CHAPTER **10**

Deep Vein Thrombosis Treatment in the Lower Extremity

Stephan J. LaPointe, DPM, PhD
Karen Moon, DPM

INTRODUCTION

The prevalence of deep vein thrombosis (DVT) is much higher than reported in the literature due to the number of silent DVTs that occur. Virchow first described the dangerous association between DVT and pulmonary embolism (PE) in 1856, stating that the 3 causes are stasis, hypercoagulable state, and endothelial injury. This article will discuss how to properly diagnose a DVT and give guidance on treatment according to the most current literature. Knowing how to prevent, diagnose, and treat this condition is important because there can be an increased risk of venous thromboembolism (VTE) during podiatric surgery and cast immobilization. Podiatric surgeons are also in a unique position to be the first line of defense in an unprovoked VTE when patients present with new onset edema or unexplained pain in an extremity.

CLINICAL PRESENTATION

Patients may present with leg swelling, calf pain, or redness. Pain is typically isolated to the calf or along the medial thigh. Edema may be present in both legs in cases of a high partial obstruction and may masquerade as congestive heart failure, fluid overload, venous, renal, or hepatic insufficiency. Homan's test for calf tenderness upon dorsiflexion of the ankle is only positive in 8% of confirmed DVTs (1). Approximately half of all patients with DVT will not present with symptoms (1,2). A patient presenting with tachycardia, shortness of breath, a cough, or a look of impending doom should be evaluated for a pulmonary embolism. Approximately 40% of patients with a symptomatic DVT may also have a silent PE (3). The diagnosis of VTE cannot be made on clinical presentation alone and requires a diagnostic work up.

DIAGNOSIS

The American College of Foot and Ankle Surgeons recommends using the Wells criteria for helping to diagnose DVT (4). Wells criteria utilizes a scoring system (Table 1) to place patients into categories that define them as low, moderate, or high probability of having a DVT (5). The Wells criteria was first validated for use in the outpatient setting, but was also tested in trauma patients and found to be validated (6). A low probability is defined as a score between -2 and 0, moderate probability is 1-2 points, and 3-8 is high probability. The algorithm using the Wells criteria for diagnosis is shown in Figure 1.

Wells Score ≤0

Patients with a score ≤0 (i.e. low probability) should have a D-dimer test. The D-dimer may be positive following surgery, however, a negative D-dimer is highly specific and does not require ultrasound. A positive D-dimer requires a venous ultrasound.

Wells Score ≥1

Patients with a score ≥1 have a moderate or high risk and require a venous ultrasound. When available, a whole leg ultrasound is recommended and a negative result rules out DVT. A proximal venous ultrasound may be performed in lieu of whole leg examination. If either test is positive, then anticoagulation therapy is considered. A negative proximal

Table 1. Wells criteria for the prediction of deep vein thrombosis (ref. 6)

Clinical Characteristic	Score
Active cancer (patient either receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis or recent cast immobilization of the lower extremities	1
Recently bedridden for >= 3 days, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	-2

Wells scoring system for DVT: -2 to 0 low probability, 1-2 points: moderate probability, 3 to 8 points: high probability

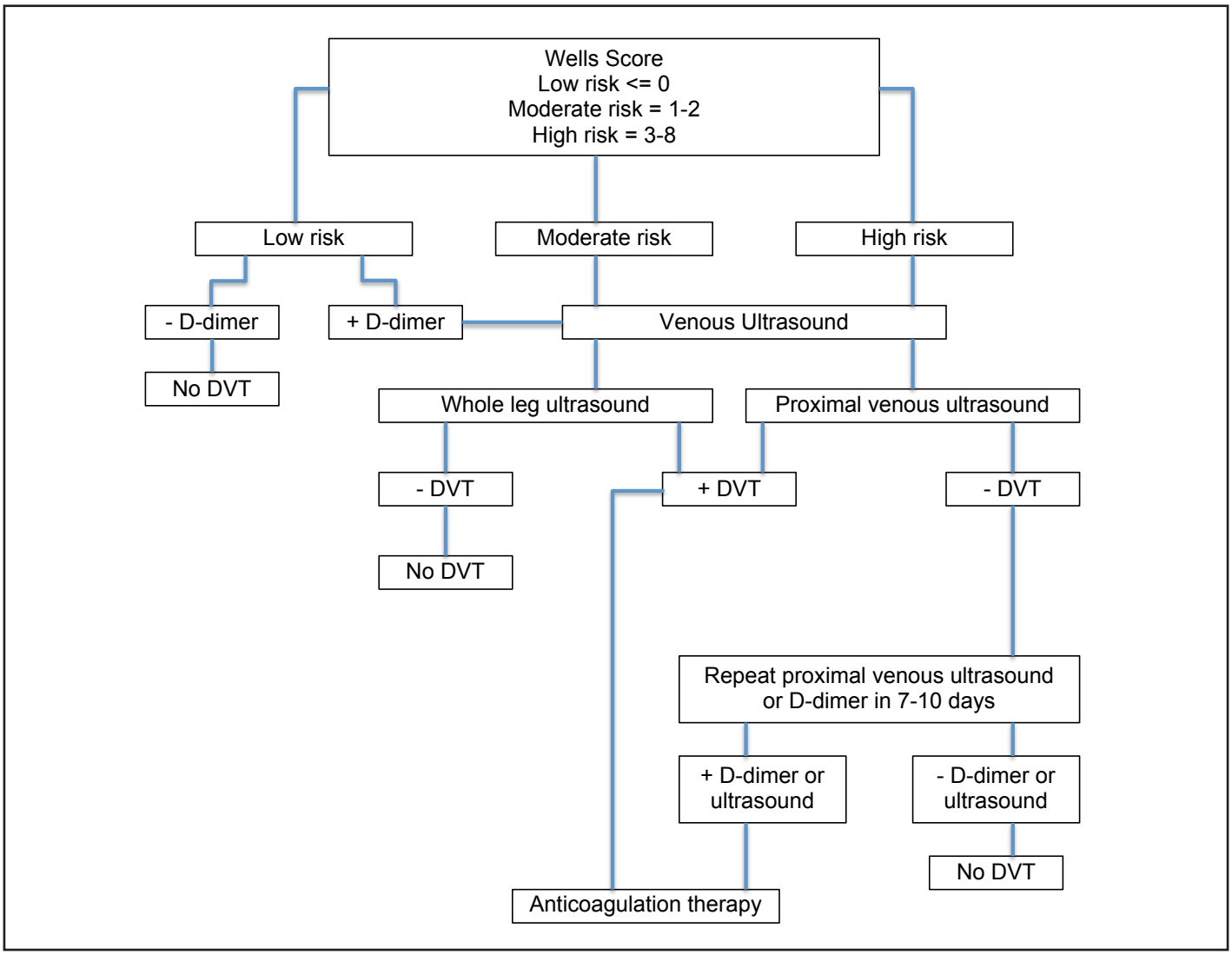

Figure 1. Diagnostic algorithm for suspected deep venous thrombosis according to the Wells criteria.

vein ultrasound requires a repeat examination or D-dimer test in 7 to 10 days. If the proximal ultrasound or D-dimer are negative, then DVT is ruled out. If positive, then anticoagulation therapy may be started.

TREATMENT

In 2016, the American College of Chest Physicians (ACCP) published their 11th edition of Antithrombic Therapy for VTE Disease (7). The treatment protocol outlined here will be consistent with their recommendations unless otherwise stated and will focus principally on lower extremity DVT treatment.

In isolated calf DVTs, two treatment strategies are offered. The first is to treat patients with anticoagulation therapy if they have severe symptoms or are at high risk for propagation of the clot. They list 7 risk factors for extension of the clot (Table 2). They also suggest that an isolated muscular (soleus,

Table 2. Risk factors for progressive or recurrent VTE

D-dimer is postive (particularly when markedly so without an alternative reason
Thrombosis is extensive (e.g., >5cm in length, involves multiple veins, >7mm in maximum diameter)
Thrombosis is close to proximal veins
There is no reversible provoking factor for DVT
Active cancer
History of VTE
Inpatient status

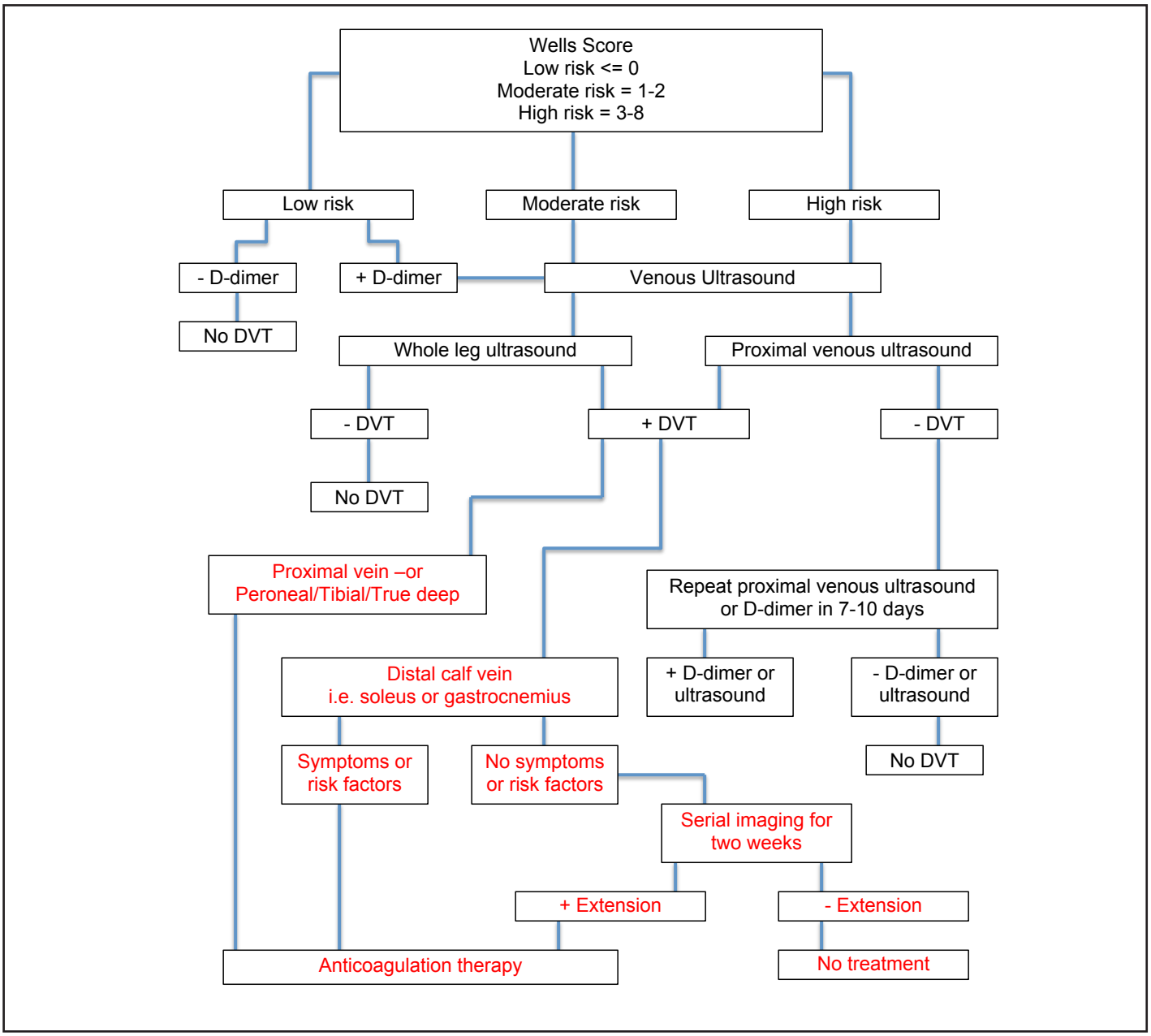

Figure 2. Diagnostic algorithm for suspected deep venous thrombosis modified according to the ACCP (CHEST) guidelines for isolated distal calf thrombosis.

gastrocnemius) vein clot is at lower risk of extension than one that involves axial (true deep, peroneal, tibial) veins. Isolated distal DVT that is diagnosed with a selective approach to whole-leg ultrasound will often satisfy the criteria for initial anticoagulation. We would suggest that using the Wells criteria approach will satisfy this latter requirement.

The second treatment strategy applies to isolated distal DVT without severe symptoms or risk factors. In these cases they recommend serial imaging of the deep veins after 1 and then 2 weeks instead of anticoagulation. Please note that this is a departure from the Wells criteria algorithm shown in Figure 1. The modified algorithm is shown in Figure 2. Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who are unwilling or unable to have serial imaging may choose anticoagulation. If serial imaging is performed, no anticoagulation is needed if the clot does not extend. If the clot extends even if this does not include the proximal veins, then anticoagulation is recommended.

According to the ACCP the first line therapy for a DVT is a non-vitamin K oral anticoagulant (NOAC) and they suggest rivaroxaban (Xarelto), dabigatran (Pradaxa), apixaban (Eliquis), and edoxaban (Savaysa) over vitamin K agonist (VKA) therapy. For patients with VTE and no cancer who are not treated with an NOAC, they suggest VKA therapy over low-molecular weight heparin (LMWH). In patients diagnosed with cancer, they recommend LMWH over VKA or NOACs.

Due to reduced bleeding risk with NOACs and greater convenience for the patient, NOACs are recommended over VKA therapy. For initial and long-term treatment of VTE in patients without cancer, Apixaban is dosed at 10 mg twice daily for 7 days, then 5 mg twice daily for the long-term therapy. After six months, the dosage of apixaban may be lowered to 2.5 mg twice daily for extended therapy.

Apixaban may have a lower risk of bleeding than the other NOACs (7). The treatment dose for rivaroxaban is 15 mg by mouth every 12 hours for 21 days (with food), then 20 mg by mouth once daily. Neither rivaroxaban or apixaban require initial parenteral anticoagulation.

Dabigatran is dosed based on creatinine clearance levels. In patients that have a creatinine clearance >30 ml/minute the dose is 150 mg twice daily. Edoaxaban is dosed at 60 mg once daily in patients who weigh more than 60 kilograms, and 30 mg once daily in patients who weigh less than 60 kilograms. Dabigatran and edoxaban are indicated for treatment in patients who were initially treated with a parenteral anticoagulant. When prescribing these medications be sure to look at the patient's renal status and adjust accordingly.

These medications have shown comparable efficacy with less risk of bleeding than that with other agents. Studies have also suggested that dabigatran should be avoided in patients with coronary artery disease. If a reversal agent may be needed, enoxaparin would be the anticoagulant of choice in acute treatment of VTE. Patients are started at 1.0-1.5 mg/kg in conjunction with Coumadin, until they reach a therapeutic international normalized ratio (INR). Enoxaparin is continued for approximately 5 days in order to ensure a therapeutic INR at 2.0-3.0.

Patients who present with recurrent VTE on VKA therapy or on NOACs (and who are believed to be compliant) should be switched at least temporarily to LMWH. Patients who have recurrent VTE on long-term LMWH and are believed to be compliant should increase the dose by one-quarter to one-third. Other factors that may help direct the agent of choice are listed in Table 3.

Table 3. Factors that may influence which anticoagulant is chosen for initial and long-term treatment of venous thromboembolism

Factor	Preferred anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR elevated because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 ml/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thombolytic therapy use thrombolytic	UFH infusion	Greater experience with its use in patients treated with therapy.
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions	

*INR = International Normalized Ratio; NOAC = non-vitamin K oral coagulant. Adapted from (7).

DURATION OF TREATMENT

In patients with a first proximal DVT or PE provoked by surgery or other nonsurgical transient risk factor, they recommend 3 months of treatment. In patients with unprovoked DVT (proximal or distal) or PE, they recommend at least 3 months of anticoagulation. In cases involving a first unprovoked proximal DVT or PE and low bleeding risk they recommend extended (no scheduled stop date) therapy over 3 months. Bleeding risk factors and scoring are listed in Table 4. If bleeding risks are high, they recommend 3 months of treatment. In patients with low bleeding risk and unprovoked proximal DVT or PE the decision to extend therapy is difficult. Men are 75% more likely than women to have a recurrence so taking into consideration the sex of the patient and the D-dimer test results after 1 month of stopping therapy may help with the decision of whether to continue therapy. A positive D-dimer test doubles the risk and these 2 factors appear additive.

A woman with a negative D-dimer test is at the same risk as if she was provoked by a minor transient risk factor, which has about 15% recurrence at 5 years. A man with a negative D-dimer test has approximately the same risk as anyone who has an unprovoked proximal DVT or PE of 25% at 5 years. So a woman is more likely to be influenced by a negative D-dimer than a male. Because there is still uncertainty about using D-dimer testing and a patient's sex to make decisions about extended therapy in patients with a first unprovoked VTE, no recommendations are based on these factors.

In patients with a second unprovoked VTE who have low to moderate bleeding risk, they recommend extended therapy again. High bleeding risk in the latter suggests 3 months of therapy. In patients with cancer, they recommend extended therapy regardless of bleeding risk. All patients on extended therapy should be reassessed annually.

In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy, they should be started on aspirin unless there is a contraindication. Aspirin is not considered an alternative to anticoagulant therapy. It is much less effective at preventing recurrent VTE than anticoagulants. New trials, since the previous CHEST guideline was published have provided evidence that aspirin may reduce the risk of recurrent VTE by as much as one-third and the increase in bleeding was not statistically significant (8-10). Extended anticoagulant therapy in comparison is expected to reduce recurrent VTE by 80% (11,12). In patients that elect to stop anticoagulant therapy ,the bleeding risks should be weighed with benefit of reduced VTE with aspirin.

Table 4. Risk factors for bleeding with anticoagulant therapy

Age >65 years
Age >75 years
Previous bleeding
Cancer
Metastatic cancer
Renal failure
Liver failure
Thombocytopenia
Previous stroke
Diabetes
Anemia
Antiplatelet therapy
Poor anticoagulant control
Comorbidity and reduced functional capacity
Recent surgery
Frequent falls
Alcohol abuse
Nonsteroidal anti-inflammatory drug
Low risk 0 risk factors; Moderate risk 1 risk factor;

High risk ≥2 risk factors. Adapted from (7).

ALTERNATIVE TREATMENTS

In more proximal DVTs at the ilio-femoral level, thrombectomy or catheter-directed thrombolysis may be indicated for some patients and referral to vascular surgery may be warranted. Some patients are unable to be treated with anticoagulants due to the high risk of bleeding. Patients that are a fall risk, have had intracranial bleeds, have recurrent DVT despite being on anticoagulation, or have conditions that put them at high risk for bleeding may require other interventions to prevent recurrence of VTEs. This group of patients may be candidates for placement of an inferior vena cava filter and may also be referred.

Compression stockings have not been found to prevent post thrombotic syndrome (PTS) in a new large multicenter placebo-controlled trial so this practice is no longer recommended for prevention. However, in patients with acute or chronic symptoms, a trial of graduated compression stockings may be prudent.

In conclusion, as podiatrists, we are often the first line of defense for DVT as patients often first share their symptoms with us. We need to be diligent with a high index of suspicion for VTE. The conditions we treat and our treatments such as surgery and cast immobilization both

increase the risk and rates of VTE. The Wells criteria and subsequent diagnostic protocols have been recommended by the American College of Foot Ankle Surgeons and others (4-6,13). Although evidence continues to evolve concerning the proper treatment, the latest recommendations for treatment of DVT have been outlined. The guidelines and doses provided should be individualized to the patient and weighed against the patient's bleeding risk. In complex cases, referral to vascular surgery or an internist may be warranted. Properly diagnosing and treating DVT may prevent potentially life threatening PEs.

REFERENCES

1. McLachlin J, Richards T, Paterson JC. An evaluation of clinical signs in the diagnosis of venous thrombosis. Arch Surg 1962;85:738-744.
2. Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. Br J Surg 1961;48:475-89.
3. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. JAMA 1994;271:223-5.
4. Fleischer AE, Abicht BP, Baker JR, Boffeli TJ, Jupiter DC, Schade VL. American College of Foot and Ankle Surgeons' Clinical Consensus Statement: risk, prevention, and diagnosis of venous thromboembolism disease in foot and ankle surgery and injuries requiring immobilization. J Foot Ankle Surg 2015;54:497-507.
5. Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, et al. Use of a Clinical Model for Safe Management of Patients with Suspected Pulmonary Embolism. Ann Intern Med 1998;129:997-1005.
6. Modi S, Deisler R, Gozel K, Reicks P, Irwin E, Brunsvold M, et al. Wells Criteria for DVT is a reliable clinical tool to assess the risk of deep venous thrombosis in trauma patients. World J Emerg Surg 2016;11:24.
7. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis. Chest 2016;141 (2 Suppl):e419S-96S.
8. Brighton TA, Eikelboom JW, Mann K Mister R, Gallus A, Ockelford P, et al. Low-dose aspirin for prevening ecurrent venous thromboembolism. N Engl J Med 2012;367:1979-87.
9. Simes J, Becattini C, Agnelli G, Eikelboom JW, Kirby AC, Mister R, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. Circulation 2014;130:1062-71.
10. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini Esilingardi M et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959-67.
11. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Efiicacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ 2013;347:f5133.
12. Sobieraj DM, Coleman CI, Pasupuleti V, Deshpande A, Kaw R, Hernandez AV. Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis. Thromb Res 2015;135:888-96.
13. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis. JAMA 2006;295:199-207.