Thrombotic Risk Factors

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Clinical Vignette 1

A 68-year-old man with past medical history notable only for hypertension and well-controlled diabetes mellitus presents with right lower leg swelling and pain. He denies recent prolonged travel, surgery, or trauma. He denies shortness of breath or chest pain. Ultrasound reveals occlusive thrombus extending from the popliteal vein proximally into the common femoral vein.

Introduction

Incidence of venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is around 100 cases per 100,000 population, based on studies in predominantly Caucasian populations, with slightly lower risks in registries focused on Hispanic, African Americans, and Asian populations (White 2003). Incidence rises with increasing age (White 2003; Naess et al. 2007).

Pathophysiologic understanding of VTE is largely credited to Rudolph Virchow, whose mid-nineteenth century writings challenged the prevailing concept that pulmonary emboli originated in situ and demonstrated their origins in the peripheral venous system. His description of the consequences of pulmonary emboli included "phenomena due to the irritation of the vessel and its surroundings…phenomena due to blood coagulation…[and] phenomena due to the interruption of the bloodstream" (Virchow 1998; Kumar et al. 2010). Through his and others' work, "Virchow's Triad" of wall stress, hypercoagulability, and stasis later became known as classic risk factors for VTE. Subsequent work has deepened and broadened the mechanistic understanding of VTE, including emphasis on the roles of low oxygen tension in stasis, activation of the endothelium, activation of innate and acquired immune systems, platelet activation, and levels of pro- and anticoagulant proteins (Reitsma et al. 2012). Understanding of the contributions of these factors to VTE risk in individuals and in particular disease states continues to evolve.

Here we present a summary of VTE risk factors for the clinician, stressing the relative importance and clinical impact of each. We begin with the factors that confer highest VTE risk and move towards those that are less significant. In presenting incidence and relative risk, we focus primarily on *symptomatic* VTE; incidence of asymptomatic VTE may be much higher but has less clinical relevance. Available data are complicated by methodological differences in detection of events and differing thresholds for considering VTE "symptomatic."

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Although certain risk factors may be listed as "minor," it is important to note that even minor risk factors are additive and multiple minor risk factors together can create substantial risk for VTE. This is particularly important when risk factors have multiplicative interactions, as with Factor V Leiden or prothrombin G20210A heterozygosity and use of combined oral contraceptives.

Approach to the Newly Diagnosed DVT or PE

A critical step in evaluation of a patient with a first VTE event is determination of whether the event is provoked or unprovoked. This classification helps determine risk of recurrence if anticoagulation is stopped and therefore informs duration of therapy. The definition of "unprovoked" varies as used in the literature, but generally refers to VTE in the absence of a transient risk factor such as recent trauma or major surgery. Patients with unprovoked VTE have higher recurrence risk than those with provoked VTE. It is this determination that will most strongly influence recommendations around duration of therapy, and therefore, significant effort should be made to identify contributing risk factors. In the setting of average risk of bleeding, patients with even a single unprovoked VTE are now considered candidates for indefinite anticoagulation, while those with VTE related to transient risk factors receive a minimum of 3 months of therapy (Kearon et al. 2012).

For up to 75 % of patients with VTE, at least one risk factor can be identified (White 2003). Routine testing of all patients with VTE for laboratory thrombophilia is discouraged, as such testing is unlikely to change the course of management in many cases. However, the following questions may help determine whether further evaluation is likely to be helpful for an individual patient:

- Will further evaluation change duration of therapy? A determination of a major inherited or acquired thrombophilia may warrant indefinite anticoagulation. For otherwise healthy younger patients with apparently unprovoked VTE, suspicion for thrombophilia may be higher and lead to further evaluation. A strong family history or an event that occurs after only mild provocation may increase suspicion for an underlying hypercoagulable state.
- Is the patient considering pregnancy? Laboratory thrombophilia may have important prognostic significance with regard to pregnancy complications and outcomes, and identification may result in recommendations for anticoagulation or antiplatelet therapy in the antepartum and peripartum period.

A search for malignancy is indicated in patients presenting with unprovoked VTE who are 50 years of age or older and in those with recurrent VTE despite anticoagulation. Cancer-related VTE calls for ongoing treatment with low-molecular-weight heparin instead of transition to warfarin.

The patient in Clinical Vignette 1 has had an unprovoked first VTE at age 68. As this was an unprovoked, proximal DVT, the patient would be considered for indefinite anticoagulation in the absence of contraindications, and further evaluation for thrombophilia is unlikely to change this recommendation. However, given his age, occult malignancy is a concern and would change the type of anticoagulation recommended. Further evaluation should focus on determination of additional historical risk factors for VTE and/or malignancy (such as tobacco use) and age-appropriate malignancy screening. Review of laboratory studies including complete blood count, electrolytes, and renal and hepatic function may also suggest abnormalities warranting further evaluation.

Major VTE Risk Factors

Clinical Vignette 2

An 80-year-old woman is admitted for hip fracture following a mechanical fall; 3 days later she is taken to the operating room for an open reduction and fixation. VTE prophylaxis with low-molecular-weight heparin is initiated on hospital day 4 (postoperative day 1). On hospital day 5 (postoperative day 2), she develops acute shortness of breath; a CT of the chest with contrast reveals bilateral segmental pulmonary emboli.

Major Orthopedic Surgery: Hip Fracture, Hip Repair, Knee Repair

Major surgery and trauma confer strong risks for VTE (Table 12.1). Arthroplastic orthopedic surgery of the hip or knee carries especially high VTE risk; up to 50 % of patients undergoing total knee or total hip replacements develop DVT and/or PE, although only 5 % or fewer are symptomatic (Anderson and Spencer 2003; Falck-Ytter et al. 2012). Improvements in surgical technique over the past decade leading to less thrombogenic protocols and routine use of prophylaxis have reduced postoperative VTE risk considerably. Limited data suggest that the risk of VTE following hip arthroplasty is greater than that for arthroplastic knee surgery (Falck-Ytter et al. 2012). Risk is increased with application of a tourniquet for over 60 min (Bergqvist and Lowe 2002).

VTE risk is highest immediately after surgery but remains elevated for several weeks. Approximately two thirds of VTE events detected in the 35-day postoperative period occur within the first 2 weeks, but up to 70 % of VTE events are not detected until after hospital discharge, and risk may not return to baseline until approximately 3 months after surgery. This period may be somewhat shorter in patients undergoing knee arthroplasty than in patients undergoing hip arthroplasty (Falck-Ytter et al. 2012; White et al. 1998; Bjornara et al. 2006). Duration of risk varies individually with degree of persistent immobility and presence of additional risk factors.

Table 12.1 Risk factors for venous thromboembolism

Major (odds ratio 10 or higher)	Moderate (odds ratio 2–9)	Minor (odds ratio 2 or lower)
Fracture (hip or leg)	Arthroscopic knee surgery	Laparoscopic surgery
Hip or knee replacement	Central venous lines	Bed rest (at least 3 days)
Major general surgery	Chemotherapy	Travel >4 h
Major trauma or spinal cord injury	Oral contraceptives	Increasing age
	Hormone replacement therapy	Obesity
	Malignancy	Pregnancy (antepartum)
	Paralytic stroke	Varicose veins
	Pregnancy (postpartum)	Tobacco use
	Previous venous thromboembolism	Dyslipidemia
	Thrombophilia	Poorly controlled diabetes
	Autoimmune disease	Chronic renal disease
	Nephrotic syndrome	
	Congestive heart failure	
	Respiratory failure	

Adapted with permission from Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9–16

Major General Surgery

While minor or outpatient procedures confer minimal DVT risk, the risk increases with major general surgery, generally defined as abdominal or thoracic surgeries involving at least 30 minutes of anesthesia (Anderson and Spencer 2003; Gould et al. 2012). Open gynecologic and urologic surgeries, as well as invasive neurosurgery, also carry particularly elevated VTE risk (Gould et al. 2012; White 2003). Patients undergoing open abdominal or pelvic surgery for cancer appear to be at highest risk, while less invasive operations such as inguinal hernia repair and mastectomy confer lower risk (Gould et al. 2012). Patients undergoing laparoscopy may have less tissue trauma, be mobilized earlier, and have shorter hospital stays than those with open surgeries, leading to lower risk for VTE (Bergqvist and Lowe 2002).

Presence of additional risk factors including cancer, advanced age, medical comorbidities, and complications of surgery contributes to VTE risk in surgical patients (Gould et al. 2012).

Trauma

VTE is a common complication of major trauma. In general, patients with higher severity of injuries are at elevated risk for DVT and PE; a prospective study of trauma patients admitted with an injury severity score of at least 9 found DVT in 58 %, although very few of these were symptomatic (Geerts et al. 1994).

In addition to general severity of trauma, specific types of trauma appear to pose additional risk, including fractures in the lower extremities, vascular injury, and spinal cord injury (Gould et al. 2012; Geerts et al. 1994). Studies from the early 1990s indicate an incidence of DVT (symptomatic and asymptomatic) approaching 40 % over 3 months following injury, with a 5 % incidence of PE (Anderson and Spencer 2003). Risk of VTE following spinal cord injury is highest immediately following the event and over the 2 weeks following injury, but persists throughout the rehabilitation period (Gould et al. 2012).

Prolonged immobilization and surgery compound the risk of VTE in trauma patients. However, the risk posed by immobility alone is much lower, as discussed below; thus other mechanisms related to the effect of trauma and inflammation on hypercoagulability are also likely to be at play.

The patient in Clinical Vignette 2 is at high risk for VTE based on her age and the type of injury she has sustained compounded by her immobility preoperatively while in hospital awaiting her procedure. Attention should be paid to VTE risk factors both pre- and postoperatively in these patients, and prophylaxis should be administered to those not proceeding immediately for surgical repair (Falck-Ytter et al. 2012).

Moderate Risk Factors

Major Inherited and Acquired Thrombophilias

The major inherited and acquired thrombophilias are antiphospholipid syndrome; deficiencies of protein C, protein S, or antithrombin; and hyperhomocysteinemia. Inherited genetic mutations including Factor V Leiden and the prothrombin G20201A gene mutation, though common, do not alone confer high VTE risk. However, they gain importance in conjunction with additional risk factors particularly in the homozygous form or in combination with each other (heterozygous Factor V Leiden and heterozygous prothrombin gene mutation).

Extensive testing for thrombophilia, though often performed, may not be helpful in patients for whom indefinite anticoagulation is indicated regardless of test result. Onset of VTE in older patients is much more likely to be associated with malignancy than with an acquired or inherited thrombophilia; therefore, evaluation in these patients should focus on age-appropriate cancer screening and a careful review of patient history

and recent laboratory work to elicit data that may suggest need for additional testing. For younger patients with unexplained VTE and higher probability of thrombophilia, testing may be warranted to help with understanding of risks and benefits associated with discontinuing anticoagulation. Testing may also have additional benefit in patients with strong family history for VTE for whom other family members may be affected by results. For women of childbearing age who present with VTE, testing carries particular importance given the need for planning around potential pregnancies.

Some patients may present a clinical picture suggestive of a major thrombophilia, and in these cases testing may help to confirm the diagnosis and plan treatment. For instance, a younger patient with arterial and venous thrombosis and/or recurrent pregnancy loss should be evaluated for antiphospholipid syndrome. Other conditions that may cause arterial and venous thrombosis include paradoxical embolism, hyperhomocysteinemia, hyperviscosity syndrome, malignancy, concurrent vascular disease, heparin-induced thrombocytopenia/thrombosis (HIT), myeloproliferative disorder, PNH, and disseminated intravascular coagulation (DIC) (Table 12.2). Recurrent thrombosis despite therapeutic anticoagulation raises suspicion for antiphospholipid syndrome, cancer, DIC, Trousseau's syndrome, HIT, and structural defects.

Testing for thrombophilia in patients taking anticoagulation or who have acute thrombosis or other inflammatory processes may provide misleading results (Table 12.3). In general, any testing should be performed selectively and ideally delayed until after the acute phase (first 1–3 months) following a VTE event.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is due to the acquisition of antibodies against phospholipids or phospholipid-binding proteins. Clinically APS may include any combination of arterial thrombosis, venous thrombosis, and recurrent pregnancy loss; it may also cause small-vessel disease and preterm delivery associated with preeclampsia or fetal growth restriction. Unlike other causes of VTE, APS may cause complications in any vascular bed and can (rarely) manifest catastrophically with multiorgan failure (Ruiz-Irastorza et al. 2010). Diagnosis is based on occurrence of clinical manifestations along with

Table 12.2 Causes of arterial and venous thromboembolism

Causes of arterial and venous thromboembolism
Hyperviscosity syndromes Sickle cell Multiple myeloma Waldenstrom's macroglobulinemia
Antiphospholipid syndrome
Hyperhomocysteinemia
Heparin-induced thrombocytopenia and thrombosis (HITT)
Disseminated intravascular coagulation (DIC)
Cancer
Paradoxical embolism
Popliteal artery aneurysm
Behcet's disease
Thromboangiitis obliterans (Buerger's disease)
Paroxysmal nocturnal hemoglobinuria
Nephrotic syndrome
Inflammatory bowel disease
Myeloproliferative disorders
Polycythemia vera
Essential thrombocytosis

Table 12.3 Caveats in laboratory testing for thrombophilia

	Confounding factors		
Assay for laboratory thrombophilia	Acute thrombosis	Heparin therapy	Coumadin therapy
Antithrombin	Can be lowered	Lowered	May be increased
Lupus anticoagulant	Potential false positives and false negatives	False positives/false negatives reported	False positives possible
Protein C	Can be lowered	No effect	Lowered
Protein S	Can be lowered	No effect	Lowered
Factor V Leiden mutation (PCR)	No effect	No effect	No effect
Prothrombin mutation (PCR)	No effect	No effect	No effect

persistently positive antibodies (beta 2 glycoprotein and anticardiolipin antibodies) or lupus anticoagulant on laboratory testing performed at least 12 weeks apart (Miyakis et al. 2006).

Probability of APS varies depending on the population. APS is more common in young to middle-aged women and in patients with autoimmune disorders, particularly systemic lupus erythematosus (SLE).

While antiphospholipid antibodies may be detected in about a quarter of patients with VTE who have positive laboratory testing for thrombophilia (Roldan et al. 2009), it is *persistent* positivity of antibodies or lupus anticoagulant assays that increases risk of future VTE. Otherwise healthy individuals with persistently positive antiphospholipid antibodies have odds for VTE of up to about ten times that in the general population; this risk varies with antibody titres and antibody category (Wahl et al. 1998). Risk is substantially higher in the setting of autoimmune disease in general and systemic lupus erythematosus (SLE) in particular; nearly 40 % of SLE patients with antiphospholipid antibodies develop VTE (Ruiz-Irastorza et al. 2010; Love and Santoro 1990).

Among antiphospholipid antibody groups, lupus anticoagulant remains the strongest predictor of thrombosis. Risk is further elevated in the presence of multiple categories of elevated antiphospholipid antibodies (Ruiz-Irastorza et al. 2011). Testing guidelines have evolved; as of this writing, recommended evaluation for antiphospholipid antibodies includes lupus anticoagulant, anticardiolipin IgG and IgM antibodies, and beta-2-glycoprotein IgG and IgM antibodies. Testing should be repeated at least 12 weeks from the initial assay to demonstrate persistence (Ruiz-Irastorza et al. 2010). Accuracy of testing is confounded by concurrent anticoagulation, particularly for lupus anticoagulants, with both false positive and false negatives being reported.

Protein S Deficiency

Protein S, a vitamin K-dependent clotting protein, complexes with activated protein C to inactivate Factors Va and VIIIa. It exists both as a free protein (60 %) and as a complex with C4b-binding protein (C4b-BP) and may be quantitatively measured by free and total antigen levels. Deficiencies of protein S activity may be due to qualitatively low levels of protein S itself (type I), dysfunctional protein S leading to a qualitative deficit with normal antigen levels but decreased activity (type II), or quantitative deficit caused by abnormal or excessive C4b-BP binding, leading to low free-protein S antigen levels but normal total levels (type III). Most of the over 100 known mutations (93 %) cause quantitative (type I or III) deficiencies (Moll 2006).

Prevalence of protein S deficiency was 7.5 % in a study of 4,494 patients with VTE who underwent thrombophilia testing and was slightly higher (9 %) in the group of patients under age 50 (Roldan et al. 2009). However, a number of concurrent conditions may decrease protein S concentrations, leading to misdiagnosis of inherited protein S deficiency. These include concurrent use of a vitamin K antagonist, liver disease, oral contraceptive use, pregnancy, nephrotic syndrome, acute thrombosis, and DIC. Activated protein C resistance as seen in patients with Factor V Leiden mutation can lead to falsely low protein S functional assay value. Sickle cell trait can cause decreased protein S activity.

Protein C Deficiency

Protein C, a vitamin K-dependent protein, complexes with protein S when activated and inactivates Factors Va and VIIIa. Protein C deficiency may involve a quantitative deficit in protein C (type I, about 85 % of cases) or a qualitative deficiency with low activity (type II) (Moll 2006). The prevalence of protein C mutations in the population has been documented at 1 in 500 to 1 in 600 (Tait et al. 1995), but protein C deficiency is diagnosed in only around 4 % of patients with VTE (Roldan et al. 2009). While numerous mutations may cause deficiency of protein C, homozygous mutation causes catastrophic complications at birth and thus is unlikely to be diagnosed later in life. Testing for protein C antigen levels identifies patients with quantitative (type I) deficiency, but testing for protein C activity is needed to identify both qualitative and qualitative deficits.

Unfortunately a number of concurrent factors may lead to erroneous diagnosis of decreased protein C activity. The most common of these is concomitant use of a vitamin K antagonist, which decreases protein C activity since the protein is vitamin K dependent; testing must be done after 2–3 weeks off anticoagulation. High levels of Factor VIII and presence of lupus anticoagulant may produce falsely decreased protein C activity levels (Moll 2006).

Antithrombin Deficiency

Antithrombin (AT, previously referred to as antithrombin III) is a natural anticoagulant which prevents clotting by inhibiting thrombin and other clotting proteins. Heparin accelerates antithrombin's normally low level of inhibitory activity; hence, AT's role is as a heparin cofactor. Clinical antithrombin deficiency may be due to low levels of antithrombin (type I) or a dysfunctional protein leading to normal levels but low activity (type II). Deficiency of antithrombin is inherited in an autosomal dominant pattern with variable penetrance, and over 100 mutations affecting antithrombin production or activity have been identified (Moll 2006).

Although uncommon (found in 1:600 in the general population (Tait et al. 1994) and 1–3 % of patients with VTE) (Roldan et al. 2009; Pabinger et al. 1992; Heijboer et al. 1990), deficiency of antithrombin carries strong risk for VTE. As with protein C and protein S, defects in antithrombin activity may be missed if only antigen level is tested; therefore, activity level is also recommended. Antithrombin levels may be decreased in the settings of acute thrombosis and heparin administration. Levels may also be decreased by impaired synthesis in liver failure and by increased excretion in nephrotic syndrome. Warfarin administration may lead to increased AT levels, causing a falsely normal result (Moll 2006).

Hyperhomocysteinemia

Elevated levels of plasma homocysteine are associated with both venous and arterial thrombosis. However, the causal relationship between homocysteine and VTE remains unclear. While mutations in the methylenetetrahydrofolate reductase (MTHFR) gene can cause hyperhomocysteinemia, they have not been shown in meta-analyses to be associated with VTE events in the absence of hyperhomocysteinemia (Den Heijer et al. 2005; Ray et al. 2002). While testing for hyperhomocysteinemia may help clarify a patient's risk for VTE and other vascular events, testing for MTHFR mutations is not currently recommended. The utility of testing for hyperhomocysteinemia is also limited by the fact that lowering levels does not decrease risk for future events.

Factor V Leiden and Prothrombin Gene Mutations

The Factor V Leiden mutation, which confers resistance to activated protein C and involves a single amino acid exchange in position 506 of the Factor V molecule, is the most common identified inherited thrombophilia. It is found in about 5 % of the US American population, with lower prevalence among groups without European Caucasian ancestry (Moll 2006). While relative risk of VTE in people heterozygous for Factor V Leiden is about three times the risk in people without the mutation, absolute risk remains fairly low (<1 % per year). Risk is about 18-fold higher in people homozygous for the mutation, however (Segal et al. 2009).

The prothrombin 20210 point mutation is a gain-of-function mutation leading to increased levels of circulating prothrombin, which in turn stimulates increased generation of fibrin. Heterozygosity for the mutation has not convincingly or consistently been shown to increase risk of VTE in absence of other risk factors, but adds significantly to risk when other factors are present (Segal et al. 2009). Homozygosity for the prothrombin mutation is rare, and thus, data are limited regarding associated risk; limited case studies suggest substantial phenotypic variation (Bosler et al. 2006), emphasizing the contributing roles of other risk factors for VTE.

Heterozygosity for Both Factor V Leiden and Prothrombin Gene Mutations

Although heterozygosity for Factor V Leiden or the prothrombin gene 20210 mutation

confers only a modestly increased risk for VTE, combined heterozygosity confers substantially greater risk. A pooled analysis of case–control studies found odds ratios for VTE of 4.9 and 3.8 for Factor V Leiden and prothrombin G20210A mutations, respectively, but an odds ratio of 20 in double heterozygotes (Emmerich et al. 2001).

Other Heritable and Acquired Thrombophilias

A number of other conditions including but not limited to excess Factor VIII levels, dysfibrinogenemia, heparin cofactor II deficiency, and plasminogen deficiency have been determined to be independent risk factors for VTE (Jenkins et al. 2012), but the importance of these in clinical practice remains to be determined.

Absence of a known major laboratory thrombophilia does not rule out the strong possibility that a patient who has had an unprovoked event carries an ongoing tendency to have recurrent VTE, as our hypercoagulability panel is limited and in constant evolution.

Medications

Clinical Vignette 3

An otherwise healthy 22-year-old woman who started taking a combined oral contraceptive pill 3 months ago presents to urgent care with acute dyspnea and is found to have a pulmonary embolism.

Numerous medications may contribute to VTE risk; here we highlight the major categories of hormonal compounds, cancer therapeutics, medications affecting red blood cell mass, and antipsychotic medications.

Hormonal Compounds

Hormonal compounds contributing to VTE risk include estrogen-containing oral contraceptives and hormone replacement therapy, as well as estrogen-modulating cancer therapeutics including tamoxifen and raloxifene.

Combined Oral Contraceptives (COCs)

The overall odds ratio for VTE in women taking estrogen-containing oral contraceptive pills versus those not taking COCs is around 3–4 and has not changed significantly in the years since OCPs began to be used. Risk increases with dose of estrogen and is greatest in women taking COCs containing the third-generation progestin desogestrel (Manzoli et al. 2012; Gomes and Deitcher 2004). In the Leiden Thrombophilia Study, COC users had 3.8-fold greater odds of VTE than non-COC users. This odds ratio increased to 8.7 in women using COCs containing desogestrel, compared to 2.2–3.8 for women using COCs with first- or second-generation progestins (van der Meer et al. 1997). Risk appears to be highest during the first several months of use and is higher for older than for younger women, reflecting the underlying increase in baseline risk with increasing age (Gomes and Deitcher 2004).

Risk is substantially higher for women taking COCs who also have Factor V Leiden or prothrombin G20210A mutations. In the Leiden Thrombophilia Study, women with concurrent Factor V Leiden mutation and COC use had 28.5 times greater odds of VTE than women with neither risk factor (Roldan et al. 2009); subsequent studies have suggested up to 99-fold increased risk (Gomes and Deitcher 2004). A case–control study of 477 women found an odds ratio of 16.3 for VTE in women taking COCs with the prothrombin G20210A mutation compared to women without the mutation who were not taking COCs (Martinelli et al. 1999). These risks have been somewhat lower in subsequent studies including a pooled analysis of case–control studies which found an OR of 10.25 for VTE in women with Factor V Leiden mutations taking OCPs and 7.14 in women with the prothrombin gene mutation taking OCPs (Emmerich et al. 2001).

The transdermal contraceptive system is associated with higher levels of circulating estrogen than oral contraceptives. Available data suggest that the VTE risk associated with the transdermal

contraceptive patch is at least equal to, and perhaps up to 2.4 times greater than, the risk from combined oral contraceptives (Jick et al. 2007; Cole et al. 2007). Risk associated with the vaginal contraceptive ring has not yet been established.

Progestin-Only Contraception

Limited data are available regarding risk associated with progestin-only hormonal contraception, including oral and injectable methods. While several studies have demonstrated slightly increased risk, this risk has not reached statistical significance in individual studies or in a 2009 meta-analysis demonstrating a relative risk for VTE of 1.45 (95 % CI 0.92, 2.26) for women using progestin-only contraceptives (Gomes and Deitcher 2004; Blanco-Molina et al. 2012; Bergendal et al. 2009; Barsoum et al. 2010). Similarly, use of the progestin megestrol acetate as an appetite enhancer has been associated with a slight but nonsignificant increase in VTE risk (Barsoum et al. 2010). Extended follow-up from a large study of hormonal therapy for postmenopausal women did, however, show a small but significant increase in VTE risk among women taking estrogen and progestin compared to those taking estrogen alone (Curb et al. 2006).

Hormone Replacement Therapy (HRT)

Two large studies, the Women's Health Initiative and the Heart and Estrogen–Progestin Replacement Study, noted increased risk for VTE among women taking hormonal replacement therapy with estrogen alone or combined estrogen and progestin (Heiss et al. 2008; Hulley et al. 2002). Multiple smaller studies and a meta-analysis have provided supporting data, with odds ratios around 2–3 for VTE in women taking HRT (either unopposed estrogen or combined estrogen–progestin) (Beral et al. 2002; Canonico et al. 2008); increased dose of estrogen correlates with higher VTE risk (Renoux et al. 2010). Risk is highest during the first year of treatment and returns to baseline following cessation of therapy. Despite consistent evidence confirming the association between oral estrogen and VTE, transdermal estrogen for hormone replacement does not appear to increase risk for VTE (Olie et al. 2011a, b).

Estrogen-Modulating Anticancer Agents

The selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene are associated with a two- to threefold increase in VTE risk. Additional cancer therapeutics with estrogen-modulating activities, including the aromatase inhibitor anastrozole, have also been shown to increase VTE risk, albeit to a lesser extent (Deitcher and Gomes 2004).

Other Cancer Therapeutics

Cancer chemotherapy has been consistently associated with VTE risk above that attributable to malignancy alone. Compared with an annual VTE incidence of around 1 per 200 in all patients with cancer (Lee and Levine 2003), annual VTE incidence in patients undergoing chemotherapy has been reported as up to 10.9 % (Otten et al. 2004; Khorana et al. 2005). Certain chemotherapeutic agents including lenalidomide and thalidomide for myeloma have been particularly associated with VTE risk; phase 3 trials of these medications showed a 2- to 14-fold higher incidence of VTE with thalidomide and a two- to ninefold greater incidence with lenalidomide, compared with control arms (Bennett et al. 2006).

Antipsychotic Medications

Several studies have demonstrated a small but significantly increased risk for VTE associated with antipsychotic medications, with odds ratios around 2. Risk may be greatest with use of low-potency first-generation antipsychotics and with clozapine, although the confounding effects of immobility, obesity, and other factors associated with VTE and with administration of antipsychotic medications have limited clear establishment of this risk (Hagg et al. 2009; Jonsson et al. 2009).

Transfusions and Erythropoiesis-Stimulating Agents

Red blood cell transfusions, platelet transfusions, and erythropoiesis-stimulating agents are associated with a slightly but significantly increased risk for VTE, although their independent contributions to risk are difficult to assess as additional factors are often present including concurrent

acute illness, malignancy, and chemotherapeutic agents (Rizzo et al. 2010; Khorana et al. 2008; Tonelli et al. 2009).

Discussion of Clinical Vignette 3

Although the overall risk for VTE in an otherwise healthy 22-year-old woman is low (around 1 in 10,000), risk is moderately elevated by a factor of 3–4 by use of combined oral contraceptive pills. Given her age and absence of other provoking factors, it is likely that this young woman also has a Factor V Leiden or prothrombin gene mutation. Although genetic testing is unlikely to affect recommended duration of anticoagulation (neither mutation would commit her to indefinite anticoagulation as long as she discontinues her hormonal contraceptive), testing may be warranted if she is considering pregnancy in the future. Evaluation for APS should be considered given implications for anticoagulation monitoring, recurrence risk, and management during pregnancy.

Malignancy

Risk of VTE is elevated about four- to sevenfold for patients with cancer (Lee and Levine 2003; Piccioli and Prandoni 2011; Rickles and Levine 2001) compared to the general population. About 10–15 % of patients with overt cancer will have VTE at some point during the course of their disease, although risk varies based on extent of disease, tumor type, and presence of numerous other factors that elevate VTE risk in cancer patients including hospitalization, surgery, immobilization, chemotherapy, and central venous access (Rickles and Levine 2001). Mucin-producing adenocarcinomas including pancreas, lung, stomach, and adenocarcinoma of unknown primary appear the most likely to cause thrombosis. However, the most common tumors found in patients with DVT, reflective of overall prevalence in the general population, are prostate, colon, lung, and brain in men and breast, lung, and ovary in women (Lee and Levine 2003). Incidence of thrombosis in hematologic malignancies was previously thought lower than for solid tumors, but is now thought similar. As with solid tumors, risk in hematologic malignancies is further increased by chemotherapeutic regimens (thalidomide and lenalidomide for myeloma in particular), central venous catheters, frequent hospitalizations, and comorbidities (Elice and Rodeghiero 2012).

VTE is a common complication among patients with known cancer, but may also present as a first manifestation of occult malignancy. Up to 10 % of patients with idiopathic VTE may be diagnosed with malignancy within 5–10 years of VTE presentation; for most of these patients, diagnosis of cancer is established within the first 6 months after presentation (Lee and Levine 2003; Piccioli et al. 2006). Most patients who present with VTE and have occult malignancy have some clinical abnormality suggestive of malignancy at the time of VTE diagnosis. Extensive screening for all patients presenting with idiopathic DVT is generally not warranted (Hettiarachchi et al. 1998; Piccioli et al. 2006). Identification of occult malignancy has implications for treatment, as cancer-related VTE is generally treated with low-molecular-weight heparin, while non-cancer patients are transitioned to warfarin.

Thromboembolic disease in malignancy is further addressed elsewhere in this book.

Other Hematologic Disorders

Risk of VTE is increased in patients with benign monoclonal gammopathy of undetermined significance (MGUS) with a risk elevated around 2–3 times that in control subjects. Occurrence of VTE has not been associated with progression of MGUS to myeloma or with monoclonal protein levels (Elice and Rodeghiero 2012). Myeloproliferative disorders, particularly essential thrombocytosis (ET) and polycythemia vera (PV), confer increased risk for both arterial and venous thrombosis; presence of venous thromboembolism at unusual sites (cerebral sinuses or splanchnic veins) or at a young age may provide clues to an underlying myeloproliferative disorder.

In patients with suggestive laboratory or clinical findings, testing for the JAK2 mutation may be helpful (Landolfi et al. 2008). Paroxysmal nocturnal hemoglobinuria, which also predisposes to both arterial and venous events, also more commonly presents in the abdominal veins than in the lower extremities (Ray et al. 2000).

Pregnancy

Risk of VTE increases by about fourfold during pregnancy but is most pronounced in the postpartum period when it increases 14- to 84-fold. Hypercoagulability during and following pregnancy is likely due to alterations in hemostatic mechanisms to prevent bleeding; as pregnancy progresses, stasis and venous compression from the gravid uterus also contribute to risk (Lussana et al. 2012). Pelvic vein thrombosis, an otherwise rare manifestation of VTE, accounts for about 10 % of DVT during pregnancy, and the postpartum period DVT during pregnancy more commonly occurs in the left leg than the right, likely due to compression of the left iliac vein by the right iliac artery, i.e., the May–Thurner syndrome (Chan et al. 2010; James et al. 2005).

Risk is dramatically increased in the presence of concurrent thrombophilia, particularly antithrombin deficiency, Factor V Leiden mutation (homozygous or heterozygous), or prothrombin G20210A mutation (homozygous or heterozygous). Additional significant risk factors contributing to peripartum VTE include hemorrhage, transfusion, prior VTE, preeclampsia, and postpartum infection (Lussana et al. 2012; James et al. 2006; Bates et al. 2012). Thrombosis risk associated with pregnancy and the postpartum period is addressed elsewhere in this book.

Minor Risk Factors

Immobility and Travel

Immobilization is a minor but significant risk factor for VTE. Although a number of studies have assessed the effect of immobilization on VTE risk, varying definitions of immobilization in terms of time period and degree of immobility make exact quantification of risk difficult. Nonetheless there is general consensus that risk of VTE increases during periods of significant inactivity (such as total bed rest or bed rest with bathroom privileges) lasting over 3 days, and that risk is approximately doubled (Anderson and Spencer 2003; Pottier et al. 2009; Hull 2012). Incidence of VTE in chronically immobilized outpatients is increased above that for ambulatory patients, but there are few studies available to further quantify risk. While annual incidence of VTE in nursing home patients is around 1 %, post-acute care patients have an annual incidence of VTE between 1.0 and 2.4 %, approaching that of hospitalized patients (Kahn et al. 2012).

Although much research on immobilization and VTE has been focused on inpatients or chronically immobilized outpatients, prolonged immobilization among otherwise healthy outpatients is also a recognized, albeit minor, risk factor. Relatively minor isolated limb injury with ensuing immobilization, with or without plaster casts or other orthopedic devices, may trigger VTE (Nilsson-Helander et al. 2009; Cogo et al. 1994). Prolonged sitting at work may also contribute to VTE (Beasley et al. 2003; West et al. 2008; Healy et al. 2010); however, this is unlikely to happen in the absence of other predisposing factors.

Travel

Prolonged travel increases risk for VTE. Case–control studies have demonstrated odds ratios between 1.5 and 4 for VTE following travel by any modality lasting greater than 3–4 hours (Gallus and Goghlan 2002). Particular attention has been given to VTE risk associated with air travel given concern about the additional effect of the hypobaric environment during flight. Estimates of incidence of travel-related VTE vary, but overall risk per travel episode is likely around 0.05 % (Philbrick et al. 2007; Kuipers et al. 2007). Travelers on flights under 4–6 hours in duration do not have significantly elevated risk, and risk increases incrementally with duration of travel over 6 hours (Philbrick et al. 2007). While overall risk is low, travelers with additional risk factors have substantially increased susceptibility

to travel-related VTE (Cannegieter 2012; Kuipers et al. 2009). Frequent ambulation and calf muscle exercise are recommended for all long-distance travelers; for those at elevated risk of VTE due to recent surgery, trauma, malignancy, prior VTE, pregnancy, estrogen use, advanced age, or known thrombophilia, graduated compression stockings have been demonstrated to decrease VTE risk and are recommended (Kahn et al. 2012).

Additional Medical Conditions

A wide range of autoimmune diseases have been shown to confer elevated risk for thromboembolism. Inflammatory bowel disease carried a standardized incidence ratio of 10–12 for pulmonary embolism in one longitudinal Swedish study, and the overall incidence ratio for PE for all autoimmune diseases studied was 6.4 (Zoller et al. 2012). The nephrotic syndrome carries well-documented risk for both venous (including renal vein) and arterial thromboembolic disease; mechanisms likely include preferential loss of antithrombin and other proteins involved in inhibition of systemic hemostasis (Singhal and Brimble 2006; Mahmoodi et al. 2008).

There is increasing awareness of elevated VTE risk in a number of chronic renal, cardiac, and pulmonary diseases. Patients with chronic kidney disease appear to have slightly increased risk for VTE (Wattanakit and Cushman 2009; Mahmoodi et al. 2012). Congestive heart failure is associated with increased VTE risk in the inpatient and outpatient settings; this independent association is particularly strong in younger (under age 40) patients with CHF (Cogo et al. 1994; Beemath et al. 2006). Patients with chronic obstructive pulmonary disease have increased VTE risk as well and may face increased morbidity and mortality from pulmonary emboli due to diminished cardiopulmonary reserves (Shetty et al. 2008).

While many acute infections transiently increase VTE risk, chronic infections also may lead to sustained risk elevation. Case–control data have suggested two- to tenfold greater incidence of VTE in people living with AIDS compared to matched controls; this risk may be exacerbated by concurrent infections and presence of additional risk factors (Auerbach and Aboulafia 2012).

Overlap with Traditional Vascular Risk Factors

There is increasing recognition of the overlap between risk factors for venous and arterial vascular disease.

Obesity has long been recognized as a risk factor for VTE; it may double risk of a first VTE, and excess body weight increases risk for VTE recurrence (Allman-Farinelli 2011; Eichinger et al. 2008). Additional risk factors for atherosclerotic vascular disease have now also been shown to modestly but significantly increase VTE incidence (odds ratios between 1 and 2); these include tobacco use, hyperlipidemia, hypertension, and diabetes mellitus (Ageno et al. 2008).

VTE in Hospitalized Patients

Clinical Vignette 4

A 72-year-old woman with morbid obesity and a history of congestive heart failure is admitted to the hospital with pneumonia. She is ambulatory and has been able to use the bathroom and take short walks with the physical therapist.

Hospitalization and long-term nursing home care are risk factors for VTE. Incidence of VTE in hospitalized patients has been reported as up to 10–30 % (Cohen et al. 2005). Critical illness carries VTE risk above that found for medical hospitalized patients (Cook et al. 2005). For medical inpatients, independent risk factors for VTE include active cancer, increased age, increased body mass index, paresis due to neurologic disease, fracture, chronic kidney disease, prior deep or superficial venous thrombosis, and prolonged immobility (Barbar et al. 2010; Heit 2008).

Table 12.4 Padua risk score for venous thromboembolism in hospitalized patients

Padua prediction model (high risk for VTE: ≥4 points)	
Risk factor	Points
Active cancer[a]	3
Previous VTE (not superficial)	3
Reduced mobility: bed rest/bathroom privileges for at least 3 days	3
Known thrombophilia[b]	3
Trauma or surgery in past month	2
Age at least 70	1
Congestive heart failure or respiratory failure	1
Acute infection and/or rheumatologic disorder	1
Body mass index at least 30	1
Ongoing hormonal treatment	1

In an initial validation study, VTE developed in 11 % of high-risk patients (score ≥4) who did not receive pharmacologic prophylaxis and in 2.2 % of high-risk patients who received pharmacologic prophylaxis

Adapted with permission from Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. Journal of Thrombosis and Haemostasis: JTH. 2010;8(11):2450–7

[a]Local or distant metastases or chemotherapy or radiotherapy in past 6 months

[b]Antithrombin, protein C, protein S, Factor V Leiden, prothrombin 20210 mutation20210 mutation, antiphospholipid syndrome

For surgical inpatients, risk factors include active malignancy and type of surgery; additional independent risk factors include intensive care admission for at least 6 days, presence of a central venous catheter, increased BMI, varicose veins, and infection (Heit 2008).

Risk scores may help stratify hospitalized patients and determine when VTE prophylaxis is warranted. For noncritically ill hospitalized medical patients, the Padua score can be used to estimate VTE risk (Barbar et al. 2010) (Table 12.4); for surgical patients, the Caprini score can be used (Caprini 2010). Other risk scores that are not as widely validated include the Vienna score for risk stratification in outpatients with cancer (Thaler et al. 2012; Khorana 2011) and the QThrombosis score, a recently developed model to predict VTE risk in primary care patients in the UK (Hippisley-Cox and Coupland 2011).

Note that the relative weights of certain risk factors may differ based on the populations addressed by specific risk scores and classification schemes. For instance, among noncritically ill hospitalized medical patients, active malignancy and known thrombophilia are major risk factors for VTE based on the Padua model (Table 12.4), although in Table 12.1 these are listed as "moderate" risk factors based on studies reflecting risk in the overall population. Likewise, *major* surgery and trauma are major risk factors for VTE in the overall population as reflected in Table 12.1, but "recent trauma or surgery" is a moderate risk factor in the Padua model, likely reflecting inclusion of nonmajor surgery or trauma and its impact on specifically medical, nonsurgical inpatients. Although risk scores can be quite helpful, it is important to keep in mind that they represent a simplification of the risk associated with heterogeneous categories such as surgery, thrombophilias, and malignancy, and each patient's individual history must be taken into account for full assessment of VTE risk.

Discussion of Clinical Vignette 4

For medical inpatients, the Padua risk stratification score (Table 12.4) may be a useful tool to identify patients who will benefit most from pharmacologic VTE prophylaxis. In a study of 1,180 patients, VTE developed in 0.3 % of those with scores less than 4, in 2.2 % of those with scores 4 or greater who received pharmacologic prophylaxis, and in 11 % of patients with scores 4 or greater who did not receive prophylaxis (Barbar et al. 2010). Although this patient is ambulatory, her Padua risk score is 4 (1 point each for age, obesity, congestive heart failure, and acute infection), placing her in the "high-risk" category of hospitalized patients for whom administration of prophylactic low-molecular-weight heparin or unfractionated heparin may provide a meaningful reduction in VTE risk.

Anatomic Anomalies

Aberrant anatomic structures causing VTE are infrequent in the population, yet recognition is important as it can have implications for the effectiveness of anticoagulation and lead to correction and mitigation of future risk. In May–Thurner syndrome, compression of the left common iliac vein by the right common iliac artery leads to development of chronic venous insufficiency and iliofemoral DVT (Kim and Choi 2006). Paget–Schroetter syndrome, an unusual cause of upper extremity DVT, involves axillary subclavian thrombosis that occurs in the setting of excessive arm activity in the presence of compressive elements in the thoracic outlet (Urschel and Razzuk 2000). Congenital anomalies of the inferior vena cava (IVC) include narrowing, duplication, or even absence of the IVC and should be suspected in young patients with bilateral, unprovoked DVT (Chee et al. 2001). Popliteal venous aneurysms may have internal thrombosis which can cause pulmonary emboli (Bergqvist et al. 2006); popliteal arterial aneurysms may also cause VTE via compression of the popliteal vein.

Conclusion

Determining the etiology of a thrombotic event is important to both provider and patient. Identifying removable or modifiable risk factors and permanent risk factors that will influence duration or type of therapy is most critical. A stepwise approach to exploring etiology may be most helpful and economical, focusing first on classifying an event as provoked or unprovoked and next on what further clinical or laboratory evaluation may be warranted based on patients' age, medical history, and personal preferences. Providers must have a knowledge of these risk factors and be committed to educating patients on risk factor modification and about the warnings signs and symptoms of DVT and PE to help reduce incidence and mortality associated with VTE.

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