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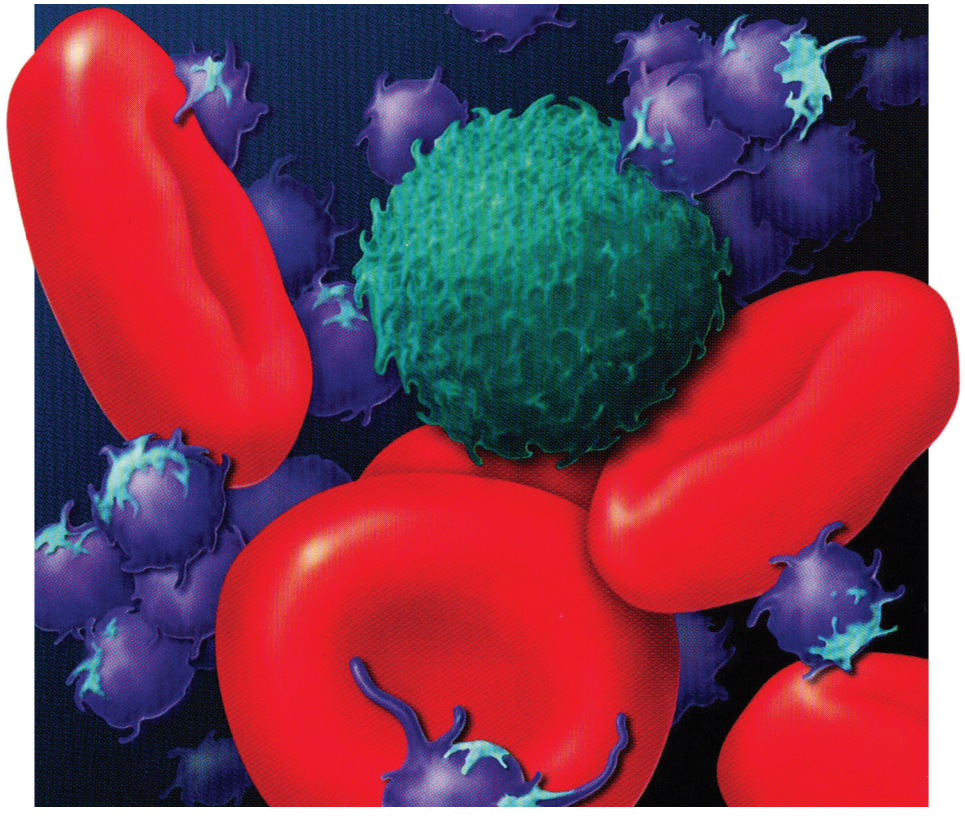

Venous Thromboembolism

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Venous Thromboembolism

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Elisabeth M. Battinelli, MD, PhD, and Jean M. Connors, MD

INTRODUCTION

Venous thromboembolism (VTE) and its associated complications account for significant morbidity and mortality. Each year between 100 and 180 persons per 100,000 develop a VTE in the Western countries. The majority of VTEs are classified as either pulmonary embolism (PE), which accounts for one third of the events, or deep vein thrombosis (DVT), which is responsible for the remaining two thirds. Between 20% and 30% of patients diagnosed with thrombotic events will die within the first month after diagnosis.[1] PE is a common consequence of DVT; 40% of patients who are diagnosed with a DVT will be subsequently found to have a PE upon further imaging. The high rate of association is also seen in those who present with a PE, 70% of whom will also be found to have a concomitant DVT. [2,3]

The main demographic factor that appears to be associated with development of a VTE is age. It is rare for children to suffer a thrombotic event, whereas older persons have a risk of 450 to 600 events per 100,000 persons.[1] The highest incidence occurs in African Americans, with Asians having the lowest incidence. Other factors that appear to be linked to increased risk of VTE include obesity, smoking, long air travel, and hormonal therapy.

PATHOGENESIS

Abnormalities in both coagulation factors and the vascular bed are at the core of the pathogenesis of VTE. The multifaceted etiology of thrombosis was first described in 1856 by Virchow, who defined a triad of defects in vessel wall, platelets, and coagulation proteins.[4] Usually the vessel wall is lined with endothelial cells that provide a nonthrombotic surface and limit platelet aggregation through release of prostacyclins and nitric oxide. When the endothelial lining becomes compromised, the homeostatic surveillance system is disturbed and platelet activation and the coagulation system are initiated. Tissue factor exposure in the damaged area of the vessel leads to activation of the coagulation cascade. Collagen that is present in the area of the wound is also exposed and can activate platelets, which provide the phospholipid surface upon which the coagulation cascade occurs. Platelets initially tether to the exposed collagen through binding of glycoprotein Ib-V-IX in association with von Willebrand factor. The thrombus is initiated as more platelets are recruited to exposed collagen of the injured endothelium through aggregation in response to the binding of glycoprotein IIb/IIIa with fibrinogen. This process is self-perpetuating as these activated platelets release additional proteins such as adenosine diphosphate, serotonin, and thromboxane A2, all of which fuel the recruitment and activation of additional platelets.

DIAGNOSIS

The key to decreasing the morbidity and mortality associated with VTE is timely diagnosis and early initiation of therapy. Various imaging modalities can be employed to support a diagnosis of VTE and are used based on clinical suspicion arising from the presence of signs and symptoms. DVT is usually associated with pain in the calf or thigh, unilateral swelling, tenderness, and redness. PE can present as chest pain, shortness of breath, syncope, hemoptysis, and/or cardiac pal-pitations.

Clinical decision rules based on signs, symptoms, and risk factors have been developed to estimate the pretest probability of PE or DVT and to help determine which patients warrant further testing. These clinical decision rules include the Wells criteria, which address both DVT and PE, as well as the Geneva score, which is focused on identifying patients likely to have a PE. Perhaps the best known clinical decision tool for PE, the Wells rule uses 7 assessment variables to determine a patient's probability of having a PE (**Table 1**). Patients receiving a score of 4 or greater have a 28% to 52% risk of PE.[5] The Geneva criteria are based on the Wells criteria, with slight modifications for clinical assessment.[6,7] Both rules can be easily applied to assess the overall risk of PE. Patients who score high are evaluated by imaging modalities, while those with lower scores should be considered for further stratification based on D-dimer testing. The goal of clinical assessment is to identify

patients at low risk of VTE to reduce the number of imaging studies performed. Most of the decision rules focus on the use of noninvasive evaluations that are easily implemented. These include not only clinical history and presentation, but also abnormalities in oxygen saturation, chest radiography findings, and electrocardiography, in addition to D-dimer testing.

D-dimer testing is at the core of all predictive models for VTE. D-dimer is a fibrin degradation product that is detectable in the blood during active fibrinolysis as occurs after clot formation. The concentration of D-dimer increases in patients with active clot. D-dimer testing is usually performed as a quantitative ELISA or automated turbidimetric assay and is highly sensitive (>95%) in excluding a diagnosis of VTE if results are in the normal range.[8] The presence of a normal D-dimer and a low probability based on clinical assessment criteria together identify patients with a low likelihood of VTE. This was demonstrated in a meta-analysis that found that the risk of PTE was low in those with unlikely probability based on Wells score and a normal D-dimer, with a pooled negative predictive value of 99.7%.[9] It should be considered, however, that other factors can lead to an increased D-dimer level, including malignancy, trauma, disseminated intravascular coagulation, pregnancy, infection, and postoperative changes, which can cloud the utility of the test at the time of diagnosis. This caveat makes the test less helpful in critically ill hospitalized patients, patients older than 65 years of age, and pregnant women.[10,11]

The mainstay of diagnosis of PE or DVT is imaging. For DVT the use of ultrasonography is considered the gold standard, with both high sensitivity (89% to 100%) and specificity (86% to 100%), especially when the DVT is located proximally.[12–14] Other diagnostic options include computed tomography (CT) venography, which is not first line as it is highly invasive and exposes the patient to iodine-based contrast dyes. Magnetic resonance venography (MRV) offers superb visualization for diagnosis of pelvic vein thrombosis, but its use is limited because of availability and cost issues. Conventional ventilation perfusion (VQ) scanning and pulmonary angiography have been replaced by helical CT pulmonary angiography as the diagnostic test of choice for PE.[15]

Table 1. Clinical Decision Rules for Pulmonary Embolism Based on Wells Criteria

Clinical Feature	**Score**
History of previous PE or VTE	1.5
Heart rate >100 beats/min	1.5
Surgery or period of immobilization in last 4 weeks	1.5
Hemoptysis	1
Active malignancy	1
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Clinical Probability	**Score**
PE unlikely	≤4
PE likely	>4
Traditional Probability Assessment	
High	>6
Medium	2–6
Low	<2

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Data from Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med 2002;113:269–75.

INITIAL TREATMENT OPTIONS

Patients who present with a PE and hemodynamic instability represent a medical emergency. These patients often present with increased heart rate and diminished blood pressure, hypoxemia, elevated jugular venous pressure, and poor tissue perfusion as evidenced by right ventricular strain or hemodynamic instability. This patient population should be considered for emergent management with thrombolytic therapy, which usually involves treatment with recombinant tissue plasminogen activator (t-PA; alteplase). Because less than 5% of patients present in this dramatic manner and due to the potential bleeding risk of t-PA, this treatment is reserved for patients who have unstable vital signs. Thrombolysis should be reserved for those who have not had any surgical procedures in the prior 2 weeks, no evidence of neurosurgical bleeding, and are not at risk of a bleeding diathesis. Contraindications to t-AP include severe hypertension, platelet count less than 100,000/μg, intracranial neoplasm, recent intracranial surgery or trauma, active or recent internal bleeding during the last 6 months, history of a hemorrhagic stroke, bleeding diathesis, non-hemorrhagic stroke within the prior 2 months, or recent surgery.[16]

In standard cases of DVT and PE without hemodynamic compromise, the current standard of care is initially parenteral anticoagulation. The goal of therapy is to prevent the thrombus from propagating further, allow the body's fibrinolytic system to break down existing thrombus, and prevent DVT from embolizing to the lungs or other vascular beds. The initial treatment

of VTE has been extensively discussed and guidelines have been established with recommendations for initiation of anticoagulation. The American College of Chest Physicians (ACCP) recently released the ninth edition of their guidelines, which are based on consensus agreements derived from primary data.[17] The role of new oral anticoagulants in treatment of VTE will be addressed later in this review.

The immediate goal is to treat these patients with anticoagulants that will work rapidly, which usually involves parenteral administration. As such, heparin-based drugs are the mainstay of treatment. Heparin drugs act by potentiating antithrombin and therefore inactivating thrombin and other coagulation factors such as Xa. Unfractionated heparin can be administered as an initial bolus followed by a continuous infusion, with dosing based on weight and titrated to activated partial thromboplastin time (aPTT) or the anti-FXa level. More often, patients are treated with a low molecular weight heparin (LMWH) administered subcutaneously in fixed weight-adjusted doses, which does not require monitoring in most cases.[18] LMWHs work in a manner similar to unfractionated heparin but have more anti-Xa activity in comparison to antithrombin activity. The efficacy of unfractionated heparin compared to LMWH has been shown to be equivalent for treatment of DVT and PE.[19]

The options for treatment of VTE have expanded in recent years with the approval of fondaparinux, a pentasaccharide specifically targeted to inhibit factor Xa. Fondaparinux has been shown to have similar efficacy to LMWH and unfractionated heparin in patients with DVT or PE.[20,21] Although these drugs all provide adequate protection against further embolization and clot propagation, caution should be used as LMWH and fondaparinux are renally cleared and therefore have increased bleeding risk in patients with renal impairment. In patients with creatinine clearance of less than 30 mL/min, dose reduction or lengthening of dosing interval are appropriate adjustments, as is monitoring of factor Xa activity.[18]

In the majority of patients in which there are no abnormalities in hemodynamic parameters, outpatient administration of these medications without hospitalization is considered safe. The drug of choice in most of the studies that looked at initiation of anticoagulation in the outpatient setting is LMWH.[22] When considering outpatient management, however, the severity of the VTE, hemodynamic status of the patient, overall bleeding risk, and medication compliance should all be considered.

Most patients who present with VTE are transitioned to warfarin for long-term therapy. Warfarin can be started on the same day as parenteral anticoagulation. Both drugs are overlapped for at least 5 days, with a target INR of 2.0 to 3.0. Patients may achieve the target INR quickly because the FVII level drops quickly; however, the overlap of 5 days is essential even when the INR is in the target range because a full anticoagulant affect is not achieved until prothrombin levels decline, and these levels decline slowly. Warfarin also causes a rapid decrease in levels of natural anticoagulants such as protein C and protein S, which further exacerbates the net hypercoagulable state. Warfarin without a bridging parenteral agent is not effective as an initial anticoagulant treatment in acute VTE as there is an associated risk of warfarin-induced skin necrosis.[23]

LONG-TERM THERAPY

DURATION OF ANTICOAGULATION

The duration of anticoagulation often depends on a myriad of factors including severity of VTE, risk of recurrence, bleeding risk, and lifestyle modification issues, and on alternative therapies such as low-intensity warfarin, aspirin, or the new oral anticoagulants. The decision tree for length of treatment starts with whether the VTE was a provoked or a spontaneous event. Provoked events occur when the event is associated with an identifiable risk factor, such as immobilization from prolonged medical illness or surgical intervention, pregnancy or oral contraceptive use, and prolonged air travel. Consensus guidelines suggest 3 to 6 months of anticoagulation are sufficient treatment for a provoked VTE.[17,24,25] Studies have attempted to determine whether less than 3 months of anticoagulation could be considered for provoked VTE. In these studies, it was clear that 6 weeks of anticoagulation was not sufficient due to a high rate of recurrent VTE during the observation period.[26] Further evidence of the benefit of prolonged anticoagulation is provided by a meta-analysis which demonstrated that patients who received anticoagulation for 12 to 24 weeks had a 40% risk reduction in recurrence rate when compared to patients who were only anticoagulated for 3 to 6 weeks.[27] In this study, the group that benefitted the most from long-term anticoagulation was those with idiopathic VTE. A recent meta-analysis demonstrated that although 3 months of anticoagulation achieves a similar risk of recurrent VTE after stopping anticoagulation in comparison to longer treatments, the risk remains highest for those with unprovoked events.[28]

Determining the duration of anticoagulation is more complex in patients with recurrent VTE or idio-

pathic VTE.[29,30] Evidence of the benefit of long-term anticoagulation was provided in the study by Kearon and colleagues demonstrating that in comparison to patients anticoagulated for 3 months, patients who were anticoagulated for 24 months had a lower risk of recurrent events (1.3% at 24 months and 27.4% at 3 months).[31] Similar studies and meta-analyses demonstrated decreased recurrence rates in patients anticoagulated for a prolonged period of time. With time, however, the benefit may wane. One study of prolonged anticoagulation revealed that at 3 years there was no difference in recurrence rate in patients with PE who were anticoagulated for 6 months versus 1 year (11.2% vs 9.1%).[32] The likelihood of recurrent DVT was also similar at 3 years, with equivalent rates of recurrence in the 3-month treatment group and the 12-month treatment group.[33] Although these studies specifically look at defined periods of anticoagulation, in clinical practice the decision is usually 3 months versus lifelong anticoagulation as the risk does not change over time. It should be noted that prolonged periods of anticoagulation do not directly influence risk of recurrence but instead may only delay occurrence of a second event.[34]

The issue of length of anticoagulation is more clear-cut in those with increased risk of recurrent events. High-risk patients are those who have suffered from multiple episodes of recurrent VTE, those who have clotted while being anticoagulated, and those with acquired risk factors such as antiphospholipid antibodies or cancer-related events. Other high-risk groups are those with high-risk thrombophilias such as deficiency of protein S, protein C, or antithrombin and homozygous factor V Leiden mutation and compound heterozygous factor V Leiden/prothrombin gene mutation in the setting of an unprovoked event. Although it is controversial if these thrombophilias are associated with increased risk of recurrent events, the evidence would suggest that the rate of first VTE in these patients is not high enough to suggest initiation of anticoagulation without evidence of a clotting event.[13,35]

Balanced against the risk of thrombotic events is the bleeding risk associated with the use of anticoagulation. A recent large meta-analysis of major bleeding in patients on anticoagulation for longer than 3 months found a rate of 2.7 major bleeds per 100 patient-years. Concomitant medical conditions such as renal failure, diabetes-related cerebrovascular disease, malignancy, advanced age, and use of antiplatelet agents in addition to anticoagulation all increase the risk of experiencing bleeding. The risk for bleeding is highest when patients first initiate anticoagulation.[36] The risk of major bleeding has been estimated at 2.4% in the first 3 months of anticoagulation with warfarin.[37] Risk assessment models to determine bleeding scores have been developed, and a number of studies have demonstrated that these risk scores can be used to predict those at high risk of bleeding on anticoagulation.[38,39] A recent review of these studies has suggested that none of the scores accurately estimates risk of bleeding, although the RIETE score does offer some promise.[40] The RIETE score is a 6-point risk assessment for bleeding that includes age 75, recent bleeding, malignancy, creatinine clearance abnormalities, anemia, or PE at baseline.[39] Using this risk assessment, patients with VTE on anticoagulation can be categorized as low, intermediate, or high risk of major bleeding during anticoagulation.

The duration of anticoagulation after an unprovoked VTE has been contested for years, with the latest recommendations leaning away from lifelong anticoagulation. The 2012 ACCP guidelines recommend long-term anticoagulation for patients with minimal bleeding risk (Grade 1B).[41]

RISK STRATIFICATION FOR RECURRENT VTE

D-dimer levels are one of the more promising methods for assessing the risk of having a recurrent VTE if anticoagulation is stopped after completion of therapy. In most of the studies designed to date, patients complete 6 months of anticoagulation and then return to have a D-dimer level drawn 1 month after cessation of anticoagulation. A number of studies have demonstrated that patients with elevated D-dimer have increased risk for a recurrent event.[42–44] Measuring an actual value of the D-dimer provides no direct risk stratification guidance as it is the negative D-dimer that provides a high negative predictive value for risk of recurrence. Two predictive models that have been developed incorporate D-dimer testing into decision making.[45,46] The DASH predictive model relies on the D-dimer result in addition to age, male sex, and association with hormone therapy as a method of risk stratification for patients with a first unprovoked event. Using their scoring system, patients with a score of 0 or 1 had a recurrence rate of 3.1%, those with a score of 2 a recurrence rate of 6.4%, and those with a score of 3 or greater a recurrence rate of 12.3%. The authors postulate that by using this assessment scheme they can avoid lifelong anticoagulation in 51% of patients.

It has been demonstrated that a normal D-dimer level measured 1 month after cessation of anticoagulation offers a high negative predictive value for risk of recurrence.[47] In patients with an elevated D-dimer level after anticoagulation was stopped, there was a 5-fold increased risk of recurrence in comparison to those

Table 2. Risk of Venous Thromboembolism (VTE) in Inherited Thrombophilia

Thrombophilia	Annual Incidence of First VTE (%)
AT deficiency	1.52–1.90
Protein C deficiency	1.52–1.90
Protein S deficiency	1.52–1.90
Factor V Leiden	0.34–0.49
Prothrombin gene mutation	0.34–0.49

Data from Makris M. Thrombophilia: grading the risk. Blood 2009; 113:5038–9.

who received anticoagulation for a longer duration.[42] A recent meta-analysis by Douketis and colleagues demonstrated that in patients with a first unprovoked VTE, D-dimer levels can be used independent of timing of testing, patient age, and assay cut-off point to predict which group of patients is at higher risk.[48] Although these results may suggest that D-dimer can be used for risk stratification, lack of agreement and different cut-off points for the various D-dimer tests available limit its mainstream use. Its use is also limited by the fact that the D-dimer can be elevated for other reasons besides VTE.

Another model used for risk stratification is imaging analysis. Clinical assessment modules have been developed that incorporate repeat imaging studies for assessment of recanalization of affected veins. In patients with residual vein thrombosis (RVT) at the time anticoagulation was stopped, the hazard ratio for recurrence was 2.4 compared to those without RVT.[49] There are a number of ways RVT could impact recurrence, including impaired venous flow leading to stasis and activation of the coagulation cascade. Subsequent studies used serial ultrasound to determine when to stop anticoagulation. In patients who were anticoagulated for 3 months and had residual thrombus identified, anticoagulation was continued for up to 9 months for provoked VTE and 21 months for unprovoked VTE. In comparison to fixed dosing of 6 months of anticoagulation, those who had their length of anticoagulation tailored to ultrasonography findings had a lower rate of recurrent VTE.[50] Others, however, have suggested that RVT is not a valuable prognostic marker and that it should not be used for assessing risk of recurrence.[51] Limitations to using RVT in clinical decision making include lack of a standard definition of RVT and variability in both timing of ultrasound and interpretation of results.

Other risk factors that can impact risk of recurrence must also be taken into consideration, including obesity, male gender, location of the DVT, and underlying thrombophilia, all of which have been associated with increased risk of VTE.[30,52]

Another option that has been considered when managing long-term anticoagulation is to decrease the intensity of anticoagulation in patients who remain on extended warfarin therapy. Since this would theoretically lower the risk of bleeding, the perceived benefit would be reduction in both bleeding and clotting risk. The PREVENT trial set a target INR of 1.5 to 2.0 instead of 2.0 to 3.0 and compared rate of recurrent VTE in anticoagulated patients to that in patients treated with placebo. In the anticoagulation group, there was a 64% risk reduction in recurrent VTE and increased bleeding compared with placebo (hazard ratio, 1.92).[53] The ELATE study compared lower intensity anticoagulation with target INR 1.5 to 2.0 with full intensity warfarin and target INR 2.0 to 3.0. The conventional intensity group had a greater than 90% reduction in recurrent VTE events compared to roughly 60% with the lower target range, with no difference between groups in rates of major bleeding. This study, however, has been criticized because of its overall low bleeding rate in both treatment groups.[54]

An option in patients in whom anticoagulation needs to be avoided is the use of aspirin. The ASPIRE trial demonstrated that in patients with unprovoked VTE, the use of 100 mg of aspirin after completion of 6 months of anticoagulation therapy was associated with a 40% risk reduction of recurrent VTE in comparison to the placebo group.[55] The absolute risk was 1% in the placebo group and 6% in the aspirin group.

HYPERCOAGULABLE STATES

INHERITED THROMBOPHILIAS

Although most provoking risk factors can be predicted and appropriate prophylaxis can be provided, patients with a hereditary predisposition to VTE are considered at increased risk for VTE (**Table 2**). These inherited mutations result in either a loss of normal anticoagulant function or gain of a prothrombotic state. Hereditary disorders associated with VTE include deficiency of antithrombin, protein C, or protein S, or the presence of factor V Leiden or the prothrombin G20210A mutations. Although uncommon, affecting only 0.5% of the population, the presence of deficiency in protein C or S or antithrombin is associated with a 10-fold increased risk of incident VTE in comparison to the general population. Factor V Leiden mutation and prothrombin gene mutation are less likely to be associ-

ated with incident thrombosis (risk of VTE increased 2 to 5 times) and are more prevalent in the Caucasian population.[56] Ideally, a clinical trial would be designed to assess whether hereditary thrombophilia testing in comparison to no testing is beneficial for patients with VTE in decision making regarding length of anticoagulation, type of anticoagulation, or risk of recurrence.

ACQUIRED THROMBOPHILIAS

Antiphospholipid Syndrome

Antibodies directed against proteins that bind phospholipids are associated with an acquired hypercoagulable state. The autoantibodies are categorized as antiphospholipid antibodies (APLAs), which include anticardiolipin antibodies (IgG and IgM), beta-2 glycoprotein 1 antibodies (anti-B2 GP), and lupus anticoagulant. These antibodies can form autonomously, as seen in primary disorders, or in association with autoimmune disease as a secondary disorder.

Criteria have been developed to distinguish antiphospholipid-associated clotting disorders from other forms of thrombophilia. The updated Sapporo criteria depend on both laboratory and clinical diagnostic criteria. The laboratory diagnosis of APLAs requires the presence of lupus anticoagulants, anticardiolipin antibodies, or anti-B2 GP on at least 2 assays at least 12 weeks apart. Testing for lupus anticoagulant is based on 3 stages, the first of which is inhibition of phospholipid-dependent coagulation tests with prolonged clotting time (eg, aPTT or dilute Russell's viper venom time [DRVVT]). The diagnosis is confirmed by a secondary test in which excess hexagonal phase phospholipids are added to incubate with the patient's plasma to absorb the APLA. If the sensitive aPTT or dRVVT is normalized by the addition of exogenous phospholipids, the presence of a lupus anticoagulant is confirmed. Other tests that are helpful in making the diagnosis of a lupus anticoagulant include the DRVVT and kaolin clotting time.[57] The presence of anticardiolipin antibodies and anti-B2 GP is determined using ELISA-based immunoassays. Medium and high titers are required for diagnosis. Unlike most other thrombophilias, antiphospholipid syndrome is associated with both arterial and venous thromboembolic events and may be an indication for lifelong anticoagulation after the first thrombotic event. The appearance of transiently positive ALPA testing is of unclear significance.

Cancer-Associated Hypercoagulable State

Patients with cancer have a propensity for thromboembolic events. The type of cancer as well as chemotherapeutic agents used are associated with different rates of VTE. Approximately 25% of all cancer patients will experience a thrombotic event during the course of their disease.[58] In fact, the presence of a spontaneous clot is often a harbinger for an underlying cancer.[59] Approximately 10% of patients who present with an idiopathic VTE are diagnosed with cancer in the next 1 to 2 years.

The utility of extensive screening for occult malignancy in patients with spontaneous clotting events is often debated. The small studies that have addressed cancer-associated clots have not demonstrated any mortality benefit of extensive screening. A prospective cohort study was performed recently to further address the utility of limited screening.[60] In this study, all patients underwent a series of basic screening tests such as history taking, physical examination, chest X-ray, and basic laboratory parameters. Approximately half of the patients underwent additional testing that involved CT of the chest and abdomen and mammography for women. In this study, screening did not result in significant lives saved, as 3.5% of patients in the extensive screening group were diagnosed with cancer in comparison to 2.4% in the limited screening group. In follow-up, cancer was diagnosed in 3.7% and 5.0% in the extensive and limited screening groups, respectively. The authors concluded that the low yield of extensive screening and lack of survival benefit did not warrant routinely ordering cancer screening tests above and beyond age-appropriate screening in patients with idiopathic VTE. It is clear, however, that screening can be useful for identifying cancer at an earlier stage of disease. Not surprisingly, cancer that is discovered within the year of the VTE episode is usually at a more advanced stage.[61] It is our practice to take a through history from patients with unprovoked clots particularly focusing on symptoms suggestive of an underlying cancer. We recommend that patients be up to date with all age-appropriate cancer screening.

The underlying mechanisms responsible for cancer-associated clotting events are multifactorial and an area of intense research. Tumor cells can initiate activation of the clotting cascade through release of tissue factor and other procoagulant molecules.[62] In addition, the tumor itself can compress vasculature leading to venous stasis. Furthermore, chemotherapy, hormone therapy, antiangiogenic drugs, erythropoietin agents, and indwelling central venous catheters all are associated with increased risk of thrombotic events.

The use of heparin has been shown to have potential anticancer effects; this benefit extends beyond its anticoagulation properties. It is believed that heparin use in patients with cancer can influence cancer progression by acting as an antimetastatic agent. The

molecular mechanisms underlying this significant observation are not completely understood, although the first documented benefit of these drugs dates back to the 1970s.[63] In reviews and meta-analysis, exposure to LMWH improved overall survival in cancer patients with VTE and this effect is distinct from its ability to prevent life-threatening VTE episodes.[64]

Estrogen-Related Thromboembolic Disease

Pregnancy is a well established acquired hypercoagulable state, and thromboembolic disease accounts for significant morbidity and mortality in pregnancy and the postpartum period. Approximately 1 in 1000 women will suffer from a thrombotic event during pregnancy or shortly after delivery. The etiology of the tendency to clot during pregnancy is multifactorial but mainly reflects venous stasis due to vasculature compression by the uterus, changes in coagulation factors as the pregnancy progresses, and endothelial damage during caesarian section.[65] Both factor VIII and von Willebrand factor levels increase, especially in the final months of pregnancy. Simultaneously, levels of the natural anticoagulant protein S diminish, leading to an acquired resistance to activated protein C which results in increased levels of thrombin generation and therefore a hypercoagulable state.[66] The risk of thrombosis in pregnancy is clearly heightened in women with inherited thrombophilias, especially in the postpartum period.

Similarly to pregnancy, hormone-based contraceptive agents and estrogen replacement therapies are also associated with increased thrombotic risk. Over the years, drug manufacturers have tried to mitigate the clotting risk associated with these drugs by reducing the amount of estrogen and altering the type of progesterone used, yet a risk still remains, resulting in a VTE incidence 2 to 7 times higher in this patient population.[67] Women with inherited thrombophilias who use oral contraceptives are especially at risk, with an incidence of VTE 4 times higher. The risk is highest in the first 4 months of use and is unaffected by duration of use. The risk extends for 3 months after cessation of estrogen-containing therapy. Although routine screening for thrombophilia is not offered to women before prescribing oral contraceptives, a thorough personal and family history should be taken to evaluate thromboembolic risk factors.

SUPERFICIAL VTE

Although the main disorders that comprise VTE are DVT and PE, another common presentation is superficial venous thromboembolism (SVT). SVT is not associated with excessive mortality, and the main concern with it is progression to DVT.[68] The risk factors for developing an SVT are similar to those for DVT, including immobilization, trauma, obesity, pregnancy or hormone use, and cancer. In addition, varicose veins also increase the incidence of developing SVT.[69] It is difficult, however, to determine which patients are at risk for developing DVT. One of the risk stratification models that has been employed considers clot location. Since SVT clots usually develop in the saphenous vein, the clot would need to progress from the saphenofemoral junction to the common femoral vein; thus, any clots located near the saphenofemoral junction are at risk of progressing into the deep vasculature.[70] Lohr and colleagues demonstrated that any clots within 3 cm of the junction were most likely to progress to DVT and therefore these patients benefited from aggressive anticoagulation.[71,72] Others have taken a more general approach, stating that all clots above the knee or in the thigh area should be treated aggressively.[70,73]

Recently, the use of anticoagulation in the treatment of SVT has shown promise. A Cochrane review included 30 studies involving over 6500 participants who had SVT of the lower extremities. The treatments used in these studies included fondaparinux, LMWH, unfractionated heparin, nonsteroidal anti-inflammatory agents, topical treatment, and surgery. According to the review's findings, the use of fondaparinux at prophylactic dosing for 6 weeks was considered a valid therapeutic option for SVT.[74] Other studies have also demonstrated the benefit of parenteral agents in the treatment of SVT. In the STEFLUX (Superficial ThromboEmbolism and Fluxum) study, the optimal dose and duration of LMWH for treatment of SVT was assessed.[75] In this study, patients received parnaparin either 8500 IU once daily for 10 days followed by placebo for 20 days or 8500 IU once daily for 10 days and then 6400 IU once daily for 20 days, or 4250 IU for 30 days. Those who received the intermediate dosing of 6400 IU for 30 days had superior resolution and no progression of their SVT. In the CALISTO trial, the anticoagulant fondaparinux at a dose of 2.5 mg per day for 45 days was an effective treatment option for patients with SVT without serious side effects.[76] Based on these and other studies, it is now common practice to consider the use of anticoagulants as part of the treatment regimen for SVT.

NEW ANTICOAGULANTS AND TREATMENT OF VTE

Because of warfarin's narrow therapeutic window, need for frequent monitoring, significant drug and

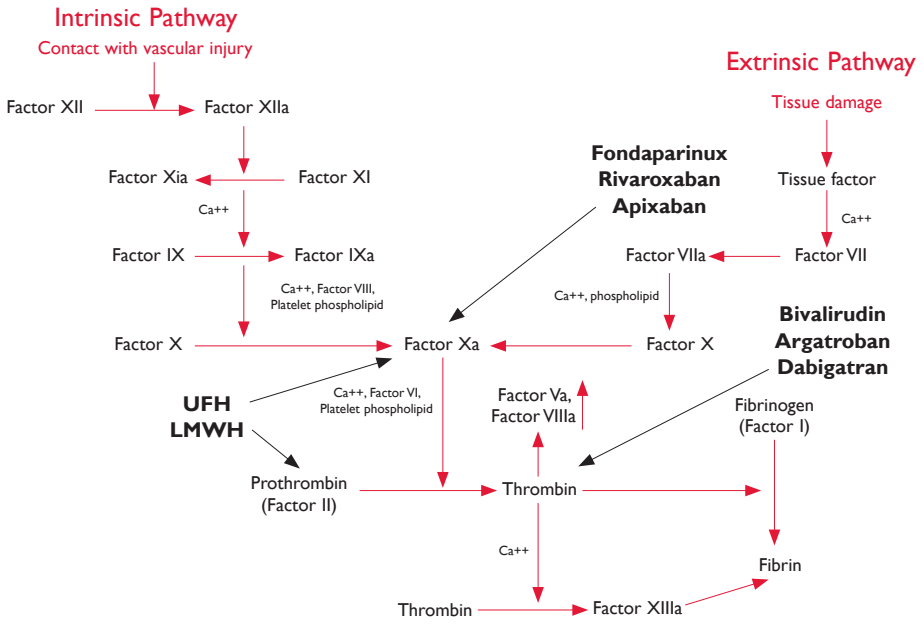

Figure. The coagulation cascade and anticoagulants.

food interactions, and unfavorable kinetics, new oral anticoagulants have been developed with the aim of offering alternatives to warfarin therapy (**Figure**). These drugs have been developed to inhibit either thrombin or factor Xa to disrupt the coagulation cascade. Since these drugs bind directly to coagulation factor, they are associated with rapid onset of action, mitigating the need for bridging anticoagulation; they also have a wide therapeutic window, few drug interactions, and predictable dose-response allowing for fixed doses, and require no lab monitoring.

The oral direct thrombin inhibitor dabigatran directly binds to thrombin in a concentration-dependent manner.[77,78] Peak plasma concentration is achieved within 0.5 to 2.0 hours after ingestion, and its half-life is 12 to 17 hours. Use of dabigatran in both primary and secondary prevention of VTE has been extensively studied, especially in orthopedic surgery, in which there were 4 main trials: RE-MOBILIZE, RE-MODEL, RE-NOVATE, and RE-NOVATE II. RE-MODEL and RE-NOVATE I and II have demonstrated that dabigatran was noninferior to enoxaparin for prevention of VTE in patients undergoing total knee replacement and hip replacement.[79–81] The side effect profile was also promising, with no significant differences in the frequency of major bleeding between dabigatran and enoxaparin. Studies that pooled the data from these clinical trials or performed meta-analysis of these studies demonstrated that for prevention of VTE associated with hip or knee surgery, dabigatran 150 mg orally twice daily was as effective as 40 mg of enoxaparin given daily or 30 mg given twice a day.[82–84]

Recently, these drugs have been studied not only as primary prophylaxis of VTE after total knee replacement and total hip replacement surgeries, but also in the acute treatment and secondary prevention of VTE. In the RE-COVER trial, the use of dabigatran 150 mg twice daily was compared to warfarin (INR 2–3) in the treatment of acute VTE for 6 months, after an initial treatment period of up to 9 days with LMWH or unfractionated heparin. The results demonstrated that dabigatran was noninferior to warfarin for treatment of acute VTE (hazard ratio [HR] for thrombosis, 1.10; 95% confidence interval [CI], 0.65 to 1.84) and had a similar side effect profile (HR for major bleeding, 0.71; 95% CI, 0.59 to 0.85).[85] The RE-SONATE trial specifically addressed the use of dabigatran to prevent recurrence of thrombosis. In this trial dabigatran was compared to placebo for the 6- to 18-month time period after completion of standard warfarin therapy, resulting in a 93% risk reduction of recurrent VTE.[86] The RE-MEDY trial compared dabigatran to warfarin (with target INR of 2–3) for prevention of recurrent VTE in the 6 to 36 months after completion of therapy and demonstrated that recurrent VTE occurred slightly more frequently in those on dabigatran (1.8%) in comparison to warfarin

(1.35%). Overall analysis demonstrated that dabigatran was noninferior to warfarin and was associated with a decreased risk of bleeding (relative risk reduction of 46%, $P<0.001$).[85] Unexpectedly, the risk of acute coronary syndrome was slightly higher in the dabigatran group than the warfarin group, as seen in other studies (RE-LY).

Rivaroxaban, a novel oral anticoagulant that targets factor Xa, has also been shown to be effective in preventing VTE in patients after knee or hip surgery. The RECORD 1–4 studies all focused on the use of rivaroxaban in comparison to enoxaparin and found that rivaroxaban was superior to enoxaparin in prevention of VTE in total knee and hip arthroplasty.[87–89] Meta-analysis of the RE-CORD studies and pooled studies also demonstrated that rivaroxaban significantly lowered the risk of VTE in these surgical patients in comparison to enoxaparin.[87]

The use of rivaroxaban for primary prevention of VTE in acutely ill hospitalized patients was studied in the MAGELLAN trial. This trial was designed to assess the optimal duration of prophylaxis and whether extended rivaroxaban therapy beyond 5 weeks was better than standard-duration enoxaparin. In this trial, rivaroxaban was compared to enoxaparin (40 mg daily) followed by placebo and was found to be noninferior to enoxaparin in reduction of VTE risk at day 10 and superior to enoxaparin at day 35.[90] The rate of bleeding, although low in both arms, was slightly higher in the rivaroxaban arm.

Rivaroxaban has also been studied in randomized phase III clinical trials for acute treatment of DVT and PE and for extended prophylaxis for recurrent VTE (EINSTEIN-DVT, EINSTEIN-PE, and EINSTEIN-extension). The treatment strategy for use of rivaroxaban differed from that of dabigatran (in RE-COVER trial) as rivaroxaban was used upfront as initial anticoagulation rather than after an initial period of parenteral therapy; there was no initial use of LMWH or unfractionated heparin. In both the DVT and PE trials, rivaroxaban was noninferior to standard treatment with enoxaparin (10 days of treatment) followed by warfarin therapy, with no significant difference in major bleeding at 6 months of treatment.[91,92] The extension trial also demonstrated that use of rivaroxaban in comparison to placebo for 6 to 12 months after standard therapy was associated with a risk reduction of 82%.[93] These studies led to FDA approval of rivaroxaban for primary prevention of VTE in patients undergoing elective total hip or knee repair surgery, for treatment of acute DVT or PE, and for extended prophylaxis in patients following initial treatment.

Recently, apixaban was approved for use in Canada and Europe and is under consideration in the United States for treating VTE. In the AMPLIFY study, apixaban as monotherapy was noninferior to LMWH followed by warfarin, with a significant decrease in bleeding rates for acute treatment of VTE; apixaban demonstrated superiority to placebo for extended prophylaxis in AMPLIFY-EXT. Two doses of apixaban, 5 mg twice daily and 2.5 mg twice daily, were studied in AMPLIFY-EXT. Remarkably, the bleeding rate for the 2.5 mg twice daily dose was the same as that for placebo.[94–96]

These novel anticoagulants should be used with caution, however, because currently there are no specific antidotes to reverse their effects. If significant bleeding manifests and cannot be controlled by usual maneuvers such as mechanical compression or surgical intervention, then limited options remain. Recently, rivaroxaban was demonstrated to be partially reversible by prothrombin complex concentrate, whereas this approach was not as successful for the drug dabigatran in healthy volunteers.[97,98] Plasma dabigatran levels can be reduced through the use of hemodialysis. Recently, antibodies capable of neutralizing dabigatran have been developed.[96] At present, the use of nonspecific hemostatic agents is suggested for reversal of these agents in patients who present with life-threatening bleeding.[99] This includes the use of recombinant factor VIIa, 4-factor prothrombin complex concentrate, and activated prothrombin complex concentrates.

TRAVEL AND THE RISK OF VTE

The pathogenesis underlying travel-associated VTE is controversial but is mainly thought to be related to a period of immobilization leading to venous stasis.[100] It is estimated that air travel increases the risk of thrombosis 2- to 4-fold.[101–103] This, however, appears to be dependent on the actual length of time in the airplane, as one study has estimated that the risk increases by 26% for each 2-hour period of air travel. This risk can last up to 8 weeks after the period of travel, putting travelers at risk during their time away from their usual mode of medical care. Because of this risk, passengers are often warned about the importance of ambulation and given exercises to perform and hydration requirements by their physicians. These factors can be exacerbated by consumption of alcoholic beverages or sedative medications which lead to further inactivity. Those with preexisting risk factors for VTE appear to be at greater risk during air travel; these factors include recent trauma or surgery, previous VTE, varicose veins, active malignancy, hormone therapy, or obesity.[104]

The actual time of air travel that increases the risk of VTE is uncertain. Recently, it has been demonstrated that there was an estimated 3.9-fold increased risk of VTE in passengers who traveled for longer than 8 hours. Others have suggested that the risk of air travel is cumulative. MacCallum and colleagues demonstrated that compared to not flying, cumulative air travel time of greater than 12 hours within a previous 4-week period was associated with a 3-fold increased risk of VTE.[105] The risk, however, was temporary, with the risk of having a VTE returning to baseline levels by 12 weeks.

For patients in which the risk of VTE at the time of travel is of concern because of prior events, it is reasonable to consider the use of anticoagulation. Since this is not a well studied area of VTE research, little is known regarding use of prophylactic anticoagulation, appropriate agent, intensity, or length of anticoagulation. The recently released ACCP guidelines provide support for the use of anticoagulation. For long-distance travel for patients who have had previous VTE, recent trauma or surgery, active malignancy, or a thrombophilia, they recommend increased ambulation, compression stockings, and calf muscle exercises while flying (Grade 2C). These guidelines do not suggest the use of anticoagulants or aspirin in this patient population. More research is needed to determine whether the use of anticoagulants during air travel can prevent VTE episodes.

CONCLUSION

Patients with VTE present with a wide range of findings and factors that impact management. Decision making in VTE management is a fluid process, which should be re-evaluated as new data emerge and individual circumstances change. There is more focus on VTE prevention and treatment today than there was even a decade ago. Diagnostic algorithms, identification of newly identified risk factors, refinement in understanding of the pathogenesis of thrombosis, and identification of new anticoagulants with more favorable risk-benefit profiles will all ultimately contribute to improved patient care.

BOARD REVIEW QUESTIONS

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