b]Low-risk patients: younger than 50 years, no cancer or prior venous thromboembolism, taking contraceptive or replacement hormonal therapy, and secondary to surgery or immobilization when complete mobilization is achieved.

appropriate, imaging. The negative predictive value of high-sensitivity D-dimer testing is high but its specificity is low, and its negative predictive value decreases when the DVT prevalence increases. In patients with a high pretest probability, the negative predictive value of a D-dimer level less than 500 ng/mL is 92%.[38] Consequently, D-dimer cannot be used to exclude DVT without an assessment of pretest probability. On the other hand, a normal D-dimer level (ie, D-dimer <500 ng/mL) essentially excludes acute VTE when combined with a low pretest probability (ie, Wells DVT score ≤1).[39] Imaging and treatment can be withheld in as many as 29% (95% CI, 20%-40%) of patients with suspected DVT who have D-dimer less than 500 ng/mL combined with a low pretest probability, of whom less than 1% will subsequently be diagnosed with VTE. This strategy is less reliable in patients with cancer. In patients with cancer, the combination of a low pretest probability score on the Wells test and a negative D-dimer test result occurred in only 9% of patients, but was associated with a 2.2% (95% CI, 0.5%-8.6%) probability of DVT presence.[39] Clinicians may consider proceeding directly to imaging in patients with cancer with suspected DVT.

D-dimer levels increase with age, leading to lower specificity for DVT diagnosis in older patients. An age-adjusted D-dimer threshold, defined as the patient's age multiplied by 10 ng/mL (fibrinogen-equivalent units), has been suggested for patients older than 50 years.[41] In an individual patient data meta-analysis including 2554 patients with suspected DVT, the age-adjusted D-dimer strategy resulted in a 9.5% (95% CI, 1.0%-18.0%) improvement in specificity compared with the standard D-dimer strategy (specificity of 54.7% [95% CI, 40.7%-68.9%] for the age-adjusted D-dimer strategy vs 45.2% [95% CI, 39.6%- 50.9%] for the standard D-dimer strategy).[42]

Imaging for Suspected DVT

In primary care and outpatient settings, patients with suspected DVT according to a clinical decision rule and positive age-adjusted D-dimer testing should be referred for diagnostic imaging.[37,38] Venous ultrasonography is the first-line imaging test (**Figure 2**). Ultrasonography findings in the presence of DVT include venous noncompressibility, direct thrombus visualization with venous dilation, and abnormal spectral and color Doppler blood flow. Abnormalities are typically classified as acute DVT, acute on chronic thrombus, chronic postthrombotic changes, or indeterminate. Acute thrombus is characterized by a deformable shape, central location, and venous dilation. A loosely adherent or free-floating edge may be seen, but is less common. In more chronic-appearing thrombus, the intraluminal material is rigid and nondeformable with transducer-applied pressure. The surface may be irregular and calcifications or hyperechoic acoustic shadows may be noted. Chronic thromboembolic material may retract and produce thin webs or thicker flat bands, referred to as *synechiae*. Incorporation of chronic thromboembolic material in the vein wall or recanalization of the occluded vein may produce regular or irregular wall thickening. When scarring of the vein is present, the vein size may be normal or decreased.[43]

Venous compression ultrasonography can be performed by examining the popliteal and common femoral veins only (2-point testing) or by extended imaging including the calf veins (whole-leg testing). A meta-analysis of 40 studies including 21 250 patients (mean age range, 29-72 years; male sex range, 0%-68%; cancer prevalence range, 0%-28.9%) demonstrated that the rates of VTE at 3-month follow-up (except for 1 study in which the follow-up was 6 months) were low and did not significantly differ after a single negative 2-point compression ultrasonography finding (1.4% [95% CI,

Box. Commonly Asked Questions About the Diagnosis and Treatment of Lower Extremity Venous Thromboembolism (VTE)

When should venous ultrasonography be performed without first obtaining a D-dimer test in a patient with suspected lower extremity deep vein thrombosis (DVT)?
For patients in whom a clinical decision rule suggests that DVT is likely, including those with cancer, venous ultrasonography should be performed without first obtaining a D-dimer test because a normal level does not reliably exclude the diagnosis when pretest probability is high.

What patients who present with newly diagnosed lower extremity DVT can be discharged home from the emergency department without admission?
Patients with lower extremity DVT and adequate home support and manageable symptoms who can afford the cost of a direct oral anticoagulant (DOAC) may be considered for outpatient treatment.

When should isolated calf DVT be managed with anticoagulation?
Anticoagulation is recommended in patients with isolated calf DVT and severe symptoms or risk factors for pulmonary embolism or extension to proximal veins (such as hospitalization, history of VTE, and cancer).

Can DOACs be used to treat patients with VTE in the setting of cancer?
DOACs are considered an alternative to low-molecular-weight heparin for management of cancer-associated VTE in patients without gastrointestinal malignancy. Patients with gastrointestinal malignancy have demonstrated an increased risk of gastrointestinal bleeding with use of some DOACs (edoxaban in particular).

What is postthrombotic syndrome and how is it diagnosed?
Postthrombotic syndrome is a clinical diagnosis made when signs or symptoms of DVT persist 3 to 6 months after diagnosis and is characterized by chronic leg discomfort; edema; venous stasis changes; and, in advanced stages, venous ulceration.

0.83%-2.5%]), a negative 2-point compression ultrasonography finding followed by a second negative 2-point examination finding after 5 to 10 days (1.9% [95% CI, 1.4%-2.5%]), or a single negative whole-leg compression ultrasonography finding (1.0% [95% CI, 0.6%-1.6%]).[44] The serial 2-point strategy requires repeat ultrasonography in 5 to 7 days. However, if clinical factors, including significant symptoms, support the management of isolated distal DVT, then single whole-leg venous ultrasonography is preferred.

Alternative imaging modalities for assessing patients with suspected acute lower extremity DVT include computed tomographic imaging, magnetic resonance (MR) imaging, and contrast venography (eTable 2 in the Supplement). These imaging techniques are used when venous ultrasonography evaluation is technically inadequate or equivocal; when there is concern for iliocaval DVT based on signs, symptoms, or abnormal spectral Doppler waveforms; or if a high clinical suspicion persists despite negative ultrasonography findings.[43] Equivocal ultrasonography may be noted when DVT affects the pelvic veins, which are anatomically located above the inguinal ligament and are not reliably visualized. Although the venous segments below the inguinal ligament may normally be compressible, overall venous velocities and phasic change with respiration may be attenuated due to the iliac venous obstruction, resulting in an equivocal result. Venous ultrasonography is the primary diagnostic test when pregnancy-associated DVT is suspected.[37]

Evaluation for May-Thurner Syndrome

May-Thurner syndrome results from compression of the left common iliac vein between the right common iliac artery and the vertebrae, resulting in venous congestion and the development of DVT (Figure 2). May-Thurner syndrome accounts for 2% to 5% of all DVTs, and typically affects young women after surgery or peripartum.[45,46] Diagnosis of May-Thurner syndrome requires computed tomographic or magnetic resonance venography.[43]

Lower Extremity Superficial Thrombophlebitis

Lower extremity superficial thrombophlebitis occurs when thrombus forms in the superficial, often varicose, veins of the leg or foot. Symptoms and signs include focal pain and tenderness, pruritus, and erythema of the skin.[47] Compared with placebo, 2.5 mg of subcutaneous fondaparinux once daily for 45 days is associated with a significantly lower rate of symptomatic deep VTE (5.9% vs 0.9%; absolute difference, −5%; $P < .001$) and more rapid symptom resolution without an increase in major bleeding.[48] Low-molecular-weight heparin (LMWH) and nonsteroidal anti-inflammatory drugs are alternative therapies, but data regarding prevention of symptomatic VTE are inconclusive.[49]

Complications of Lower Extremity DVT

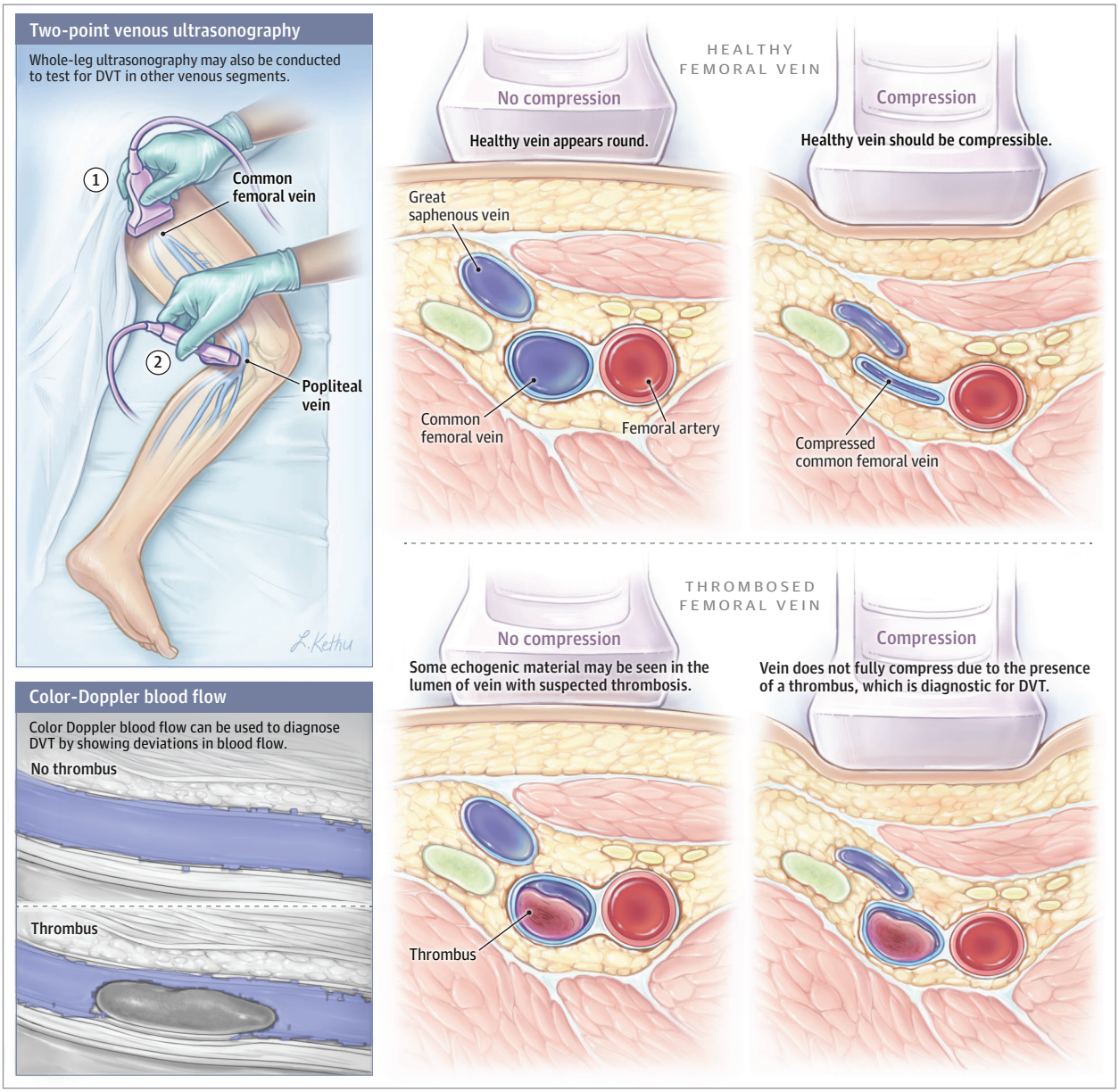
Postthrombotic Syndrome

Postthrombotic syndrome, defined as persistent symptoms, signs of chronic venous insufficiency, or both 3 to 6 months from the initial diagnosis of DVT, occurs in 30% of patients treated with anticoagulation for DVT.[50] Postthrombotic syndrome causes disability, loss of functional status, lost days at work, and substantial health care expenditures, especially if venous ulcerations of the skin of the lower extremity, typically around the medial malleolus, form.[51]

The pathophysiology of postthrombotic syndrome involves persistent venous outflow obstruction, venous valvular damage and incompetence, venous hypertension, and inflammation of the vein wall. The combination of local inflammation and venous hypertension leads to capillary leak, chronic leg discomfort, edema, hyperpigmentation, and often ulceration.[51] The warmth, erythema, and edema of postthrombotic syndrome may mimic cellulitis, but fever is typically absent. Signs of chronic venous insufficiency, such as venous varicosities and hyperpigmentation, support the diagnosis of postthrombotic syndrome. Factors associated with postthrombotic syndrome include iliofemoral DVT, recurrent ipsilateral DVT, persistent symptoms after 1 month of therapeutic anticoagulation, increased BMI, advanced age, and suboptimal anticoagulation, most often due to medication nonadherence or failure to achieve a consistently therapeutic international normalize ratio (INR) during the first 3 months after DVT diagnosis.[51,52]

Postthrombotic syndrome is diagnosed based on persistent symptoms or signs of chronic venous insufficiency 3 to 6 months after DVT in the absence of recurrent thrombosis. Neither catheter-based therapy, compression stockings, nor extended-duration anticoagulation reduce the risk of postthrombotic syndrome.

Figure 2. Duplex Ultrasonography Diagnostic Testing for May-Thurner Syndrome



Compression stockings after DVT diagnosis may be useful in managing symptoms of postthrombotic syndrome.[37]

Management

Management of lower extremity DVT consists of 2 phases: the acute phase, encompassing the first 3 to 6 months after diagnosis, and the chronic phase, extending from 6 months to the rest of the patient's life (Box).

Acute Treatment

Anticoagulation

Anticoagulation should be initiated promptly when DVT is diagnosed or a high clinical suspicion exists. Anticoagulant therapy aims to reduce mortality from pulmonary embolism (PE) and the morbidity of thrombus extension, recurrence, and postthrombotic syndrome. Options for initial management of VTE include immediate treatment with a direct oral anticoagulant (DOAC) (rivaroxaban and apixaban), initial parenteral anticoagulation followed by a DOAC, or initial parenteral anticoagulation overlapped by warfarin for at least 5 days and until the INR is more than 2.0 on 2 occasions 24 hours apart (**Table 2**). LMWH is typically used for parenteral anticoagulation, but unfractionated heparin may be preferred when the ability to discontinue anticoagulation rapidly is required, for instance, in a patient undergoing catheter-based therapy for DVT. Evidence-based clinical practice guidelines recommend DOACs as the preferred choice for most patients with non–cancer-related DVT (**Table 3**).[37,64,65] Initial parenteral anticoagulation overlapped with warfarin is favored in patients who

Table 2. Anticoagulant Options for the Management of Acute Deep Venous Thrombosis (DVT)

Drug	Mechanism of action	Efficacy	Adverse effects
Unfractionated heparin	Inhibitor of thrombin and factor Xa through an antithrombin-dependent mechanism	Recurrent VTE: 6.3% at 6 months (after an initial treatment with heparin in the first 5-14 days) in patients with DVT (vs 3.6% with LMWH) (n = 4451)[53]	Major bleeding: 2.1% at 6 months (after an initial treatment with heparin in the first 5- 14 days) in DVT patients (vs 1.0% with LMWH) (n = 4451)[53] HIT incidence rate ranges from 0.1% to 7%, depending on the duration of heparin exposure and patient population (surgical vs medical) (study sample sizes, 744-24 068 participants)[54]
Low-molecular-weight heparin (LMWH)	Inhibitor of factor Xa through an antithrombin-dependent mechanism	Recurrent VTE: 3.6% at 6 months (after an initial treatment with LMWH in the first 5-14 days) in patients with DVT without cancer (compared with 6.3% with UFH) (study sample size, n = 4451)[53]; between 7.9% and 8.8% at 6 months in patients with cancer-associated VTE treated with LMWH (compared with 4.0%-7.9% with DOAC) (study sample sizes, 203-1155 participants)[55-57]	Major bleeding: 1.0% at 6 months (after an initial treatment with LMWH in the first 5-14 days) in patients with DVT without cancer (compared with 2.1% with UFH) (n = 4451)[53]; between 2.9% and 4.0% at 6 months in patients with cancer-associated VTE treated with LMWH (compared with 3.8% to 6.9% with DOAC) (study sample sizes, 203-1155 participants)[55-57] HIT, incidence rate of 0.2% (n = 7287)[54]
Fondaparinux	Synthetic pentasaccharide that inhibits factor Xa	Recurrent VTE: 3.9% at 3 months in patients with DVT (compared with 4.1% with LMWH) (n = 2205)[58]	Major bleeding: 2.6% at 3 months in patients with DVT (compared with 2.4% with LMWH) (n = 2205)[58]
Argatroban (primarily in patients with suspected or confirmed HIT)	Specific and reversible direct thrombin inhibitor	Thrombosis: 5.8% and 6.9% any new thrombosis at 30 days in HIT patients (vs 15.0% and 23.0% in historical control groups) (n = 177 and n = 328)[54]	Major bleeding: between 3.1% and 5.3% at 30 days in patient with HIT (compared with between 8.2% and 8.6% in historical control groups) (n = 177 and n = 328)[54]
Bivalirudin (primarily in patients with suspected or confirmed HIT)	Specific and reversible direct thrombin inhibitor	Thrombosis: 4.6% any new thrombosis at 30 days in patients with HIT (no comparator) (n = 461)[54]	Major bleeding: 7.6% at 30 days in patient with HIT (no comparator) (n = 461)[54]
Warfarin	Inhibits vitamin-k dependent gamma-carboxylation of factors II, VII, IX, and X	Recurrent VTE: between 3.0% and 3.3% at 1 y in patients with DVT without cancer (compared with 2.1% and 3.4% with DOAC) (study sample sizes, n = 3449 and 4921)[59,80]; 12.7% at 6 months in patients with cancer-associated VTE (compared with 7.3% with LMWH) (n = 1781)[60]	Major bleeding: between 1.2% and 1.6% at 1 y in patient with DVT without cancer (compared with 0.8% and 1.4% with DOAC) (study sample sizes, n = 3449 and 4921)[59,61]; 4.2% at 6 months in patients with cancer-associated VTE (compared with 4.8% with LMWH) (n = 1781)[60] Other major/common: skin or muscle necrosis vasculitis, alopecia, pruritus, urticaria, nausea, vomiting, diarrhea
Factor II inhibitor (dabigatran)	Direct thrombin inhibitor	Recurrent VTE: 2.4% at 6 months in patients with VTE without cancers (compared with 2.2% with warfarin) (n = 2539)[62]	Major bleeding: 1.4% at 6 months in non-cancer VTE patients (vs 2.0% with warfarin) (n = 2539)[62] Other major/common: dyspepsia, abdominal pain, and gastritis-like symptoms
Factor X inhibitors (apixaban, rivaroxaban, edoxaban)	Direct factor Xa inhibitor	Recurrent VTE: between 2.1% and 3.4% at 1 y in patients with DVT without cancer (compared with 2.7% to 3.4% with warfarin) (study sample sizes, 3449-5244)[59,61,63];5.6% at 6 months; 4.0% and 7.9% at 1 year in cancer-associated VTE patients (vs 7.9% at 6 months; 8.8% and 11.3% at 1 year with LMWH) (study sample sizes, 203-1155)[55-57]	Major bleeding: 0.60% and 1.4% at 1 y in patients with DVT without cancer (compared with 1.2% to 1.8% with warfarin) (study sample sizes, 3449-5244)[59,61,63] 3.8% at 6 months; 3.9% and 6.0% at 1 year in cancer-associated VTE patients (vs 4.0% at 6 months; 2.9% and 4.0% at 1 year with warfarin with LMWH) (study sample sizes, 203-1155)[55-57] Other major/common: increased serum transaminases

Abbreviations: AT, antithrombin; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; Factor Xa, activated factor X; HIT, heparin-induced thrombocythemia; INR, international normalized ratio; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 3. International Recommendations for Acute-Phase Treatment of Noncancer Venous Thromboembolism With Direct Oral Anticoagulants (DOACs) vs Warfarin

International guideline	Recommendations
ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration with the European Respiratory Society (2019)[64]	When oral anticoagulation is started in a patient with PE who is eligible for an NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), an NOAC is recommended in preference to a VKA (class of recommendation: I; level of evidence: A)
Diagnosis and Management of Acute Deep Vein Thrombosis: a Joint Consensus Document from the European Society of Cardiology Working Groups of Aorta and Peripheral Circulation and Pulmonary Circulation and Right Ventricular Function (2017)[37]	In the absence of contraindications, DOACs should be preferred as first-line anticoagulant therapy in patients without cancer with proximal DVT
Antithrombotic Therapy for VTE Disease ACCP Guideline and Expert Panel Report (2016)[65]	In patients with DVT of the leg or PE without cancer, dabigatran, rivaroxaban, apixaban, or edoxaban are suggested as long-term (first 3 months) anticoagulant therapy over VKA therapy (Grade 2B recommendation) For patients with DVT of the leg or PE without cancer who are not treated with DOAC, we suggest warfarin therapy over low-molecular-weight heparin (Grade 2C recommendation)

Abbreviations: ACCP, American College of Chest Physicians; DVT, deep vein thrombosis; ESC, European Society of Cardiology; NOAC, non–vitamin K antagonist oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table 4. Management of Anticoagulation for the Treatment of Patients With Acute Deep Venous Thrombosis (DVT)

Clinical setting	Caution	Preferred strategy
Kidney function[a]		
Stage I-III (GFR >30)[a]	None	DOACs
Stage IV (GFR of 15-29)[a]	Avoid DOACs[b]	Warfarin or half-dose LMWH
Dialysis	Avoid DOACs and LMWH	Warfarin
Pregnancy	Avoid DOACs and warfarin	LMWH
Breastfeeding women	DOACs contraindicated	Warfarin or LMWH
Cancer-associated DVT		
Non-gastrointestinal tract cancer	None	LMWH or DOACs[55-57]
Gastrointestinal tract cancer	Avoid rivaroxaban or edoxaban[55,56]	LMWH (apixaban might be considered)[c,57]
Chemotherapy	Assess chemotherapy-DOAC interaction	LMWH or DOACs

Abbreviations: DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; LMWH, low-molecular-weight heparin.

[a] Based on Kidney Disease Outcomes Quality Initiative guidelines. Measured as mL/min/1.73 m^2.

[b] Creatinine clearance [CrCl] <30 mL/min for edoxaban, rivaroxaban (15 mg and 20 mg), and dabigatran; CrCl <25 mL/min for apixaban; or CrCl <15 mL/min for rivaroxaban (10 mg).

[c] The 2019 European Society of Cardiology guidelines for the management of acute pulmonary embolism[64] did not include the 2020 CARAVAGGIO trial, which demonstrated the efficacy and safety of apixaban for the management of cancer-related venous thromboembolism.[57]

may have difficulty affording DOACs, especially when cost may reduce medication adherence.

In a meta-analysis of randomized trials, treatment with DOACs demonstrated noninferiority for first recurrent VTE or VTE-related death compared with warfarin (2.0% vs 2.2%; absolute difference, −0.2%; P = .21).[66] However, they were associated with lower rates of major bleeding (1.1% vs 1.8%; absolute difference, −0.7%; P = .002), intracranial hemorrhage (0.1% vs 0.3%; absolute difference, −0.2%; P = .001), and fatal bleeding (0.1% vs 0.2%; absolute difference, −0.1%; P = .02).[66] DOACs also have a rapid onset of action, more predictable pharmacokinetics, and avoid the need for routine laboratory monitoring and dose adjustments. Cost is important when selecting an antithrombotic strategy for management of DVT. The out-of-pocket cost of DOACs exceeds that of warfarin for many patients.

Although dabigatran and edoxaban require short-term initial treatment with a parenteral anticoagulant, rivaroxaban and apixaban can be initiated without parenteral anticoagulation by starting with a higher initial dose followed by a lower maintenance dose. Indirect comparisons between DOACs showed no differences in rates of recurrent VTE or VTE-related death for all DOACs.[67] The choice of one DOAC over another should consider patient comorbidities (such as the presence of chronic kidney disease favoring an agent such as apixaban that is less dependent on kidney clearance), likelihood of adverse effects, cost, and patient preference (once-daily vs twice-daily oral administration) (**Table 4**).

In patients with antiphospholipid antibodies, warfarin may be associated with a lower rate of thromboembolic events than DOACs.[64] In a study of 120 high-risk patients with antiphospholipid syndrome (positivity for 3 different antiphospholipid antibodies [ie, lupus anticoagulant, anticardiolipin antibody, and anti-β2-glycoprotein-1 antibody] and a history of thrombosis), the use of 20 mg of rivaroxaban once daily (n = 59) was associated with a higher risk of thromboembolic events, major bleeding, and vascular death compared with warfarin (n = 61) (19.0% vs 3.0%; P = .01).[68]

Overall, cancer is present in 18% (95% CI, 13.4%-22.6%) of patients diagnosed with VTE.[8] LMWHs have been standard therapy for cancer-associated VTE. In a randomized clinical trial including 900 patients with active cancer and acute symptomatic VTE, the use of therapeutic-dose LMWH daily compared with warfarin for 6 months did not significantly reduce the rate of recurrent VTE (6.9% vs 10.0%) or major bleeding (2.7% vs 2.4%), but was associated with a lower rate of clinically relevant nonmajor bleeding (10.9% vs 15.3%).[69]

However, daily injections are associated with lower adherence and premature discontinuation compared with warfarin or DOACs. Randomized trials of DOACs vs LMWHs in cancer-related VTE have demonstrated not significantly different efficacy for prevention of recurrent VTE. In the randomized HOKUSAI VTE Cancer trial including 1050 patients, edoxaban was noninferior to LMWH for preventing recurrent VTE (7.9% vs 11.3%; absolute difference, −3.4%; P = .09), but showed a significantly higher rate of major bleeding (6.9% vs 4.0%; absolute difference, 2.9%; P = .04), mainly due to gastrointestinal events (60.6%) in patients who entered the trial with gastrointestinal cancer.[55] Rivaroxaban, compared with LMWH, was associated with a significantly lower rate of recurrent VTE (4.0% vs 11.0%; absolute difference, −7%), no significant difference in major bleeding (6.0% vs 4.0%; absolute difference, 2%), and a significantly higher rate of clinically relevant nonmajor bleeding (13% vs 4%; absolute difference, 9%) in the SELECT-D trial, which randomized 203 patients with VTE and cancer.[56] Additionally, the CARAVAGGIO trial of 1170 participants with VTE showed noninferiority of apixaban compared with LMWH therapy for prevention of recurrent VTE (5.6% vs 7.9%), without an increased risk of major bleeding (3.8% vs 4.0%; absolute difference, −0.2%; P = .60) in 578 patients with malignancy.[57] Based on these findings, DOACs are considered an alternative to LMWH for management of cancer-associated VTE, especially in patients without gastrointestinal cancer (Table 4).

The Role of Catheter-Based Therapy

Evidence supporting reperfusion therapy, consisting of catheter-directed delivery of fibrinolytic and thrombus aspiration or maceration, with or without stenting, is limited. A meta-analysis of 6 randomized clinical trials, including data from 1481 patients, showed that catheter-based therapy was not associated with a reduction of the frequency of postthrombotic syndrome (45.5% vs 49.8%; absolute difference, −4.3%; P = .31) and was associated with no difference in major bleeding (4.8% vs 2.5%; absolute difference, 2.3%; P = .05).[70] The ATTRACT trial randomly assigned 692 patients with acute iliofemoral or femoral DVT to receive either anticoagulation alone (LMWH or unfractionated heparin followed by long-term anticoagulant therapy according to evidence-based guidelines) or anticoagulation and catheter-based therapy.[71] Catheter-based therapy did not reduce postthrombotic syndrome as assessed by the Villalta Score for Post-thrombotic Syndrome, a specific scoring system for categorizing the severity of postthrombotic syndrome (range, 0-33; score of 5-9 signifies mild disease; 10-14, moderate disease; and

≥15, severe disease)[72] (47% in the catheter-based therapy group vs 48% in the anticoagulation alone group; absolute difference, −1%; *P* = .56) and resulted in a significantly higher risk of major bleeding (1.7% vs 0.3%; absolute difference, 1.4%; *P* = .049). Patients treated with catheter-directed thrombolysis had lower rates of moderate to severe postthrombotic syndrome (18% of patients assigned to receive catheter-based therapy vs 24% in the control group; absolute difference, −6%; *P* = .04), but quality of life did not differ between the groups. Catheter-based therapy for acute lower extremity DVT is reserved for highly select patients with severe symptoms or limb-threatening disease and low risk of bleeding, and is performed at centers that have experience with this procedure.[37,65]

Outpatient Management of DVT

Evidence-based clinical practice guideline recommendations favor outpatient treatment, with a DOAC-based regimen in most patient with DVT with adequate home support and manageable symptoms who can afford the cost of a DOAC.[65] A completely oral regimen may be prescribed with either 15 mg of rivaroxaban twice daily for 21 days followed by 20 mg once daily thereafter or 10 mg of apixaban twice daily for 7 days followed by 5 mg twice daily thereafter. If warfarin is selected, it may be initiated in an outpatient setting with use of parenteral anticoagulation (injectable) until the INR is stable within the target range of 2 to 3. Patients with cancer or those with extensive or highly symptomatic DVT often require hospitalization.

Management of Isolated Calf DVT

A randomized trial of LMWH therapy for 6 weeks in low-risk patients with isolated calf DVT did not demonstrate any reduction in adverse outcomes, including extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism, at day 42 vs no treatment (3% vs 5%; absolute difference, −2%, *P* = .54). However, LMWH was associated with increased bleeding compared with no treatment (4% vs 0%; absolute difference, 4%; *P* = .025).[73] In contrast, a meta-analysis found that anticoagulation was associated with lower rates of recurrent VTE compared with no treatment (6.5% vs 12.0%; absolute difference, −5.5%), without an increased risk of major bleeding (0.4% vs 0.7%; absolute difference, −0.3%).[74] International guidelines recommend anticoagulant therapy for 3 months in patients with isolated calf DVT and severe symptoms or risk factors for extension to proximal veins (eg, hospitalized patients, patients with prior history of VTE, and patients with cancer). Surveillance using serial venous ultrasonography without initiating anticoagulation or a short course of anticoagulant therapy (ie, 3 months) could be considered in low-risk patients (Figure 1).[37,65]

Inferior Vena Cava Filter Insertion

Retrievable inferior vena cava (IVC) filter insertion should be reserved for patients with proximal DVT and contraindications to anticoagulation or those with PE despite therapeutic anticoagulation.[37,64,65] Although patients undergoing IVC filter insertion have a lower risk for PE compared with those not receiving an IVC filter over the first month (1.9% vs 4.6%; absolute difference, −2.7%), the risk for DVT is higher after the first year in patients who receive an IVC filter compared with patients who do not receive an IVC filter (4.7% vs 2.7%; absolute difference, 2%).[75] Anticoagulants should be implemented as soon as feasible and then the filter removed. IVC filter complications increase over time and include strut fracture (fragmentation of the filter's supportive metal structure) and embolization, migration and tilt, perforation of the IVC and surrounding structures, and thrombosis.

Chronic Management

After the acute treatment period of 3 to 6 months, the goal of extended-duration secondary prevention is to prevent VTE recurrence in high-risk patients with VTE. However, the optimal duration of anticoagulation remains unclear, in part due to uncertainty of the individual long-term risk of recurrent VTE. Recurrence risk must be counterbalanced against the risk of bleeding with anticoagulation.

Until recently, most guidelines have categorized DVT as "provoked," defined as events with an identifiable provoking factor (such as major surgery or trauma), and "unprovoked," defined as events without an identifiable causative factor, with extended treatment recommended in patients with "unprovoked" VTE. However, the definition of "provoked" VTE can be unclear and recurrence risk can be high in those with enduring predisposing factors.[4,76,77] The European Society of Cardiology guidelines no longer support the terminology "provoked" and "unprovoked." Instead, these guidelines rely on estimated long-term recurrence risk (if anticoagulation is discontinued after 3 months), in which only patients with an estimated recurrence risk of less than 3% per year should receive time-limited treatment (Figure 1).[64] In clinical practice, this means that most patients with VTE are considered candidates for extended-duration treatment.

Options for Extended-Duration Secondary Prevention

Apixaban, rivaroxaban, and dabigatran have all been shown to safely and effectively reduce VTE recurrence in randomized trials of extended treatment.[59,77-79] Low-dose aspirin has been investigated as an alternative for extended treatment (frequency of VTE recurrence, 7.5%/y with low-dose aspirin vs 5.1%/y with the placebo; *P* = .007).[80,81] Recent meta-analyses demonstrated that DOACs were associated with lower rates of VTE recurrence (1.6% for DOACs vs 6.3% for aspirin or placebo) when prescribed for extended-duration secondary prevention.[82,83]

Limitations

This review has some limitations. First, a separate systematic literature search was not performed for each subcategory discussed. Therefore, some relevant studies may have been missed. Second, guideline recommendations are limited by the quality and availability of evidence and sometimes rely on expert opinion. Third, some of the evidence on risk factors and epidemiology have not been updated recently. In total, 7.0% of references used in this review were older than 10 years.

Conclusions

Greater recognition of VTE risk factors and advances in anticoagulation have facilitated the clinical evaluation and treatment of patients with DVT, respectively. Direct oral anticoagulants are noninferior to warfarin with regard to efficacy and are associated with lower rates of bleeding, but costs limit use for some patients.

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