

Overview of Venous Thromboembolism

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Venous thromboembolism (VTE) describes the diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE). As many as 900,000 people in the United States may be affected by VTE each year, with up to 100,000 dying as a result.¹ The risk of VTE increases with age, with 60% of all VTE events occurring in those 70 years and older. The overall incidence of VTE is 1 to 2 per 1000 person-years in the general population, which rises to 8 per 1000 person-years in people older than 85 years.²

DVT is the formation of thrombi in the deep veins, most commonly the large veins of the legs or pelvis.³ PE develops when thrombi dislodge from clots in vein walls and travel through the heart to pulmonary arteries.⁴ There is a 50% chance for patients with untreated proximal DVT to develop symptomatic PE within 3 months.⁵ For 25% of patients, the presenting manifestation of PE is sudden death.^{5,6}

Concepts of Coagulation

Multiple prothrombotic and antithrombotic components exist in the body. Under normal conditions, an appropriate balance of inhibitors regulate and limit clot formation. In the case of decreased or deficient antithrombotic factors or increases in coagulation factors, thrombotic events may occur. Thrombosis may transpire as the result of vessel wall abnormalities or increases in circulating thrombogenic elements.⁷

Blood hemostasis is controlled by a complex interaction of enzymes and coagulation proteins. Most clotting factors are precursors of enzymes that are normally in an inactive form. When described in the classic clotting cascade, once a factor has been enzymatically activated, it is denoted with the letter “a” in addition to the Roman numeral designation. Four of the 12 clotting factors are usually referred to by their common names, without Roman numeral designation. These factors include fibrinogen (factor I), prothrombin (factor II), tissue factor (TF; factor III), and calcium (factor IV). More recently discovered clotting factors do not have a Roman numeral designation. These are prekallikrein and high-molecular weight kininogen, which are a part of the intrinsic pathway.⁷

ABSTRACT

Venous thromboembolism (VTE) describes the diagnoses of deep vein thrombosis (DVT) or pulmonary embolism (PE). DVT is the formation of thrombi in the deep veins, most commonly the large veins of the legs or pelvis. PE develops when thrombi dislodge from clots in vein walls and travel through the heart to pulmonary arteries. In many patients, the presenting manifestation of PE is sudden death. VTE may be categorized as provoked or unprovoked. This categorization influences the risk of recurrent VTE and duration of anticoagulation therapy. It is important for primary care providers to clearly understand the pathogenesis and causes of thrombosis in order to create evidence-based therapeutic and prophylactic patient care plans that adequately prevent recurrent VTE.

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The 2 concepts of thrombus formation are the coagulation cascade and the cellular model of hemostasis. The traditional model is the coagulation cascade; current evidence also supports a cellular concept of coagulation.⁷ The coagulation cascade is a series of biochemical reactions describing interactions leading to thrombus formation (Figure 1).⁷ This is divided into intrinsic and extrinsic pathways, which converge on a common pathway at the activation of factor X. Activated factor X and factor V produce the complex that generates prothrombin. Prothrombin splits into smaller proteins, converting to thrombin. Thrombin leads to production of fibrinogen. Fibrinogen is the precursor of fibrin, which promotes platelet aggregation and stabilization of the clot.⁷

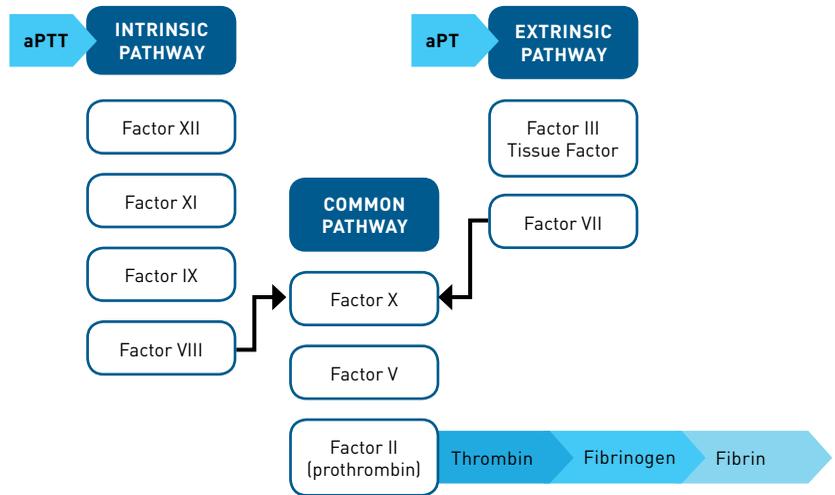
The extrinsic pathway is initiated by TF, which is located primarily in blood vessels, with a smaller amount circulating on monocytes. TF may be activated by various stimuli such as direct vascular injury, hypoxia, sepsis, malignancy, or inflammation. After vascular injury, TF is exposed to plasma procoagulants, which activate factor VII. Activation of factor VII plus calcium causes activation of factor X in the common pathway.⁷ The intrinsic pathway involves interactions with factors XII, XI, IX, and VIII, which ultimately lead to activated factor X, in the common pathway.

The cellular model of coagulation involves steps of initiation, amplification, propagation, and stabilization. Initiation of coagulation occurs via expression of TF in damaged blood vessels. The expression of TF promotes the interaction of factors VII and IX to activate factor X. Activation of factor X leads to prothrombin, which then generates a small amount of thrombin formation.⁷ The small amount of thrombin serves to amplify the procoagulant signal by activation of platelets and coagulation cofactors. The next phase of the cellular theory is propagation of thrombin generation via accumulation of factors Va and VIIIa on the platelet surface. Lastly, activated factor X supports a burst of thrombin generation, which in turn stabilizes the fibrin clot.^{7,8}

Pathophysiology of Thrombosis

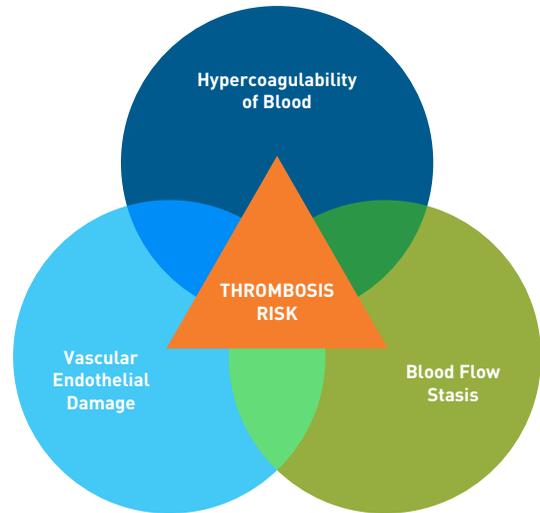
Rudolph Virchow first proposed a triad of causes, Virchow's triad, which lead to venous thrombosis: venous stasis, blood hypercoagulability, and vascular wall injury (Figure 2).^{9,10} Venous stasis may be a product of immobility. Several hematologic abnormalities of coagulation factors or natural anticoagulants increase blood hypercoagulability and thrombotic risk. Vascular wall injury promotes circulation of coagulation enzymes and cofactors. In addition to advanced age, all these components influence current known risk factors for VTE. The risk factors for VTE may be provoked or unprovoked,

FIGURE 1. Coagulation Cascade⁷



aPT indicates activated prothrombin time; aPTT, activated partial thromboplastin time. Adapted from Palta S, Saroa R, Palta A. *Indian J Anaesth.* 2014;58(5):515-523. doi: 10.4103/0019-5049.144643.

FIGURE 2. Virchow's Triad¹⁰



Adapted from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation.* 2003;107(23 suppl 1):I9-I16. doi: 10.1161/01.CIR.0000078469.07362.E6.

transient or persistent. They may be described as strong, moderate, or weak in the propensity to induce a thrombotic event (Table 1).¹⁰

Provoked or Unprovoked VTE

An event may be categorized as provoked or unprovoked VTE. An unprovoked VTE refers to a thrombotic event that is not associated with an environmental risk factor. Examples of nonenvironmental

TABLE 1. Risk Factors for VTE¹⁰

Strong	Moderate	Weak
<ul style="list-style-type: none"> • Fracture of pelvis, hip, or long bones of leg • Hip or knee arthroplasty • Major general surgery • Major trauma • Spinal cord injury 	<ul style="list-style-type: none"> • Arthroscopic knee surgery • Central venous lines • Congestive heart failure • Estrogen therapy • Malignancy • Paralytic stroke • Pregnancy/postpartum • Genetic thrombophilia 	<ul style="list-style-type: none"> • Bed rest >3 days • Prolonged immobility • Age • Laparoscopic surgery • Obesity • Varicose veins

Adapted from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I9-I16. doi: 10.1161/01.CIR.0000078469.07362.E6.

risk factors are hereditary thrombophilia, male gender, or older age.¹¹ Provoked refers to a thrombotic event that has been caused by an environmental or acquired known risk factor for VTE. Furthermore, provoked events may be divided into transient or persistent causes. A transient variable is expected to resolve after the VTE event, and this has a bearing on treatment and prognosis for recurrence.^{11,12}

Understanding of provoked or unprovoked and the persistent nature of risk factors is very important for creating appropriate anticoagulation therapy plans that address the risk of VTE recurrence.¹¹ If thrombosis is preceded by a major risk factor that is transient, there is lower risk of recurrence after stopping anticoagulation therapy. However, if thrombosis is provoked by a risk factor that is progressive and persistent, there is a higher risk of recurrent thrombosis upon discontinuation of anticoagulation.¹²

Active cancer, congestive heart failure (CHF), obesity, and varicose veins are examples of persistent provoked risk factors.¹² Examples of transient provoked risk factors include bed rest for more than 3 days, immobility, estrogen therapy, trauma or surgery, pregnancy, hip or leg injury associated with immobility, and foreign object/device. If VTE is provoked by a transient risk factor, there is a lower risk of recurrence after stopping therapy.

Transient Risk Factors

Hip fracture has been identified as a high-risk condition associated with VTE. An incidence of up to 50% of asymptomatic DVT has been reported, with a rate of fatal PE up to 10%. A prospective study of more than 5000 patients with a hip fracture revealed that among this group, patients with a higher hemoglobin level on admission were at greater risk for VTE. The majority, more than 80% of thrombotic events, occurred within the first 5 weeks after the fracture.¹³ Continued follow-up of patients with VTE demonstrates that comorbidities, such as history of prior VTE and varicose veins, greatly increase the risk of subsequent symptomatic VTE following a hip fracture.¹⁴ In addition, patients with fracture of the long bones of the leg are at increased risk of VTE.

In patients undergoing total hip or knee arthroplasty or surgery for hip fracture without prophylaxis, the incidence of asymptomatic

postoperative DVT may occur in 40% to 60% of cases. In patients undergoing arthroplasty or experiencing a fracture who receive thromboprophylaxis during hospitalization, time to presentation of DVT is typical about 3 weeks after surgery. In the same group, expected time to presentation of clinical PE is about 2 weeks for hip fracture and knee arthroplasty and close to 5 weeks for patients undergoing hip arthroplasty.¹⁵

In general surgery patients, the risk of VTE varies depending on several patient and

procedure-based factors. Some patient-specific variables that have been shown to increase VTE risk are being older than 60 years, prior VTE, and malignancy.¹⁶ Procedure-related risk factors include longer duration of surgical procedure, type of anesthesia, surgical procedure performed, and bed rest longer than 3 days.¹⁶⁻¹⁸

Several models are used to predict patients at higher risk of VTE. One such model for general surgery patients is the Caprini assessment. This model assigns points based on specific patient characteristics and medical history. Multiple scored components of the assessment include history of VTE, hypercoagulable genetic states, patient age, type of surgery, and presence of hip, pelvic, or leg fracture.¹⁶ Among pediatric patients, the Peds-Clot Clinical Decision Rule model is a prediction tool developed to determine the risk of VTE. Factors identified as predictors for the highest-risk patients are positive bloodstream infection, hospital stay longer than 7 days, direct admission to an intensive care unit, central venous catheter, prolonged immobilization, use of oral contraceptives, mechanical ventilation, and perinatal trauma.¹⁹

Acute traumatic coagulopathy is related to several factors that cause coagulation impairment. Tissue injury, inflammatory factors, anticoagulant factors, hypothermia, acidosis, and hypoperfusion all influence the coagulation state of trauma patients.^{20,21} For patients in shock, both PT and PTT are prolonged as injury severity increases. Hypoperfusion of shock is associated with a decrease in protein C levels.²¹ Trauma patients have a general reduction in proteins that regulate or inhibit coagulation. They have reduced levels of all plasma proteins due to blood loss, consumption, and hemodilution. Lower factor levels correlate to prolonged time for PT results.²²

The increased frequency of VTE in patients with spinal cord injury stems from a combination of all aspects of Virchow's triad, with venous stasis being of greatest concern.²³ The frequency of VTE in patients with spinal cord injury had a vast range in early studies, from 51% up to 100% of subjects. In the presence of mechanical prophylaxis, more modern studies report that VTE still occurs in more than 40% of patients.²⁴ The rate of VTE following spinal cord injury also varies with the level at which injury occurs. Patients with a high thoracic injury have been

shown to have the highest risk, while those with lumbar injury are noted to have the lowest.²⁴

Patients who have survived ischemic stroke are at increased risk of VTE. Several components impact this risk. If significant neurologic deficits occur after stroke, this leaves the patient in a state of prolonged immobility. Patients unable to move upper extremities who have venous access will be predisposed due to both immobility and vessel wall injury. As a consequence of lost neurological capacity, patients may be unable to take liquids orally, creating a situation of dehydration and hypercoagulability. Most VTE events arise within 3 months after the stroke, with the highest incidence being during the first month. Compared with a nonstroke population, the incidence of VTE during the first 3 months post stroke is 15% versus 0.2% for the general population.²⁵

Pregnant and postpartum women are at increased risk of VTE. Pregnant women have a 5-fold higher risk of VTE than nonpregnant women. Postpartum, the risk rises to 20-fold higher.²⁶ Pregnant women who are African American and older than 35 years are at highest risk.²⁷ The most important VTE variable for pregnant women is hypercoagulability. During a normal pregnancy, there are increases in factors VII, VIII, and X, and in von Willebrand factor. Immobility and obstruction of venous outflow by the uterus may also contribute to VTE in pregnancy.²⁶

The presence of central venous access is a risk factor for development of VTE. Asymptomatic rates for VTE are reported to be 19% to 41%, based on different modes of detection. Most cases of central venous-associated VTE are subclinical, with 1% to 5% becoming symptomatic. Insertion of a central venous catheter produces local venous injury. Deposition of fibrin and the growth of smooth muscle and endothelial cells are also prompted by catheter insertion. In addition, blood flow velocity may be reduced by more than 90% around the insertion site of an intravenous catheter, based on the size of the lumen and anatomical vein placement.²⁸ Continued movement of the catheter inside the vessel produces endothelial damage and development of thrombi, which lead to occlusion of the vein. Properties of the catheter determine higher or lesser risk of thrombosis. These include type of device, access site, diameter of the catheter, and location of the catheter tip.²⁹

Individuals who have immobility due to prolonged travel are at increased risk of VTE. For air travel, a flight duration of more than 8 hours greatly increases the risk of VTE. In addition, being older than 40 years, hormone replacement therapy, varicose veins, obesity, and inherited clotting disorders compound the risk of VTE during long flights.³⁰ Prolonged sitting causes venous stasis and is the triggering event in travel-related VTE. The endothelium of the leg veins may also be damaged by pressure from the edge of the seat or from keeping legs crossed or maintained in cramped conditions. In flight simulation models, platelets are increased after 6 hours. Patient conditions such as dehydration and dry atmosphere inside

an airplane increase the risk of hemoconcentration. Oxygen tension and pressure inside the airplane also impair fibrinolysis and induce activation of coagulation.³¹ VTE can develop after long trips via car, train, or bus as well.³²

Persistent Risk Factors

CHF is an independent risk factor for VTE, applicable to both hospitalized and ambulatory patients with CHF. CHF in patients younger than 40 years carries a much higher risk of PE, DVT, and VTE events. For example, the overall risk of PE in patients younger than 40 years is 11.72 as opposed to 1.28 for patients older than 80 years.³³

The pathophysiology of VTE in patients with CHF is multifactorial. The initial insult is the presence of venous stasis due to decreased cardiac output and patient immobility. CHF-associated endothelial dysfunction causes abnormalities in the vessel wall. In addition, a hypercoagulable state in CHF is induced by increases in plasma viscosity, fibrinogen and von Willebrand factor, TF, D-dimer, and thrombin-antithrombin (AT) complex.³⁴ Patients with CHF also have a component of venous stasis as a result of left ventricular systolic impairment, adding another element of Virchow's triad. The incidence of VTE varies from 12.3% to 21.7%, depending on the severity of heart failure.^{35,36}

Cancer and chemotherapy treatments are associated with higher rates of VTE than in the general population. The exact incidence of VTE in patients with cancer is not known; however, the overall risk of VTE is increased 7-fold for patients with cancer compared with the general population. The incidence is dependent on the type of malignancy, with highest VTE rates for non-Hodgkin lymphoma, gastrointestinal malignancies, and cancers of the lung, brain, ovary, and pancreas.³⁵⁻³⁷

Several factors determine which cancer patients have the highest risk of VTE, including aggressiveness of disease. Cancers that have early metastatic spread, with a rapid rate of growth and short survival time, have a high risk of VTE.³⁸ The presence of other health conditions affects the incidence of cancer-related VTE as well, with the incidence of cancer-related VTE higher as the number of chronic comorbidities increases. The impact of comorbidities on VTE incidence has a greater influence than advanced age in predicting incidence of VTE. Blood biomarkers, too, may be used to help predict which patients with cancer are at highest VTE risk. A pre-chemotherapy platelet count greater than 350,000 per microliter, a leucocyte count greater than 11,000 per microliter, and elevated D-dimer and C-reactive protein levels have all been shown to predict the risk of VTE in patients with cancer.³⁸

Obesity, defined by body mass index (BMI), varicose veins, and waist circumference are associated with an increased risk of VTE. Obese individuals are twice as likely as people with a normal BMI to have VTE.^{39,40} A weak risk factor for VTE is varicose veins, which are the result of inflammation, venous hypertension, and structural changes in the vein walls.^{10,41}

TABLE 2. Drug-Induced Thrombosis⁴²⁻⁴⁹

Medication	Mechanism
Systemic estrogen	<ul style="list-style-type: none"> Increase markers of thrombin and fibrin production
Oral contraceptives	<ul style="list-style-type: none"> Increase factor VII and factor X Increase fibrinogen Activate protein C resistance
Tamoxifen	<ul style="list-style-type: none"> Decrease antithrombin Decrease protein C
Corticosteroids	<ul style="list-style-type: none"> Decrease clearance rate of clotting factors
Serotonin inhibitors	<ul style="list-style-type: none"> Potentiates platelet aggregation
Cisplatin	<ul style="list-style-type: none"> Increase von Willebrand factor Endothelial damage
Thalidomide Lenalidomide	<ul style="list-style-type: none"> Promote platelet activation and aggregation

Drug-Induced Thrombosis

Drug-induced thrombosis may be considered a transient or persistent risk factor depending on the duration of the drug therapy. Several medications are noted to increase the risk of thrombosis (Table 2).⁴²⁻⁴⁹ Drugs induce various elements of Virchow's triad in various ways. Vascular damage has been noted with 5-fluorouracil (5-FU) administration, and several cases of patients with cancer on 5-FU therapy have been diagnosed with symptomatic VTE.^{42,43} Medications that influence serotonin uptake cause changes in platelet function. Platelet aggregation is influenced by accumulation of serotonin. The immediate effect of serotonin reuptake inhibitors is an increase in serotonin in discrete regions of the body, prior to downregulation of serotonin receptors. A product of the initial increase in serotonin is enhanced platelet aggregation, which may occur in patients starting serotonin-responsive therapies for depression or schizophrenia.⁴³⁻⁴⁵

Medications that facilitate an increase in clotting factors are also implicated as elevating the risk of VTE. Exogenous estrogen, prescribed as hormone replacement therapy or in combination oral contraceptives, increases the risk of VTE. Systemic estrogen therapy stimulates thrombin and fibrin production, thereby increasing the risk of thrombosis. Patients taking oral contraceptives have higher levels of fibrinogen, factor VII, and factor X, in addition to resistance to activated protein C.⁴³ Progestin-only oral contraceptives carry minimal or no thrombosis risk.⁴⁶ The anti-estrogen medication tamoxifen has weak estrogenic activity, which may contribute to the drug's prothrombotic characteristics. Tamoxifen reduces levels of AT and protein C.⁴⁴ Corticosteroids decrease the clearance of clotting factors, allowing for an increase in fibrinogen and factors VII, VIII, and XI. Use of corticosteroid therapy for various indications

has been shown to increase risk of VTE.^{43,47,48} The chemotherapy agent cisplatin is thought to increase risk of VTE via mechanisms of increased von Willebrand factor and endothelial damage.^{48,49}

Hereditary Risk Factors

The most potent genetic risk factors for VTE are deficiencies of the natural anticoagulants protein C, protein S, and AT. Protein C is activated by thrombin. Activated protein C inactivates factors Va and VIIIa on the surface of endothelial cells and platelets. Proteins C and S are both vitamin K-dependent molecules. Protein C requires protein S as a cofactor. AT deficiency may result from reduced synthesis, reduced plasma functional activity, or impaired interaction with AT and heparin. An inherited deficiency in any one of these 3 proteins is found in approximately 15% of patients younger than 45 years who present with VTE.⁵⁰ Deficiency in one of these 3 proteins incurs a risk of VTE 10-fold or more.⁵¹

Genetic variants that impact coagulation, that are less potent but more common in the general population, are factor V Leiden mutation, which is also termed activated protein C (APC) resistance, and non-O blood groups.⁵¹ A defect in factor V makes it less prone to proteolysis by activated protein C. As a consequence of factor V not being cleaved by APC, more activated factor V is available, causing an increase in the generation of thrombin.⁵⁰ Elevations in plasma homocysteine may be genetic, as an inborn error in metabolism; due to nutritional deficiencies; or associated with certain medications. There is evidence of increased rates of thrombosis with elevated homocysteine levels; however, the pathophysiology is not well understood.⁵⁰ Multiple studies' results have shown that the incidence of VTE in patients in a non-O blood group is higher than in those with type O. Individuals with type O blood have lower von Willebrand factor and factor VIII levels than those in a non-O group.⁵²⁻⁵⁴

Clinical Presentation and Diagnosis

DVTs typically present with unilateral leg pain, redness, and swelling. PEs frequently present with chest pain, shortness of breath, tachypnea, and tachycardia. Due to the nonspecific nature of DVTs and PEs, objective tests are required to confirm a diagnosis. D-dimer, a fibrin clot degradation product, is increased in patients with acute thrombosis. Although this test is a very sensitive marker of clot formation, its use is limited due to low specificity. Many conditions can lead to D-dimer elevations, such as recent surgery or trauma, pregnancy, increasing age, and cancer. Therefore, an elevated D-dimer level, defined as greater than 500 ng/mL, cannot be used alone for diagnosis of VTE.⁵⁵

Venography and pulmonary angiography are the most accurate diagnostic methods for VTE; however, these are used less in clinical practice due to their high cost, invasive nature, and possible adverse effects associated with the contrast medium. Less invasive, more common tests include compression ultrasound of the leg,

computed tomography pulmonary angiography, and ventilation-perfusion scans.⁵⁵

Recurrence

Recurrence of VTE may be influenced by multiple factors. Patients with provoked or unprovoked VTE who receive anticoagulation for less than 3 months have a higher rate of VTE recurrence in the first 6 months following the initial event. Based on location of the initial thrombus, the risk of recurrent VTE is lower for patients with isolated distal DVT than those with proximal DVT or PE. Additionally, the risk of recurrence when a temporary risk factor is present is much lower than the recurrence risk in unprovoked VTE.⁵⁶⁻⁵⁸ Male gender and elevated D-dimer have also been shown to relate to higher VTE recurrence risk.⁵⁷

Two prediction models are used to assess patients at high risk for recurrent VTE.⁵⁹ The Vienna prediction model uses a nomogram to calculate risk scores. Values are assigned to patient gender, location of first VTE event, and the D-dimer value after discontinuation of anticoagulation therapy. Each variable is scored for a numeric value. The total points are added for all numeric values and compared with a nomogram to derive the expected 12-month and 60-month cumulative recurrence rate.⁵⁸

The DASH (D-dimer, age, sex, hormones) prediction score uses characteristics of D-dimer, age, patient gender, and hormone use in females to predict rates of recurrence. Assessing risk using the DASH model is via graphic representation. A DASH score is determined from numerical values assigned to each risk factor. The total DASH score is graphed on the X axis to arrive at the expected annual recurrence rate on the Y axis.⁶⁰

Postthrombotic Syndrome

Postthrombotic syndrome (PTS) is a long-term complication that develops in up to 50% of patients with DVT. PTS is a consequence of venous hypertension, which causes impaired venous return, reduced blood perfusion to the calf muscle, increased tissue permeability, and abnormal function of the microvasculature. DVT can lead to chronic venous hypertension by venous obstruction and venous valvular reflux due to inflammation and fibrous scarring because of thrombus formation. Patients with PTS experience swelling, cramping, heaviness, itching, pain, or tingling in the affected limb. Severe PTS involves the formation of ulcers. Symptoms may be persistent or intermittent.⁶¹

Conclusion

Every year, hundreds of thousands of patients in the United States are affected by VTE. To recognize the need for VTE management in high-risk groups, it is essential to understand the associated risk factors, which can be acquired or hereditary. Acquired risk factors can be described as transient or persistent. Recurrence of VTE is also

influenced by a number of factors. Treatment recommendations should be based on the etiology of VTE, risk factors, and patient comorbidities to achieve favorable outcomes in patients with VTE. ■

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