

Diagnosis and Management of Venous Thromboembolism: An Update A Decade into the New Millennium

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Abstract

Venous thromboembolism refers to thrombotic events in the venous system that are most commonly manifested as deep vein thromboses in the upper or lower extremity and/or pulmonary embolism. Venous thromboembolism is a common disorder that is associated with significant mortality, morbidity and health care-related cost. An array of hereditary and acquired risk factors are associated with venous thromboembolism. In recent years, a number of pivotal studies have expanded our understanding of the pathophysiology of venous thromboembolism, and served as the basis for evidence-based guidelines on prevention, diagnosis and treatment of venous thromboembolism. Furthermore, several novel therapeutic agents with different pharmacokinetics, pharmacodynamics and safety profiles have recently become available for treatment and prevention of venous thromboembolism. The purpose of the current paper is to review the pathogenesis and epidemiology of venous thromboembolism as well as an evidence-based approach to the diagnosis and management of venous thromboembolism.

Venous Thromboembolism

Epidemiology

Venous thromboembolism (VTE) includes deep vein (Figure 1) thromboses (DVT) of the proximal and distal deep veins of the leg (i.e., popliteal, femoral, or iliac veins) and upper extremity as well as pulmonary embolism (PE). Symptomatic VTE has been estimated to affect approximately 900,000 patients per year in the United States, of which an estimated 300,000 succumb to PE.¹ Among the remaining 600,000 cases of nonfatal VTE each year, approximately 60% are DVT and 40% are PE. The direct medical costs for the treatment of nonfatal VTE is thought to be between 5.8 to 7.8 billion dollars (based on 2004 provider payments).¹⁻² A Mayo Clinic study conducted in Olmstead County, Minnesota estimated that the average annual incidence of VTE over the past 30 years was 108 per 100,000 among the U.S. white population.³

VTE is predominantly a disease of older age. The incidence of VTE increases significantly with age in both men and women. Established independent risk factors for VTE include, 1) a previous VTE, 2) hereditary thrombophilias such as the factor V Leiden (FVL) gene mutation which results in an activated protein C resistance, Prothrombin G20210A mutation, antithrombin, protein C and protein S deficiency, and acquired thrombophilias such as antiphospholipid antibody syndrome, 3) surgery (particularly major general surgery, hip or knee replacement, or cancer surgery) or major trauma (particularly associated with spinal injury, or hip, leg or pelvic fracture) within the previous 3 to 6 months, 4) hospitalization (8-fold increase in VTE),⁴ 5) nursing home residency, 6) active cancer or treatment with chemotherapy, 7) leg paralysis or immobilization, 8) travel greater than 4 hours,⁵ 9) medical conditions such as myocardial infarction, congestive heart or respiratory failure, stroke, nephrotic syndrome, systemic lupus erythematosus

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Accepted for publication: 17 August 2011

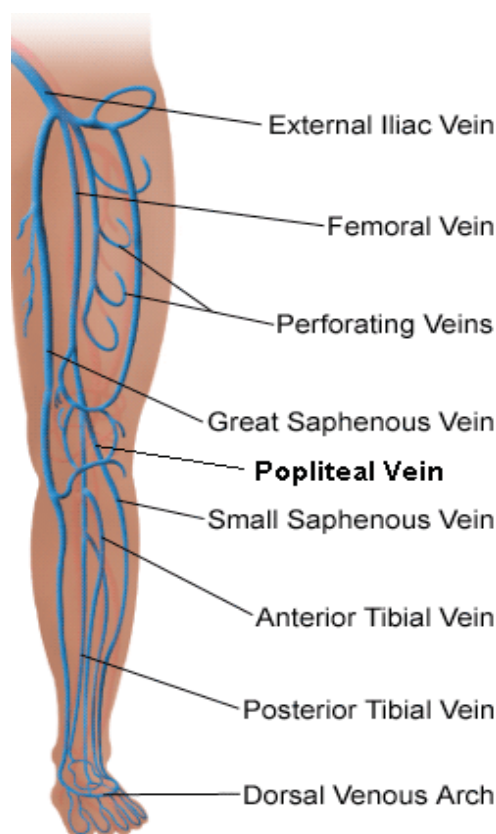


Figure 1. Veins of the leg.

and inflammatory bowel disease, 10) myeloproliferative disorders including polycythemia vera, essential thrombocytemia and primary myelofibrosis, 11) paroxysmal nocturnal hemoglobinuria (PNH), 12) obesity, 13) venous catheterization, 14) pregnancy and the postpartum period, 15) exogenous estrogen use, and 16) cigarette smoking.⁶ Of all VTE occurring in the community, approximately 60% are associated with recent hospitalization or nursing home stay.⁷ Active cancer accounts for 20% of all VTE in the community.⁶

Among surgical patients, factors that may increase the risk of

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postoperative VTE include female gender, ventilator dependence, preoperative dyspnea, higher American Society of Anesthesiologists class, metastatic cancer, chemotherapy within 30 days, greater than 4 units red blood cell transfusion in the 72 hours prior surgery, albumin less than 3.5 mg/dL, bilirubin greater than 1.0 mg/dL, sodium greater than 145 mmol/L, hematocrit less than 38%, emergency surgery, increasing complexity of the surgical procedure, and infected or contaminated wounds.⁸

Pathogenesis of venous thromboembolism: an orchestration of platelet activation and thrombin formation

Hemostasis preserves the integrity of the vasculature after an injury. The vascular endothelium contains three thromboregulators: nitric oxide, prostacyclin, and the ectonucleotidase CD39, which together antagonize thrombus formation.⁹ In the subendothelial matrix, collagen and tissue factor play important roles in maintaining hemostasis. Damage to the endothelium exposes collagen and tissue factor to platelets and coagulation factors in the blood, which initiates clot formation. Exposed collagen triggers the accumulation and activation of platelets, whereas exposed tissue factor initiates the generation of thrombin, which not only converts fibrinogen to fibrin but also activates platelets.⁹

The interactions of platelet glycoprotein VI with the collagen of the exposed vessel wall and of platelet glycoprotein Ib-V-IX with collagen-bound von Willebrand factor result in the adhesion of platelets to the site of injury. Glycoprotein VI also initiates platelet activation and granule release.¹⁰ Thrombin cleaves protease-activated receptor 4 on the platelet surface, which further activates platelets and triggers the release of adenosine diphosphate (ADP), serotonin, and thromboxane A₂. These chemicals activate other surrounding platelets and amplify thrombus formation.¹¹ Activation of platelets induces a conformational change in the platelet integrin $\alpha_{IIb}\beta_3$, which increases its affinity for its ligands, fibrinogen and von Willebrand factor.¹² Fibrinogen and von Willebrand factor are the main ligands for integrin $\alpha_{IIb}\beta_3$ at low and high blood shear rates, respectively.¹³ It is noteworthy to mention, however, that von Willebrand factor and fibrinogen are not absolutely necessary for platelet accumulation.¹⁴

Tissue factor is constitutively expressed on fibroblasts, monocytes and pericytes in the adventitia and medial smooth muscle cells of the vessel wall.¹⁵ Tissue factor is also present in circulating blood associated with microparticles.¹⁶ P-selectin expressed by activated platelets at the surface of the injured vessel wall binds to the microparticles displaying tissue factor derived from monocytes via P-selectin glycoprotein ligand 1 (PSGL-1).¹⁷ Tissue factor exists either in an encrypted form that lacks coagulant activity or in an active form that initiates blood coagulation.¹⁸ The equilibrium between sulfhydryl (-SH) and disulfide (-S-S-) chemical bonds of tissue factor may explain the switch between the encrypted and active forms.¹⁹ Oxidation of free thiols in encrypted tissue factor forms a disulfide bond and yields a conformation that allows the tissue factor-factor VIIa complex to bind and to activate factor X.²⁰ Activated endothelial cells and platelets at the site of injury release protein disulfide isomerase, which catalyzes the formation and cleavage of disulfide bonds within proteins. This may explain why circulating tissue factor does not initiate *de novo* thrombus formation in the absence of vessel wall injury.

The traditional blood coagulation cascade is divided into the intrinsic (contact), extrinsic (tissue factor) and common pathways. The contact factors of the intrinsic pathway are not required for ini-

tiation of hemostasis *in vivo*, although they remain a powerful tool for studying coagulation *in vitro*.²¹ A complete deficiency of factor XII, high-molecular-weight kininogen, or prekallikrein is associated with a markedly prolonged activated partial-thromboplastin time (aPTT) but patients with these deficiency states do not have a hemorrhagic disorder.

The current data support a model of blood coagulation, which is divided into an initiation phase and propagation phase. In this model, tissue factor plays the most important role as the sole initiator of thrombin generation and fibrin formation. The activation of encrypted tissue factor by protein disulfide isomerase secreted by platelets and endothelial cells converts inactive tissue factor on cells or circulating microparticles to its active form.²² In the case of direct tissue damage, tissue factor in the vessel wall or on cell surfaces may already exist in its active form, and the isomerase may not be required. Activated tissue factor forms a complex with circulating factor VIIa.²³ Tissue factor-factor VIIa has three substrates: factor VII, factor IX,²⁴ and factor X. The tissue factor pathway activation of factor IX or factor X, before generation of thrombin, is inefficient because factors VIII (required in the tenase complex) and V (required in the prothrombinase complex) do not exist in their most active cofactor forms. Although inefficient, this mechanism generates a small amount of thrombin. Once formed, this thrombin converts factors VIII and V to their most active forms, factor VIIIa and factor Va, which now efficiently participate in the tenase and prothrombinase complexes to generate a large amount of thrombin. This newly formed thrombin positively feeds back to activate more factors VIII and V and ultimately amplifies formation of additional thrombin. Factor XI, which is also activated by thrombin,²⁵ creates a pool of initiator activity after downregulation of the tissue factor pathway by tissue factor pathway inhibitor.²⁶

Prevention of venous thromboembolism

For most high-risk patients, either anticoagulant prophylaxis using subcutaneous low-dose heparin (unfractionated heparin (UFH) 5000 units 2 to 3 times daily) or low-molecular weight heparin (LMWH) (such as enoxaparin 40 mg daily or dalteparin 5000 units daily), or a mechanical method such as intermittent pneumatic leg compression, are effective for preventing VTE. A meta-analysis of prophylactic anticoagulation in at-risk medical patients demonstrated significant reduction in any PE (relative risk (RR), 0.43 [confidence interval (CI), 0.26 to 0.71]) and fatal PE (RR, 0.38 [CI, 0.21 to 0.69]), a non-significant reduction in symptomatic DVT (RR, 0.47 [CI, 0.22 to 1.00]), a non-significant increase in major bleeding (RR, 1.32 [CI, 0.73 to 2.37]), but no effect on all-cause mortality (RR 0.97 [CI, 0.79 to 1.19]).²⁷ Low-dose UFH postoperatively does reduce the rate of fatal PE from 0.7% to 0.1%,²⁸ with major bleeding complications of less than 0.1% and minor bleeding complications such as injection-site bruising of 6.9%.²⁹ Prophylaxis with LMWH is associated with a lower risk for DVT and PE in hospitalized medical and high-risk orthopedic patients.³⁰⁻³¹ A meta-analysis comparing twice versus three times daily administration of subcutaneous UFH revealed no difference in the overall rate of VTE (5.4 per 1000 patient-days for twice daily vs. 3.5 per 1000 patient-days for thrice daily, $P=0.87$). However, administration of thrice daily heparin was associated with a trend toward fewer PE (1.5 for bid vs. 0.5 for tid per 1000 patient-days, $P=0.09$). The risk for major bleeding was significantly increased with three times daily UFH versus twice daily heparin (0.35 vs. 0.96, $P<0.001$).³²

If patients cannot receive pharmacologic prophylaxis due to

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a high risk of bleeding, then mechanical VTE prophylaxis with graduated compression stockings and / or pneumatic compression devices should be used. Unless there is a contraindication such as fragile skin, severe peripheral arterial disease or severe edema, graduated compression stockings or intermittent pneumatic compression devices should be used as primary prophylaxis against postoperative DVT in these patients. For selected patients at high risk of bleeding, in whom intermittent compression cannot be applied (e.g., multiple traumas with tibia fracture and head injury), case finding of DVT using repeated testing with ultrasound may be of benefit.³³ The Agency for Healthcare Research and Quality (AHRQ) has identified thrombosis prevention as the top priority among approximately 80 evidence-based practices with the greatest potential to improve the safety of hospitalized patients.

Prevention of venous thromboembolism in hypercoagulable states

Thrombophilic disorders are inherited or acquired alterations of the coagulation mechanism that predispose patients to VTE. Hereditary thrombophilia can be divided into high risk and low risk hypercoagulable states. High-risk congenital thrombophilia include antithrombin (AT) deficiency, protein C or protein S deficiency, factor V Leiden (FVL) homozygosity or the prothrombin gene mutation homozygosity as well as compound heterozygosity for FVL and prothrombin G20210A mutation. Antiphospholipid antibody syndrome is a high-risk acquired thrombophilia. Low risk congenital thrombophilia include heterozygosity for FVL or the prothrombin G20210A mutations.

In the past, the results of thrombophilia testing were looked upon as an important factor in decision-making on the duration of anticoagulation therapy for VTE. However, the most common thrombophilic defects, heterozygosity of FVL or the prothrombin gene mutation, have been demonstrated to only modestly increase the risk of recurrent VTE.³⁴ More potent thrombophilic states such as homozygosity for FVL or the prothrombin gene mutation or deficiencies of antithrombin, protein C or protein S which do significantly increase the risk of recurrent thromboembolism are rarely identified. In contrast, recent studies indicate that the presence or absence of strong situational acquired risk factors for thrombosis such as surgery is much more predictive of recurrent VTE. VTE following a major surgical procedure is associated with a low risk of recurrence (0.7% per year) after completion of 3 – 6 months of therapy while idiopathic events are associated with a much higher risk of recurrence (7.4% per year) and thus warrant consideration of indefinite anticoagulation. Patients who develop VTE in association with a less potent non-surgical trigger have an intermediate risk of recurrence (4.2% per year). Since the risk of major bleeding is at least 1 – 2% per year and the case fatality rate of bleeding is at least as high as recurrent VTE, patients with idiopathic VTE are likely to benefit the most from continued anticoagulation.³⁵ Despite the high recurrence rate associated with idiopathic VTE only 50% of patients with idiopathic VTE suffer recurrent thrombosis over 10 years of follow up.³⁶ This realization has led to the development of clinical models to identify patients with idiopathic VTE who are low risk for recurrence.^{37–38}

Therefore, thrombophilia testing may identify a contributing reason for a thrombotic event but it is less likely to identify the appropriate duration of therapy. Patients more likely to carry a thrombophilic mutation have the following characteristics, 1) age 50 years or less, or 2) a positive family history for DVT or PE, or 3) thrombosis in unusual sites such as cerebral venous sinuses, renal veins,

splanchnic veins, and ovarian veins, or 4) recurrent thrombosis, or 5) idiopathic thrombosis, or 6) warfarin-induced skin necrosis, or 7) life-threatening VTE.³⁹ Nevertheless, some of these characteristics would make providers consider long-term anticoagulation in the absence of information on thrombophilia. Therefore, the value of these criteria for testing and the results of thrombophilia testing remain a subject of much debate. Thrombophilia testing should not be conducted on asymptomatic family members as there are no data at the present to support the value of primary thromboprophylaxis in asymptomatic carriers of thrombophilic mutations.

Here we briefly review the congenital thrombophilic states of FVL, the prothrombin G20210A mutation, protein C, protein S and AT deficiency with emphasis on their risk for VTE. More comprehensive reviews can be found in hematology textbooks.

Factor V Leiden (FVL) is a mutation that results in the replacement of arginine 506 with glutamine due to a base change in the factor V gene (G1691A). This amino acid replacement eliminates one of the three sites where activated protein C can attach, cleave and deactivate factor Va. As a result of this mutation, factor V is inactivated at a slower rate, which results in more thrombin generation. FVL is the most common genetic hypercoagulable disorder. In the United States, heterozygote FVL is prevalent in 5% of Caucasians, 2.2% of Hispanic, and 1.2% of African Americans.⁴⁰ In a systematic review, heterozygosity and homozygosity for FVL was associated with a pooled odds ratio for recurrent thrombosis of 1.56 (95% CI, 1.14 – 2.12) and 2.65 (95% CI, 1.18 – 5.97), respectively, compared with patients without the mutation.³⁴ Resistance to activated protein C can be detected by a clotting assay of patient plasma mixed with reagent factor V-deficient plasma. This is useful if the level of protein C antigen is determined to be normal; however, many critically ill patients develop low protein C levels. Abnormal functional results can be confirmed by different genetic testing procedures which are not affected by the patients' medical condition.⁴¹

Prothrombin G20210A mutation is the second most common inherited risk factor for VTE. Heterozygosity for the prothrombin G20210 mutation is present in 1.1% of Caucasians and Hispanic Americans and in 0.3% of African Americans.⁴² The G20210A mutation is associated with an increase in prothrombin levels by approximately 30% in heterozygotes and by 70% in homozygotes. In the same systematic review³⁴ the pooled odds ratio for recurrent thrombotic events was 1.45 (95% CI, 0.96–2.21) for probands heterozygous for the Prothrombin G20210A mutation, compared with mutation-free subjects. Homozygous prothrombin G20210A is rare.

The rate of recurrent VTE in individuals with both the FVL and the prothrombin G20210A mutation (double- or compound-heterozygous) compared with mutation-free control patients has been reported in a few articles.^{43–45} Overall, 10 double-heterozygous individuals had 4 recurrent events and 833 mutation free controls had 95 recurrent thromboses. The pooled odds ratio was 4.81 (95% CI, 0.50 – 46.3).³⁴ In one study, all 3 double heterozygotes developed recurrent thrombosis.⁴⁵

Protein C deficiency. The main function of protein C is the degradation of factors Va and VIIIa. Protein C deficiency can result from quantitative defects affecting protein C levels (low produc-

tion or short protein half life) or qualitative defects, in which its interaction with other molecules such as thrombomodulin, phospholipids, factors Va or VIIIa is abnormal.⁴⁶ Heterozygosity for mutations producing protein C deficiency is found in 0.2% of the general population, and 4% of patients with their first thrombosis. In affected individuals, the absolute level of protein C antigen in plasma is reduced by approximately 50%. Additional risk factors, including factor V Leiden, may commonly provoke thrombosis in patients heterozygous for protein C deficiency.⁴⁶ Homozygous protein C deficiency is a serious condition that produces life-threatening thrombotic complications immediately after birth, a condition often referred to as *neonatal purpura fulminans*.

Protein S deficiency results in reductions in protein S which functions principally as a cofactor for activated protein C to facilitate inactivation of factors Va and VIIIa. Protein S deficiencies include quantitative (low antigen level), and qualitative (low activity) defects, which reduce degradation and inactivation of factors Va and VIIIa. Approximately 60% of Protein S is bound to complement and 40% is free; the latter possesses greater activated protein C cofactor activity.

Hereditary protein S deficiency is an autosomal dominant condition. Three types of hereditary protein S deficiency include decreased protein S activity AND decreased total protein S (both bound and free protein S) levels (Type I), decreased protein S activity AND normal free protein S levels AND decreased total protein S levels (Type II), and decreased protein S activity AND decreased free protein S levels AND normal total protein S levels (Type III). Less than half of those diagnosed with protein S deficiency will experience thrombosis.

It is important to note that there are several etiologies for acquired protein C and protein S deficiencies, which include vitamin K deficiency, treatment with warfarin, acute thrombosis or disseminated intravascular coagulation, pregnancy, liver disease, and HIV disease.

Antithrombin deficiency. Antithrombin (AT) can inhibit all the active enzymes of the coagulation pathway. AT is a slow inhibitor, but the heparan sulfate glycosaminoglycans on intact vascular endothelium stimulates AT inhibitory activity like a catalyst. This provides the pathophysiologic basis of heparin pharmacodynamics. The AT-binding region in heparin has been localized to a pentasaccharide sequence, which provides the chemical explanation for the design and action of LMWH and fondaparinux.⁴⁷

AT deficiency is present in 1 – 2% of patients with history of thrombosis. Type I AT- deficiency causes reduced synthesis of AT. Complete AT deficiency is incompatible with life. Heterozygous

type I AT deficiency is relatively rare (about 1 in 25,000) and is associated with an approximately 10-fold increased risk of thrombosis. There have been several type II homozygotes described with mutations in the heparin-binding, thrombin binding or both regions of AT.⁴⁸ The risk of venous thromboembolism may be more than 50% during pregnancy among women with AT deficiency.⁴⁹

The diagnosis of inherited AT deficiency is impractical in a critically ill ICU patient, who often has acquired reduction in AT levels. A low AT level is one of the hallmarks of disseminated intravascular coagulation (DIC). It is not known whether acquired AT deficiency contributes directly to morbidity in the ICU patient or whether replacement of the factor alters clinical outcomes.^{50–53}

Antithrombin concentrates for the treatment of severe sepsis.

The anti inflammatory effects of AT may be important in the critically ill patient; however, a very large, multinational trial of high-dose AT concentrate in severe sepsis showed no survival benefit among treated patients.⁵⁴ A Cochrane systematic review⁵⁵ included 20 randomized trials with a total of approximately 3500 participants and when all trials were combined, AT did not statistically significantly reduce overall mortality compared with the control group (RR 0.96, 95% CI 0.89 to 1.03; no heterogeneity between trials). On the hand, AT increased bleeding events (RR 1.52, 95% CI 1.30 to 1.78).⁵⁵

Approach to the patient with venous thromboembolism, diagnosis and work-up

The American College of Chest Physicians Guideline does not recommend routine screening of asymptomatic patients for DVT even for those at increased risk.³³ D-dimer (particularly in a hospitalized patient), ultrasound imaging and plethysmography all have a low sensitivity, even though good negative predictive value, for detecting asymptomatic DVT in such patients.⁵⁶

Clinical Evaluation. DVT should be suspected in patients with lower extremity pain or swelling. Active cancer or ongoing chemotherapy, previous VTE, recent surgery, hospitalization or immobilization, and increased calf diameter more than 3 cm increase the likelihood of DVT. Homan sign has limited diagnostic value for DVT.⁵⁷ The most widely evaluated clinical score for DVT is the Wells score, which stratifies patient to high (≥ 3), intermediate (1 – 2), or low (≤ 0) risk for DVT, Table 1.⁵⁸ The likelihood ratio of DVT for high and low categories are 5.2 and 0.25, respectively. The Wells score does not accurately stratify patients for distal DVT, does not apply as well in excluding DVT in primary care setting as inpatient setting, and has not been validated for certain high risk patients like intravenous drug abusers.⁵⁹ There are some other, less

Table 1. The Modified Wells Clinical Score for DVT.

Clinical characteristic	Score
Active cancer (treatment ongoing, within last 6 months or palliative)	1
Calf swelling >3 cm compared to other calf (measured 10 cm below tibial tuberosity)	1
Collateral superficial veins (non-varicose)	1
Pitting edema (confined to symptomatic leg)	1
Swelling of entire leg	1
Localized pain along distribution of deep venous system	1
Paralysis, paresis, or recent cast immobilization of lower extremities	1
Recently bed-ridden >3 days, or major surgery requiring regional or general anesthetic in past 12 weeks	1
Previously documented DVT	1
Alternative diagnosis at least as likely	-2

Table 2. Anticoagulants for the treatment of VTE.

Anticoagulant	Initial Dosage
Unfractionated heparin	40 – 80 units/Kg IV bolus, followed by 14 – 18 units/Kg/hr to keep aPTT \geq 1.5 – 2
Low molecular weight heparin	
Enoxaparin	1 mg/Kg subcutaneously (SC) Q12h or 1.5 mg/Kg SC Q24hr
Dalteparin	100 IU/Kg SC Q12hr or 200 IU/Kg SC Q24hr
Tinzaparin	175 IU/Kg SC Q24hr
Direct Thrombin Inhibitors	
Argatroban	2 μ g/Kg/min (for normal liver function)
Lepirudin	0.1 mg/Kg/hr (for normal renal function)
Bivalirudin	0.75 mg/Kg IV bolus, then 1.75 mg/Kg/hr
Fondaparinux	5 – 7.5 mg SC daily (depends on the weight range)
Warfarin	Initial dose of 5 – 10 mg orally on day 1 of heparin, overlap with heparin until INR becomes therapeutics for two consecutive days, dose needs to be adjusted for INR goal between 2 and 3

validated, scores that combine clinical evaluation with D-dimer results to determine further need for ultrasound testing.^{60–62}

D-dimer can be used effectively to rule out DVT in patients with a low clinical risk for DVT, which precludes patients with prolonged hospitalizations or patients in ICU. D-dimer assays generally have very good sensitivity but poor specificity for diagnosis of DVT. ELISA-based assays for D-dimer generally have higher sensitivity and lower specificity compared to whole-blood agglutination assays. The point-of-care whole-blood agglutination D-dimer assay is a widely used and can rule-out DVT in emergency department or out-patient setting in low risk patient populations.⁶³

Diagnostic imaging. Among patients with symptomatic DVT approximately 50% have evidence of PE. Approximately 30 – 70% of patients with symptomatic PE detected by angiography have identifiable DVT in the legs.⁶⁴ Hence, diagnosis of VTE should include both tests for detection of PE and tests for detection of DVT of the legs. Pulmonary angiography is the gold standard for diagnosis of PE. Spiral CT scan or ventilation/perfusion scan (V/Q scan or lung scintigraphy), which shows that some areas of the lung are being ventilated but not perfused due to obstruction by a clot are also widely used for diagnosis of PE. A recent randomized clinical trial noted that CT angiography appears to be more sensitive for PE diagnosis than V/Q scans.⁶⁵ Doppler ultrasound or venography are common tests for diagnosis of DVT.

A meta-analysis of 100 studies demonstrated that venous ultrasound has a 94% sensitivity for detecting proximal DVT, 63% sensitivity for detecting distal DVT and 94% specificity for both.⁶⁶ Ultrasonography using vein compression as the diagnostic criterion has a very high inter-rater reliability in symptomatic patients. Thus, physicians should utilize venous ultrasound to diagnose or exclude DVT in patients with a high clinical probability of DVT or a positive D-dimer result. In a quantitative decision making model, if proximal DVT is detected in a symptomatic patient, the patient should be treated with anticoagulation without further investigation. A negative ultrasound result effectively rules out proximal DVT but not distal DVT.

In asymptomatic patients, venous ultrasound is less accurate.^{67–68} Approximately 1 – 2% of patients with a normal initial ultrasound have calf DVT which will extend into the proximal veins in 5 – 8 days.⁶⁹ Thus, if clinical suspicion remains high and the D-dimer is positive, the physician can repeat an ultrasound one week later if the initial investigation was negative. Magnetic resonance venography (MRV) is an alternative to ultrasound with equal accuracy.⁷⁰

The clinical impact of PE depends on the size of the embolus and the patient's cardiorespiratory status. Multi-row detector CT scan has substantially improved the diagnosis of PE. In a multicenter study aimed to prospectively investigate the accuracy of multi-row detector computed tomographic angiography (CTA) for the diagnosis of acute PE, excluding inconclusive studies, the sensitivity of CTA was 83% and the specificity was 96%. Positive predictive values were 96% with a concordantly high or low probability on clinical assessment, 92% with an intermediate probability on clinical assessment, and non-diagnostic if clinical probability was discordant. When CTA was combined with venous-phase imaging (CTA-CTV), the results were inconclusive in approximately 10% of the patients because of poor image quality. The sensitivity of CTA-CTV for PE was 90%, and the specificity was 95%. CTA-CTV was also non-diagnostic with a discordant clinical probability.⁷¹ The inter-rater reliability of CT imaging for PE is very good among appropriately trained and credentialed radiologists.⁷²

We recommend that patients with unexplained DVT undergo age-appropriate cancer screening, even if the clinical picture does not suggest underlying malignant condition. In all patients with DVT or PE, before starting treatment, complete blood cell count, PT, aPTT and serum creatinine level must be checked.

Treatment of venous thromboembolism

Anticoagulation is the mainstay of DVT and/or PE treatment. In acute DVT or PE, initial treatment with heparin analogues for at least 5 days rather than a shorter period is recommended in conjunction with initiation of vitamin K antagonists on the first treatment day, and discontinuation of heparin when the International Normalized Ratio (INR) is greater than 2.0 for at least 24 hours.⁷³ Generally the treatment of the upper extremity DVT is similar to the treatment of the lower extremity DVT.^{74–76}

Table 2 summarizes different anticoagulants with their dosages. Unfractionated heparin (UFH) works by enhancing AT activity. Low Molecular Weight Heparins (LMWHs) also bind to and accelerate the activity of AT, by which potentiate the inhibition of factors Xa and IIa. LMWHs also directly inhibit factor Xa, hence, inhibit conversion of prothrombin to thrombin, (II \rightarrow IIa). Penta-saccharide fondaparinux inhibits factor Xa. Argatroban, lepirudin and bivalirudin directly inhibit thrombin activity. Warfarin acts as an anticoagulant by inhibiting hepatic gamma carboxylation of glutamic acid residues of vitamin K-dependent coagulation factors II, VII, IX, and X. Warfarin also inhibit production of vitamin K-dependent antithrombotic protein C and protein S.

We performed a systematic review of trials comparing LMWH

with UFH for the treatment of VTE.⁷⁷ All but one study showed that LMWH significantly decreased mortality during the 3 to 6 months of follow up compared with UFH. None of the studies showed that UFH is superior in preventing of recurrent DVT. Also patients treated with LMWH compared with UFH had fewer episodes of major bleeding.

Fondaparinux (7.5 mg subcutaneous daily) appears to be as effective as LMWH for treatment of acute DVT with similar rate of the major bleeding.⁷⁸ Direct thrombin inhibitors are usually used in cases of hypersensitivity to heparin or heparin induced thrombocytopenia (HIT) and they should be administered by a trained hematologist.

In selected patients with acute iliofemoral DVT (with symptoms for less than 7 days, good functional status, and life expectancy more than one year), operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available.⁷⁹⁻⁸¹ In such patients the same intensity and duration of anticoagulant therapy afterwards as for comparable patients who did not undergo venous thrombectomy applies. A randomized trial in 35 patients with iliofemoral DVT compared catheter-directed thrombolysis followed by anticoagulation with anticoagulation alone.⁸² At six months, the patency rate was higher (72% vs. 17%, $P<0.001$) and venous reflux was lower (11% vs. 41%, $P=0.01$) in patients treated with thrombolysis.

Complications of anticoagulation. Anticoagulation carries a small but important risk for bleeding. A meta-analysis of patients taking anticoagulants for VTE estimated that over the 3–6 months treatment period, there was a 0.34% probability of fatal bleeding, a 0.12% probability of nonfatal intracranial bleeding, and a 2.1% probability of other nonfatal major bleeding.⁸³ Complications of heparin analogues include heparin-induced thrombocytopenia (HIT); hypersensitivity reactions including urticaria, angioedema, and anaphylaxis; osteoporosis after long-term use; hyperkalemia; transaminitis; anemia and purpura (with fondaparinux). Important complication related to warfarin include hypercoagulability for the first 24 to 48 hours of treatment, a long list of drug-drug interactions (Table 3), teratogenicity, and skin necrosis associated with

protein C and S deficiency.⁸⁴

Duration of anticoagulant therapy for patients with DVT.⁸⁴⁻⁸⁷ Patients with major *transient* risk factors for VTE, such as major surgery, serious medical conditions or leg casting are usually treated for 3 months. Patients with unprovoked DVT or PE should be treated with a vitamin K antagonist or LMWH for at least 3 months, and that all patients are then evaluated for the risk-benefit of prolonged anticoagulation therapy. On the other side of the spectrum, patients with major *persistent* risk factors, such as cancer are usually treated indefinitely. Patients who did have more than one unprovoked event, or had a provoked event in milieu of high-risk thrombophilia, or had a massive PE are also usually treated life-long. Patients with minor risk factors, such as hormone replacement therapy or oral contraceptive pills, who did have an unprovoked event, in the absence of a hypercoagulable state, usually are treated for 6 months. Such patients must avoid future risk factors that potentially triggered the VTE event.

In patients who take long term vitamin K antagonists, the dose of the drug must be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations. Table 3 summarizes the common food and drugs interactions with warfarin. Although more expensive, long-term treatment with LMWH is a safe and effective alternative for patients in whom warfarin intake is difficult due to difficulty in titrating dose to stay at INR target, poor patient adherence to INR monitoring, or adverse effect.

D-dimer measurement might be helpful in determining the duration of anticoagulation. A study published in the New England Journal of Medicine⁸⁸ showed that patients with an abnormal D-dimer one month after the discontinuation of anticoagulation for idiopathic VTE had a significant incidence of recurrent event, which could be reduced by the resumption of anticoagulation.

Graduated Compression Stockings. Graduated compression stockings with pressures ranging from 20–40 mmHg depending on severity of DVT and potential edema should be used within one month of diagnosis of symptomatic proximal DVT for a minimum of one year to reduce the incidence of the postthrombotic

Table 3. Food and drugs interactions with warfarin (Herbal medicine not included).

Increase warfarin effect (i.e. require a decrease in the dose of warfarin to avoid supratherapeutic INR)
•Warfarin metabolism inhibitors
Amiodarone
Clofibrate
Fluconazole
Fluoroquinolone antibiotics
Cimetidine (other H ₂ -blocker are fine)
Miconazole
Omeprazole
Phenylbutazones
Sulfonamide antibiotics
Propafenone
Tamoxifen
•Warfarin action enhancers
Acetaminophen
•High vitamin K food
Green leafy vegetables (broccoli, Brussel sprouts, turnip greens, kale, spinach, beet greens)
Cauliflower, legumes, mayonnaise, canola and soybean oils
Decrease warfarin effect (i.e., require an increase in the dose of warfarin to avoid subtherapeutic INR)
o Decrease warfarin absorption
Cholestyramine
Colestipol
o Warfarin clearance enhancers
Phenytoin
Rifampin
Glutethimide
Griseofulvin

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syndrome by 50%.^{89–90} Patients must be instructed to replace their stockings after six months of repeated use because the stockings usually lose the elasticity needed to maintain adequate pressure. Pneumatic compression in the out-patient setting is often reserved for patients who do not respond to leg elevation and graduated compression stockings.

Superficial vein thrombosis. Peripheral vein infusion thrombophlebitis occurs in approximately 25 to 35% of hospitalized patients who have peripheral IV catheters.⁹¹ Diclofenac emulsion gel used topically three times daily and oral diclofenac (75 mg bid) have been shown to be superior to placebo in relieving local symptoms of thrombophlebitis at 48 hours in hospitalized patients with infusion thrombophlebitis, with positive responses in 60% of active treatment groups versus only 20% in the control group.⁹² Heparin sodium gel has also proved to be more effective than placebo in one week resolution of infusional thrombophlebitis.⁹³ A Cochrane Collaboration systematic review assessed the efficacy and safety of topical, medical, and surgical treatments in patients presenting with superficial thrombophlebitis (ST) of the legs.^{94–95} Twenty-four studies involving approximately 2500 participants with ST of the legs were included in this review. Both LMWH and Non-Steroidal Anti Inflammatory Drugs (NSAIDs) significantly reduced the incidence of ST extension or recurrences by about 70% compared with placebo and both seemed to have a similar efficacy and safety. Surgical treatment combined with elastic stockings in ST was associated with a lower VTE rate and ST progression, compared with elastic stockings alone. No controlled trials have evaluated systemic anticoagulants for the treatment of infusional thrombophlebitis.

For patients with *spontaneous* superficial vein thrombosis, prophylactic (enoxaparin 40 mg SC daily) or intermediate (1.5 mg/kg SC daily) doses of LMWH⁹⁶ or intermediate (12,500 IU twice daily for one week, followed by 10,000 IU twice daily) doses of UFH⁹⁷ for at least 4 weeks is recommended. As an alternative to 4 weeks of LMWH or UFH, warfarin (target INR, 2.5; range, 2.0 to 3.0) can be overlapped with 5 days of UFH and LMWH and continued for 4 weeks.⁹⁸ A recent randomized controlled trial demonstrated that fondaparinux 2.5 mg daily for 45 days was more effective than placebo. Only 13 of 1502 patients (0.9%) receiving fondaparinux developed symptomatic DVT, PE or thrombosis extension or death compared with 88 of 1500 placebo recipients (5.9%). These data strongly support the use of an anticoagulant for superficial venous thrombophlebitis.⁹⁹ It is possible that less extensive superficial vein thrombosis (i.e., where the affected venous segment is short in length or farther from the saphenofemoral junction) does not require treatment with anticoagulants. It is reasonable to use oral or topical NSAIDs for symptom control in such cases.⁷³

Inferior Vena Cava (IVC) Filters. IVC filters may be used when anticoagulation is contraindicated in patients at high risk for proximal extension of DVT or PE. Such patients include those with bilateral or massive DVT, prolonged immobility, chronic heart or renal failure, or active cancer. It is noteworthy to mention that IVC filters may increase the long-term incidence of recurrent proximal DVT. In practice, IVC filter are often placed in patients with recurrent VTEs while on anticoagulation to prevent further recurrence. However the efficacy of such approach remains unproven. A systematic review and meta-analysis of patients who received an IVC filter showed that continuation of anticoagulation did not

significantly decrease the risk for recurrent VTE (odds ratio, 0.639 [CI, 0.35 to 1.16]).¹⁰⁰

Thrombolytic therapy for pulmonary embolism. Thrombolytic therapy for PE remains controversial for patients with sub-massive pulmonary embolism. Three meta-analyses have summarized the randomized trials which have compared thrombolysis plus anticoagulation versus anticoagulation alone in the treatment of PE.^{101–103} Generally, these studies showed in patients with PE of varying severity that thrombolysis was associated with non-statistically significant trends toward a reduction in recurrent PE, a reduction in all-cause mortality, and an increase in major bleeding.

In the International Cooperative Pulmonary Embolism Registry,¹⁰⁴ which enrolled more than 2400 PE patients from 52 hospitals in seven countries, intracranial bleeding occurred in 3.0% of the patients who received thrombolytic therapy, compared with 0.3% among patients who received anticoagulation alone. The overall mortality rate from PE was approximately 8% after 3 months,¹⁰⁵ which was double the frequency reported in randomized trials. This higher mortality rate may reflect sample bias by exclusion of the sickest patients from participating in randomized trials. There was no apparent survival benefit from thrombolysis in this registry, even among the sickest patients with massive PE.

The 8th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guideline⁷³ recommends that patients with confirmed PE be assessed early for the risks and benefits of thrombolytic therapy. For patients with hemodynamically significant PE short-course thrombolytic therapy is recommended. For those with non-massive PE, the guideline recommends against the use of thrombolytic therapy.

In the absence of hemodynamic instability, assessments to justify the utilization of thrombolysis depends on clinical evaluation (such as vital signs, presence of distended jugular veins, systolic murmur of tricuspid regurgitation, or an accentuated P2), cardiac biomarkers such as troponin for right ventricular microinfarction, and assessment of right ventricular size and function by EKG (right-bundle branch block, S₁Q_{III}T_{III}, and T wave inversion in leads V1 through V4) or echocardiography.^{106–109} Right ventricular enlargement on the CT pulmonary angiogram, defined as a right ventricular diameter ≥90% than the left ventricular diameter, is an independent risk factor for death and nonfatal clinical complications.^{110–111} Clinical models such as the Pulmonary Embolism Severity Index (PESI) have been demonstrate to be useful in identifying patients at high risk for adverse outcomes.¹¹² Major contraindications to thrombolytic therapy include intracranial disease, uncontrolled hypertension at presentation, and recent major surgery, trauma, stroke or bleeding.¹¹³

Choice of thrombolytic therapy. Nine randomized trials compared the rate of thrombus resolution after administration of various thrombolytic regimens.^{114–121} The regimens included streptokinase (in 2 hr,¹¹⁸ in 12 hr,¹¹⁹ or in 24 hr¹¹⁴), urokinase (in 2 hr,¹¹⁷ or 12 hr^{114,120}), and recombinant tissue plasminogen activator (rt-PA) (in 15 min,^{115,121} or 2 hr¹²¹). These studies showed that 1) 2 hr infusions of thrombolytics attain more rapid clot lysis than 12- or 24 hr infusions, 2) there was no difference in the efficacy or safety of rt-PA versus streptokinase when administered in a 2-hr infusion at high concentration, 3) prolonged (≥ 12 hr) infusions of thrombolytic agents were associated with higher rates of bleeding, 4) infusion of rt-PA directly into a pulmonary artery as opposed to a peripheral

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vein did not accelerate thrombolysis but did cause more frequent bleeding at the catheter insertion site.¹²² rt-PA, at a dose of 100 mg over 2 hr, is currently the most widely used and evaluated regimen.

In summary, there is good evidence that thrombolytic therapy accelerates resolution of PE and results in more rapid hemodynamic improvement. The evidence that thrombolytic therapy improves clinical outcome is less secure. In the absence of risk factors for bleeding, patients who are hemodynamically compromised are very likely to benefit, as are sick patients with major pulmonary arterial obstruction, although the evidence supporting the latter is indirect.⁷³

New oral anticoagulants

Vitamin K antagonists have remained the sole oral anticoagulants for the past 50 years. VKA have a number of shortcomings including many diet- and drug-drug interactions, a slow onset and offset of activity and significant inter-individual variations in dose requirements (up to 70 fold). Consequently, close laboratory monitoring is essential. In the last few years, several new oral anticoagulants including dabigatran etexilate, rivaroxaban and apixaban have undergone extensive testing for thromboprophylaxis in patients with atrial fibrillation, venous thromboembolism and acute coronary syndromes.

Dabigatran etexilate is a pro-drug that is converted into dabigatran by plasma esterases. Dabigatran is an oral selective direct thrombin inhibitor that reaches peak levels within 2 – 3 hours of administration. It has a half-life of 14 – 17 hours and approximately 80% of the drug is excreted via the kidneys. It is a substrate of the transport protein p-glycoprotein so co-administration with potent inhibitors (e.g., quinidine, amiodarone, verapamil, clarithromycin) or inducers (rifampin, St John's wort) should be avoided.^{123–124} In the RE-LY study, a randomized controlled trial of dabigatran in thromboprophylaxis of patients with non-valvular atrial fibrillation, two different doses, 150 mg twice daily and 110 mg twice daily were compared with dose adjusted warfarin. The 150 mg twice daily dose provided superior protection against thromboembolism compared with warfarin with a similar risk of major bleeding while the 110 mg twice daily dose proved to be equally effective in thrombosis prevention as warfarin with a lower risk of bleeding.¹²⁵ Based upon these results, the US Food and Drug Administration approved a dose of 150 mg twice daily for non-valvular atrial fibrillation in patients with a creatinine clearance of at least 30 milliliters per minute (mL/min). A 75 mg twice daily dose was approved for patients with an estimated creatinine clearance of 15 – 30 mL/min, however there is very limited clinical experience with this dose so it should probably be used with great caution. Dabigatran has also been found to be equally effective compared with warfarin in the long-term treatment of patients with venous thromboembolism.¹²⁶ Dabigatran is not reversible by protamine, vitamin K, or plasma. Hemodialysis can be used to remove dabigatran and activated prothrombin complex concentrates have been shown to reduce bleeding in an animal model of dabigatran reversal.¹²⁴

Rivaroxaban is a selective oral factor Xa inhibitor. It has been demonstrated to be effective in VTE prophylaxis in patients undergoing hip and knee arthroplasty as well as thromboprophylaxis of non-valvular atrial fibrillation and acute and chronic treatment of VTE.^{127–129} Rivaroxaban is rapidly absorbed achieving peak plasma levels in 2 – 4 hours after oral administration. It is excreted by the kidney and metabolized by the liver P450 microsomal enzyme system. It has a half life of 5 – 9 hours in healthy individuals. Medi-

cations which influence the P450 microsomal enzyme CYP3A4 or p-glycoprotein could influence rivaroxaban levels. Rivaroxaban was recently approved by the FDA for thromboprophylaxis of patients undergoing hip and knee arthroplasty at a dose of 10 mg daily. It should not be used in patients with a creatinine clearance less than 30 mL/min or moderate to severe liver disease. (Child-Pugh classes 2 and 3). Like dabigatran, rivaroxaban is not reversible by conventional means but requires use of a procoagulant such as recombinant human factor VIIa.^{130–131}

Acknowledgement

In memory of Dr. Rasoul Sherafat Kazemzadeh

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