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Management of lower-extremity venous thromboembolism: An updated review

ABSTRACT

According to the 2021 updated guidelines of the American College of Chest Physicians, the location of venous thromboembolism, the severity of symptoms, the risk of thrombus extension vs that of bleeding, and comorbidities all affect the decision to treat, the choice of antithrombotic agent, and the duration of therapy. In patients with isolated distal deep vein thrombosis without high-risk features, monitoring progression is recommended over initiating anticoagulation. However, treatment of proximal deep vein thrombosis with anticoagulation is strongly recommended by the guidelines. More evidence now supports the treatment of superficial vein thrombosis with anticoagulation in high-risk patients.

KEY POINTS

Patients requiring anticoagulation should undergo additional risk-factor assessment to select an appropriate agent and duration of therapy.

In patients requiring extended anticoagulation, the risks of bleeding and recurrent venous thromboembolism should be reassessed on an ongoing basis.

In patients with isolated distal deep vein thrombosis without high-risk features, monitoring progression is recommended over starting anticoagulation.

TREATMENT OF VENOUS THROMBOEMBOLISM (VTE), including deep vein thrombosis (DVT), depends on a variety of factors. The location of the VTE, severity of symptoms, risk of extension of thrombus, bleeding risk, comorbidities, and patient preferences affect the decision to treat, the choice of antithrombotic agent, and the duration of therapy, as outlined in the 2021 updated guidelines of the American College of Chest Physicians (CHEST).¹ In patients with isolated distal DVT (below the popliteal vein) without high-risk features, monitoring progression is recommended over starting anticoagulation. However, it is strongly recommended to treat proximal DVT with anticoagulation. More evidence now supports the treatment of superficial vein thrombosis with anticoagulation in high-risk patients.¹

In this article, we review risk factors, supportive management, choice of anticoagulation therapy, and treatment considerations in special patient populations.

■ INCIDENCE AND RISK FACTORS

According to the US Centers for Disease Control and Prevention (CDC), approximately 900,000 people in the United States are affected by VTE each year, and 3 out of 10 will have recurrence of a clotting event within 10 years.² The prevalence of distal DVT, which varies widely because of different patient populations and diagnostic strategies used in studies, ranges from 23% to 59% in patients who received a diagnosis of DVT.³

TABLE 1
High-risk features of distal deep vein thrombosis

Severe symptoms (severe pain, throbbing pain when standing that improves with leg elevation, leg discoloration, swelling of the entire limb)
Extensive thrombosis (> 5 cm in length, involving multiple veins, > 7 mm in diameter)
Thrombosis close to the proximal veins
No reversible provoking factor (ie, no transient or persistent risk factor up to 3 months before venous thromboembolic event)
Active cancer (newly diagnosed cancer or cancer being treated with surgery, chemotherapy, radiotherapy, hormonal therapy, support therapy for terminal cancer, or combined treatments)
History of venous thromboembolism
Prolonged immobility (> 3 days)
Patient currently has COVID-19 infection

Based on information in references 1, 7–9.

In a population-based study, the most common risk factors for VTE included limited mobility for more than 48 hours in the past 30 days (defined as, at most, from bed to chair or bathroom), recent or current hospitalization, recent surgery, recent infection, and active malignancy.⁴ The annual diagnosis rate for lower-extremity superficial vein thrombosis (SVT) was 0.64% in a prospective study.⁵ The diagnosis rate increased with age, and SVT was more common in women. Patients at greater risk of developing SVT include women older than age 60 and individuals with obesity, pregnancy, smoking, infection, chronic venous insufficiency, and varicose veins.⁵

LOCATION OF THE THROMBOSIS

Isolated distal thrombosis

Isolated distal DVT (“calf DVT”) is VTE below the popliteal vein.⁶ The 2021 CHEST guidelines¹ recommend anticoagulation for at least 3 months for patients with a high risk of thrombus extension (Table 1)^{1,7–9} as these patients are at greater risk of progression to proximal DVT and pulmonary embolism.¹

In contrast, patients with a low risk of thrombus extension (ie, they do not meet the criteria in Table 1) should be monitored for extension with serial ultrasonography once weekly for 2 weeks, as well as for worsening of symptoms.¹ However, this is a weak recommendation with moderate-certainty evidence.¹ In patients for whom the inconvenience of weekly imaging out-

TABLE 2
Risk factors for major bleeding on anticoagulation

Age greater than 75
Recent major bleeding, ie, requiring transfusion of 2 or more units of blood; retroperitoneal, spinal, or intracranial bleeding
Severe liver dysfunction (baseline abnormal prothrombin time)
Severe renal impairment (creatinine clearance rate < 30 mL/min)
Severe thrombocytopenia (platelet count < 50 × 10 ⁹ /L)
Cancer
Acute hemorrhagic stroke or cerebral lesions at high risk of bleeding
Severe uncontrolled hypertension

Based on information in references 1, 8, 11, 13, and 14.

weighs the potential bleeding risk, anticoagulation for 3 months is a reasonable alternative.¹

When the decision is to monitor with serial duplex venous ultrasonography, patients without extension of the thrombus require no anticoagulation, a strong recommendation with moderate-certainty evidence.¹ Proximal propagation (ie, to the popliteal vein or higher) occurs in 8% to 15% of cases of isolated distal DVT followed with duplex ultrasonography surveillance.¹⁰ For patients with evidence of proximal extension, there is a strong recommendation to anticoagulate for 3 months.¹

A retrospective study showed that 9 of 212 patients monitored with Doppler ultrasonography had new DVT in a distal branch of the original lesion.⁷ For extension confined to distal veins or for new distal thrombosis, the recommendation is to anticoagulate for 3 months, but this is a weak recommendation with a very low certainty of evidence.¹

Proximal deep vein thrombosis

Proximal DVT is defined as thrombus in the popliteal, femoral, or iliac veins.^{7,11} The 2021 CHEST guidelines recommend treating proximal DVT with anticoagulation for at least 3 months.^{1,6} Proximal DVT confers up to a 50% risk of pulmonary embolism if left untreated,¹² so treatment with anticoagulation is recommended even in the absence of symptoms (“incidental DVT”).^{1,11}

Use of an inferior vena cava filter should be considered only in patients deemed to have an unacceptably high bleeding risk (Table 2).^{1,8,11,13,14} Because the filters confer significant risk (eg, occlusion, inferior vena cava strut penetration, filter embolization, movement or

fracture, and complications of insertion), it should be removed as soon as possible after anticoagulation is resumed.^{1,13}

Superficial vein thrombosis

SVT is defined as thrombus involving superficial veins of the upper or lower extremities.¹⁵ The 2021 CHEST guidelines recommend treatment of patients with SVT having high-risk features (Table 3)^{1,15,16} with 45 days of anticoagulation (weak recommendation based on moderate-certainty evidence).¹ Patients with SVT and high-risk features should also be screened for DVT with bilateral ultrasonography due to the high likelihood of undiagnosed DVT.¹⁵ Patients with SVT who do not have high-risk features do not require additional treatment with anticoagulation or screening for DVT. Anticoagulant therapy is generally not recommended to treat SVT associated with intra-venous therapy.¹

It is important to note that patients with DVT and SVT should be screened for signs and symptoms of pulmonary embolism because of the risk of progression from SVT to DVT and subsequently to pulmonary embolism.¹⁵ One study reported concomitant symptomatic pulmonary embolism in 4.7% of patients with SVT at the time of presentation.⁵ Another study reported concomitant pulmonary embolism in approximately half of patients with DVT.¹⁷

■ POSTTHROMBOTIC SYNDROME PREVENTION

Postthrombotic syndrome is a common complication of lower-extremity DVT, reported in 20% to 50% of patients after proximal DVT.^{18,19} Previous CHEST guidelines had recommended the use of compression stockings in patients with DVT to reduce the likelihood of developing postthrombotic syndrome.¹¹ However, the 2021 CHEST guidelines¹ and the 2023 National Institute for Health and Care Excellence guidelines²⁰ no longer recommend this practice.

■ OUTPATIENT ANTICOAGULATION THERAPIES FOR VTE

Oral anticoagulants used in the treatment of VTE include the direct oral anticoagulants (DOACs) apixaban, rivaroxaban, edoxaban, and dabigatran, and the vitamin K antagonist warfarin. Parenteral options include low-molecular-weight heparin (LMWH) and fondaparinux. The choice of agent depends on comorbidities, renal and liver function, risk of bleeding, affordability, and patient preferences (Table 4).^{11,21–24}

TABLE 3

High-risk features of superficial vein thrombosis

Extensive superficial vein thrombosis (> 5 cm)
Involvement above the knee, particularly if 3 cm or less from the saphenofemoral junction
Severe symptoms
Involvement of the greater saphenous vein
History of venous thromboembolism
Active cancer
Recent surgery

Based on information in references 1, 15, and 16.

DOACs offer a predictable anticoagulation effect with fixed dosing and do not require laboratory monitoring.²¹ However, they should be used with caution in patients with renal and hepatic dysfunction. They are also significantly more expensive than warfarin.²⁵

Warfarin requires frequent laboratory monitoring and dosing adjustments to ensure that the international normalized ratio is within therapeutic range. It also has many drug-drug interactions, requires dietary restrictions, causes fluctuations in the international normalized ratio, and can increase the risk of bleeding or recurrent thrombosis, as well as first events in patients taking it for other indications such as atrial fibrillation.^{21,22}

The 2021 CHEST guidelines recommend the use of DOACs over warfarin whenever possible, based on data showing a lower risk of major bleeding (especially intracranial hemorrhage) with DOACs vs warfarin (strong recommendation with moderate-certainty evidence).^{1,21}

The 2021 CHEST guidelines recommend fondaparinux as the agent of choice for the treatment of SVT, but rivaroxaban is an acceptable alternative.^{1,24} A randomized trial showed that fondaparinux was associated with a lower incidence of SVT extension compared with placebo in patients with acute symptomatic SVT of the legs.²⁶ The SURPRISE trial (Superficial Vein thrombosis Treated for Forty-five Days With Rivaroxaban Versus Fondaparinux) found rivaroxaban to be noninferior to fondaparinux for the treatment of SVT in terms of development of symptomatic DVT or pulmonary embolism, progression or recurrence of SVT, and all-cause mortality, and was not associated with more major bleeding.²⁴

TABLE 4
Comparison of outpatient anticoagulant drugs

	Vitamin K antagonists	Direct oral anticoagulants				Parenteral anticoagulation	
	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	Low-molecular-weight heparins	Fondaparinux
Target	Vitamin K	Thrombin	Factor Xa	Factor Xa	Factor Xa	Antithrombin III	Factor Xa
Dosing	Once daily	Twice daily	Twice daily	Once daily	Once daily	Once or twice daily	Once daily
Monitoring needed	Yes (INR)	No	No	No	No	No	No
Comorbidity-specific recommendations	Recommended for patients with antiphospholipid syndrome	Recommended for patients with active cancer with no gastrointestinal or genitourinary involvement: rivaroxaban, apixaban, or edoxaban Recommended for patients with cancer with gastrointestinal or genitourinary involvement: apixaban For patients with recent acute coronary syndrome, avoid dabigatran				Recommended for patients with active cancer and for pregnant patients	Recommended for patients with high-risk superficial vein thrombosis
Liver dysfunction considerations	Can be used in patients with increased prothrombin time or INR	Avoid in patients with increased prothrombin time or INR				Can be used in patients with increased prothrombin time or INR	Recommended for patients with high-risk superficial vein thrombosis; use with caution, monitor closely for signs of bleeding
Renal dysfunction considerations	Can be used in patients with creatinine clearance rate < 30 mL/min	For patients with creatinine clearance 30–50 mL/min, preferred agents are rivaroxaban, apixaban, or edoxaban Avoid all direct oral anticoagulants in patients with creatinine clearance rate < 30 mL/min				Use doses adjusted for renal function as recommended in product labeling	Avoid in patients with creatinine clearance rate < 30 mL/min

INR = international normalized ratio

Based on information in references 11 and 21–24.

SPECIAL PATIENT POPULATIONS

Cancer-associated thrombosis

Patients with cancer have a markedly increased risk of thromboembolism and bleeding.^{27,28} In patients with cancer-associated VTE, oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) are recommended over LMWH or vitamin K antagonists because of the oral administration of DOACs and their safety and efficacy without the need for laboratory monitoring.¹ In a recent meta-analysis of patients with cancer-associated VTE, oral factor Xa inhibitors reduced the risk of recurrent VTE similarly to LMWH, without a significantly higher likelihood of major bleeding.²⁷

Patients with gastrointestinal and genitourinary malignancies may constitute an exception to the above recommendation, as there is an increased risk of bleeding in these patients with use of rivaroxaban and edoxaban when compared with LMWH,^{29–31} but apixaban seems to be noninferior to LMWH, with no increased risk of major bleeding.^{1,30} Thus, apixaban or LMWH is recommended in patients with high risk for mucosal bleeding.^{1,30} Vitamin K antagonists are not favored in patients with cancer-associated thrombosis given the moderate-certainty evidence that LMWH is more effective in reducing recurrence of VTE, as well as the difficulty with maintaining a therapeutic range. In addition, LMWH would be easier to withhold or adjust

TABLE 5

2021 American College of Chest Physicians guidelines on duration of anticoagulation for deep vein thrombosis, based on risk factors for venous thromboembolism

Risk factors ^a	Recommendation
<p>Major transient risk factors, occurring up to 3 months before the thrombotic event:</p> <ul style="list-style-type: none"> • Surgery with general anesthesia for longer than 30 minutes • Confined to bed in hospital (only "bathroom privileges") for at least 3 days with an acute illness • Cesarean delivery 	<p>The guidelines recommend against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence)</p>
<p>Minor transient risk factors, occurring up to 2 months before the thrombotic event:</p> <ul style="list-style-type: none"> • Surgery with general anesthesia for less than 30 minutes • Admission to hospital for less than 3 days with an acute illness • Estrogen therapy • Pregnancy or puerperium • Confined to bed out of hospital for at least 3 days with an acute illness • Leg injury associated with reduced mobility for at least 3 days 	<p>The guidelines suggest against offering extended-phase anticoagulation (weak recommendation, moderate-certainty evidence)</p> <p>In patients with venous thromboembolism diagnosed in the absence of a transient provoking factor, offer extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence)</p>
<p>Persistent risk factors:</p> <ul style="list-style-type: none"> • Active cancer (untreated, ongoing treatment or no potential curative treatment) • Inflammatory bowel disease • Antiphospholipid syndrome 	<p>In patients with antiphospholipid syndrome, vitamin K antagonists are suggested over DOACs as first-line treatment (weak recommendation with low-certainty evidence); a vitamin K antagonist can be offered for patients who can't receive or who decline DOACs (weak recommendation, moderate-certainty evidence)</p>
<p>Unprovoked thrombotic event (no transient or persistent risk factor identified)</p>	<p>The guidelines recommend offering extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence); in patients who can't receive a DOAC, extended-phase anticoagulation with a vitamin K antagonist is recommended (weak recommendation, moderate-certainty evidence)</p>

^aPrevious venous thromboembolism is not mentioned clearly in the guidelines as affecting the duration of treatment.

DOAC = direct oral anticoagulant

Based on information in references 1 and 34.

than vitamin K antagonists for invasive interventions, if needed.¹

Antiphospholipid syndrome-associated thrombosis

Patients with antiphospholipid syndrome are at increased risk of VTE as well as arterial thrombosis.³² The use of DOACs to treat VTE in antiphospholipid syndrome is not well studied, but emerging data suggest a higher risk of arterial thrombosis with DOACs than with vitamin K antagonists.³² Current recommendations favor the use of vitamin K antagonists over DOACs for VTE treatment in these patients, especially those with triple-positive antiphospholipid syndrome (presence of lupus anticoagulant, anticardiolipin, and anti-beta-2-glycoprotein 1 antibodies).^{1,33} If patients experience a thrombotic event while on a therapeutic

dose of warfarin, treatment options include increasing the target international normalized ratio, LMWH, and fondaparinux, or the addition of an antiplatelet agent.¹

■ DURATION OF TREATMENT

When anticoagulation is indicated in patients with DVT, treatment should continue for at least 3 months after the initial thrombotic episode.¹ Anticoagulation beyond 3 months, without a specific end date, is recommended for patients at particularly high risk of recurrence (Table 5)^{1,34} or for those with a history of prior VTE.¹ Regardless of initial risk factors, a reassessment of risk for VTE recurrence, risk of bleeding, and patient preferences should be pursued annually and at times of significant changes in health status.¹

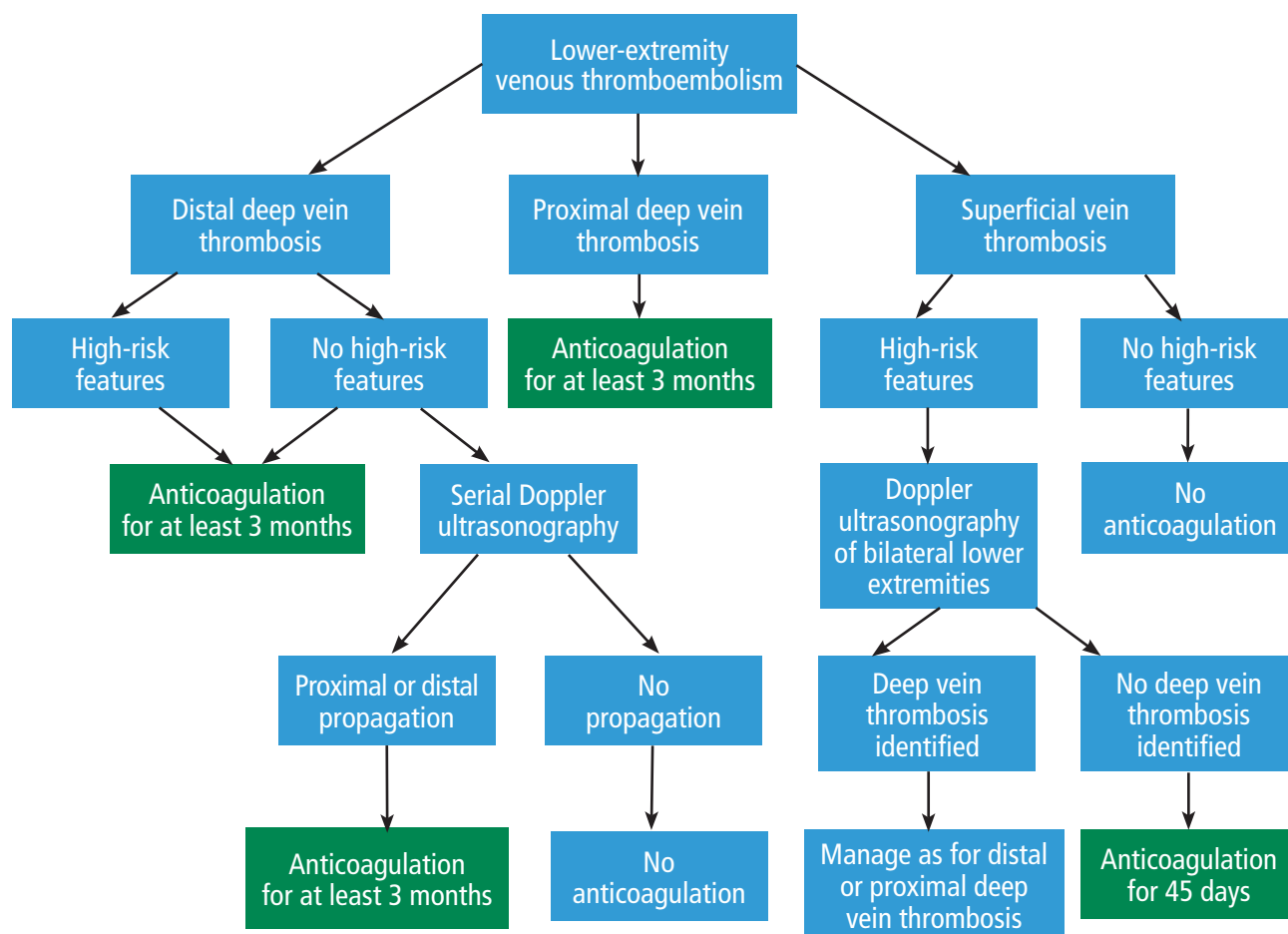


Figure 1. Approach to lower-extremity venous thromboembolism.

Based on information in references 1,15, 24, and 26.

For extended anticoagulation, a reduced dose of apixaban or rivaroxaban is recommended (weak recommendation with a very low certainty of evidence).¹

AN ALGORITHMIC APPROACH TO MANAGEMENT OF LOWER-EXTREMITY VTE

Figure 1 summarizes the various considerations in the management of patients with distal, proximal, and superficial lower-extremity VTE.^{1,15,24,26}

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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