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Risk Factors of Deep Vein Thrombosis

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1. Introduction

Deep vein thrombosis is a clinical challenge for doctors of all disciplines. It can complicate the course of a disease but might also be encountered in the absence of precipitating disorders. Thrombosis can take place in any section of the venous system, but arises most frequently in the deep veins of the leg. Long-term morbidity due to post-thrombotic syndrome is common and can be substantial. The major concern, however, is embolisation of the thrombus to the lung, which can be fatal. Deep vein thrombosis is highly prevalent and poses a burden on health economy. The disorder and its sequelae are also among the best examples of preventable diseases. Relevant data for the frequency of deep vein thrombosis derive from large community-based studies because they mainly reflect symptomatic rather than asymptomatic disease. In a systematic review, the incidence of first deep vein thrombosis in the general population was 0·5 per 1000 person-years.[1] The disorder is rare in children younger than 15 years,[2,3] but its frequency increases with age, with incidence per 1000 person-years of 1·8 at age 65–69 years and 3·1 at age 85–89 years.[4] Two-thirds of first-time episodes of deep vein thrombosis are caused by risk factors, including surgery, cancer, immobilisation, or admission for other reasons.[5,6] Risk for first deep vein thrombosis seems to be slightly higher in men than in women.[6,9] In a population-based cohort study, the age-adjusted incidence of first venous thromboembolism was 1·3 per 1000 person-years in men and 1·1 per 1000 person-years in women.[2] It is noteworthy that the risk for recurrence of this disorder is higher in men than in women.[6,10]

Conditions associated with increased risk for deep vein thrombosis
Advancing age
Obesity
Previous venous thromboembolism
Surgery
Trauma
Active cancer
Acute medical illnesses – eg, acute myocardial infarction, heart failure, respiratory failure, infection
Inflammatory bowel disease

Antiphospholiped syndrome
Dyslipoproteinaemia
Nephrotic syndrome
Paroxysmal nocturnal haemoglobinuria
Myeloproliferative diseases
Behçet's syndrome
Varicose veins
Superficial vein thrombosis
Congenital venous malformation
Long-distance travel
Prolonged bed rest
İmmobilisation
Limb paresis
Chronic care facility stay
Pregnancy/Puerperium
Oral contraceptives
Hormone replacement theraphy
Heparin-induced thrombocitopenia

Other drugs
    Chemotheraphy
    Tamoxifen
    Thalidomide
    Antipsychotics

Central Venous catheter
Vena cava filter
İntravenous drug abuse

Rudolph Virchow is recognized as the first person to link the development of VTE to the presence of at least 1 of 3 conditions: venous stasis, vascular injury, and/or hypercoagulability. 11 Each of these factors can alter the delicate hemostatic balance toward hypercoagulability and development of thrombosis. Several aspects of surgery can be linked to Virchow's triad. Coleridge-Smith et al12 reported in 1990 that venous stasis occurs during general surgery, with veins dilating 22% to 28% in patients undergoing general anesthesia and surgery and up to 57% in those who also received an infusion of 1 L of saline during surgery. The investigators suggested that it is this intraoperative venous distension that underlies the risk for DVT in patients undergoing surgery. They suggested that the venous distension is the result of loss of muscle tone that is caused by the muscle relaxants used during surgery. Muscle paralysis resulting from regional anesthesia also can lead to venous dilatation. These effects can be modified to some extent by the use of graduated compression stockings during surgery.13 In a study of 40 patients undergoing surgery of the abdomen or neck, the median vein diameter in the extremity studied was 2.6 mm at the beginning of surgery in both the control and intervention groups (control group, n = 20; median vein diameter, 2.6 mm; interquartile range [IQR], 2.1–3.3 mm; stocking group, n =20; median vein diameter, 2.6 mm; IQR, 2.1–3.7 mm). This decreased to a median vein diameter of 1.6 mm (IQR, 1.3–2.8 mm) after application of a stocking, whereas vein diameter

increased from 2.6 to 2.9 mm (IQR, 2.3– 4.0 mm) in the control group.13 Comerota et al14 found that in patients undergoing total hip replacement surgery, handling of soft tissue (muscle) during surgery leads to venodilation, whereas bone manipulation leads to venoconstriction. The venous dilatation that occurs during surgery causes cracks in the endothelium, which provides a nidus for thrombosis as the blood coagulation system is activated. The researchers also showed that pharmacologic control of venodilation during surgery reduced postoperative DVT.14 Microscopic vessel wall damage, 15 such as that demonstrated in patients undergoing hip and knee replacement surgeries, also contributes to the development of VTE. 16,17 Tissue factor released from the blood vessel wall after injury drives thrombus formation,18 which may help explain the increased risk of VTE in patients undergoing surgery. The third factor in Virchow's triad, hypercoagulability, is linked to a number of factors, including certain genetic traits. Deficiencies of antithrombin, protein C, or protein S, or mutations of factor V Leiden or factor II (prothrombin) G20210A genes lead to hypercoagulable states.11 Although these genetic factors account for only a small percentage of the total cases of VTE, more than half of all patients with juvenile or idiopathic VTE have been identified with an inherited thrombophilic condition.11. Given that VTE is the leading preventable cause of in-hospital deaths,19 every patient should be screened before other lesser screens are performed (bedsores, risk of falls, nutritional evaluation, and so forth). Stated another way— every patient deserves a proper history and physical to uncover any possible factors that might increase their risk of a VTE.

	Deep vein thrombosis		Pulmonary embolism	
	Calf	Proximal	Clinical	Fatal
Low risk (minor surgery in patients < 40 years with no additional risk factors)	2%	0-4%	0-2%	<0,01%
Moderate risk (minor surgery and additional risk factor	10-20%	2-4%	1-2%	0,1-0,4%
High risk (surgery in patients > 60 years or age 40-60 years with additional risk factors (previous venous thromboembolism, cancer, thrombophilia)	20-40%	4-8%	2-4%	0,4-1,0%
Highest risk (surgery in patients with multiple risk factors [age > 40 years, cancer, previous venous thromboembolism]: hip or knee arthroplasty, hip fracture surgery; major trauma – spinal cord surgery)	40-80%	10-20%	4-10%	0,2-5%
Modified from reference 16 with permission of the American College of Chest Physicians.				

Table 1. Risk of venous thromboembolism in surgical patients without prophylaxis

In 1992, the Thromboembolic Risk Factors (THRIFT) Consensus Group identified acquired risk factors for VTE.20 Sixteen years later, the most recent update of the American College of Chest Physicians (ACCP) guidelines for VTE prophylaxis reveals essentially the same risk factors for VTE as those identified by THRIFT, with the addition of a few new ones, including acute medical illness, and the removal of smoking as a separate risk factor (Table

1). 19 The incidence of VTE increases dramatically in tandem with the number of risk factors identified in patients.11,21 Most hospitalized patients have at least one risk factor for VTE, and the most recent ACCP review of VTE estimated that approximately 40% have 3 or more risk factors.19 These include fracture (hip or leg), hip or knee replacement, major general surgery, major trauma, and spinal cord injury,11 as well as a history of VTE,11 thrombophilia, 11 inflammatory bowel disease,22 postoperative infection, 19 and cancer.23 Bed rest for more than 72 hours,11,24 use of hormones,11 and impaired mobility11 are additional risk factors. Many of these factors are not simple binary (ie, yes/no) risks. For example, age is a significant risk factor, with the risk approximately doubling with each decade beyond age 40.11,25 It is not sufficient to use a single age cut-off level to define high or low risk.11 Similarly, the incidence of VTE increases with length of surgery.26,27 In addition, Sugerman et al28 found higher rates of VTE in obese patients (mean body mass index, 61) who also had venous stasis syndrome; a simple cut-off level based on a definition of obesity would not capture this increased risk. In fact, Anderson and Spencer11 suggest that the association of risk of VTE and weight alone is a weak one. As noted earlier, hospitalized patients usually have at least 1 risk factor for VTE, and more than a third of hospitalized patients have 3 risk factors or more.19 Risk factor weighting can be used to calculate the risk for an individual patient, and the results may be used to determine several aspects of prophylaxis, such as the length of prophylaxis (including out-of-hospital prophylaxis), selection of prophylactic agent, timing of first dose, and the need for combined use of physical and pharmacologic methods.

Risk assessment typically has taken 1 of 2 approaches, group risk assessment or individual risk assessment. The group risk assessment approach assigns patients to one of a few broad risk categories, whereas individual risk assessment seeks to define risk more accurately by using individualized risk scores.19 The system recommended by the 2001 ACCP guidelines used a group risk assessment in which the type of surgery ("major" vs "minor"), age bracket, and presence of additional risk factors were used to assign patients to 1 of 4 risk groups29; however, this was based on older studies, arbitrary age cut-off levels, and inexact definitions.19 The ACCP has refined this recommendation with a newer one in which patients are assigned 1 of 3 VTE risk levels based on type of surgery, patient mobility, overall risk of bleeding, and moderate/high risk of VTE based on the presence of additional risk factors 19 As the investigators note, this group risk assessment approach ignores the substantial variability in patient-specific risk factors, but it does take into account what they view as the principal risk factor (surgery vs acute medical illness). This approach is most appropriate for patients who fit the criteria of the randomized clinical trials that were used to develop the model; the investigators include a disclaimer for patient groups that have not been included in clinical trials or for types of patients who have not been tested.19 However, the group risk assessment approach recommended by the ACCP may not be appropriate for all individual patients.30 Out-of-hospital prophylaxis is not addressed except for a few very high risk groups (major cancer surgery, total joint replacement).19 It may be more appropriate to use the individual risk assessment approach to identify and evaluate all possible risk factors to determine the true extent of risk for a patient.30 The ACCP guidelines, in fact, point out that "specific knowledge about each patient's risk factors for VTE" is an essential component of the decision-making process when prescribing thromboprophylaxis. 19 Also, if many risk factors are present and a planned procedure is

based on a quality-of-life decision rather than a critical medical need, the patient may come to a different decision about whether to proceed.30 A common misconception among physicians is that individual risk assessment takes longer and is more cumbersome than group risk assessment. However, individual assessment can be accomplished with, for example, a simple assessment form that merely captures information from the history and physical examination of the patient.

Among all patients with PE in the PIOPED II trial 94% had 1 or more of the following assessed risk factors: bed rest within the last month of 3 days or more, travel within the last month of 4 hours or more, surgery within 3 months, malignancy, past history of DVT or PE, trauma of lower extremities or pelvis, central venous instrumentation within 3 months, stroke, paresis or paralysis, heart failure or chronic obstructive pulmonary disease (COPD).31 Immobilization of only 1 or 2 days may predispose to PE, and 65% of those who were immobilized were immobilized for 2 weeks or less.32

2. Obesity and height

Investigations that reported an increased risk for VTE caused by obesity have been criticized because they failed to control for hospital confinement or other risk factors.33 High proportions of patients with VTE have been found to be obese,13,34 but the importance of the association is diminished because of the high proportion of obesity in the general population.35 Some investigations showed an increased risk ratio for DVT or PE in obese women,21,36,38 but data in men were less compelling. The Nurses' Health Study showed that the age-adjusted risk ratio for PE women with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) 29.0 kg/m2 or higher was 3.2 compared with the leanest category of less than 21.0 kg/m2.36 The Framingham Heart Study showed that metropolitan relative weight was significantly and independently associated with PE among women, but not men.39 However, the Study of Men Born in 1913 showed that men in the highest decile of waist circumference (>100 cm) had an adjusted relative risk for VTE of 3.92 compared with men with a waist circumference less than 100 cm.40 Among 1272 outpatients (men and women), the odds ratio for DVT, comparing obese (BMI> 30 kg/m2) with nonobese patients, was 2.39.41 Others showed a similar odds ratio for DVT of 2.26 compared with nonobese patients.37 BMI correlated linearly with the development of PE in women.42 On the other hand, the Olmsted County, Minnesota case-control study found no evidence that current BMI was an independent risk factor for VTE in men or women.33,43 Others did not show obesity to be a risk for VTE in men.21,38 Analysis of the huge database of the National Hospital Discharge Survey44 showed compelling evidence that obesity is a risk factor for VTE.45 Among patients hospitalized in short-term hospitals throughout the United States, in whom obesity was coded among the discharge diagnoses but not defined, 91,000 of 12,015,000 (0.8%) had PE.45 Among hospitalized patients who were not diagnosed with obesity, PE was diagnosed in 2,366,000 of 691,000,000 (0.3%). DVT was diagnosed in 243,000 of 12,015,000 (2.0%) of patients diagnosed with obesity, and in 5,524,000 of 691,000,000 (0.8%) who were not diagnosed with obesity. The relative risk of PE, comparing obese patients with nonobese patients, was 2.18 and for DVT it was 2.50.45 The relative risks for PE and DVT were age dependent. Obesity had the greatest effect on patients less than 40 years of age, in whom the relative risk for PE in obese patients was 5.19 and the relative risk for DVT was 5.20.45 The higher relative risk of obesity in younger patients may have reflected that younger patients uncommonly have multiple

confounding- associated risk factors, which make the risk of obesity inapparent. Previous investigators used several indices of obesity including a BMI greater than 35 kg/m2 as well as BMI 30 to 35 kg/m2,46 BMI 29 kg/m2 or greater,36 weight more than 20% of median recommended weight for height,13 and for men, waist circumference 100 cm or greater.40 It is likely that all patients diagnosed with obesity in the National Hospital Discharge Survey database were obese, irrespective of the criteria used. However, some obese patients may not have had a listed discharge diagnosis of obesity, and they would have been included in the nonobese group. This situation would have tended to reduce the relative risk of obesity in VTE. Various abnormalities of hemostasis have been described in obesity, in particular increased plasminogen activator inhibitor-1 (PAI-1).47,48 Other abnormalities of coagulation have been reported as well,48 including increased platelet activation,39 increased levels of plasma fibrinogen, factor VII, factor VIII, and von Willebrand factor.49 Fibrinogen, factor VIIc, and PAI-1 correlated with BMI.50 Regarding height, in the study of Swedish men, those taller than 179 cm (5′ 10″) had a 1.5 times higher risk of VTE than men shorter than 172 cm.51 The Physicians' Health Study of male physicians also showed that taller men had a significantly increased risk of VTE.52

3. Air travel

The possibility of VTE after travel is not unique to air travel.53,54 Prolonged periods in cramped quarters, irrespective of travel, can lead to PE.55 The term economy class syndrome was introduced in 1988,56 but has since been replaced with flight-related DVT in recognition that all travelers are at risk, irrespective of the class of travel[57] Rates of development of PE with air travel lasting 12 to 18 hours have been calculated as 2.6 PE/million travelers.58 With air travel of 8 hours or longer, 1.65/million passengers had acute PE on arrival.59 With 6 to 8 hours of air travel the rate of acute PE on arrival was 0.25/million and among those who traveled for 6 hours or less none developed acute PE on arrival.59 The trend showing increasing rates of PE with duration of travel is compelling, but the incidence of DVT was about 3000 times higher in a prospective investigation.60 In a prospective investigation of travelers who traveled for 10 hours or longer, 4 of 878 (0.5%) developed PE and 5 of 878 (0.6%) developed DVT.60

4. Varicose veins

Varicose veins were found by some to be an agedependent risk factor for VTE.43 Among patients aged 45 years the odds ratio for VTE was 4.2.43 In patients aged 60 years the odds ratio was 1.9 and at aged 75 years, varicose veins were not associated with an increased risk of VTE.43 However, others did not find varicose veins to be a risk factor for DVT61 or PE found at autopsy.21

5. Oral contraceptives

Although the risk of VTE is higher among users of oral estrogen-containing contraceptives than nonusers, 62,63 the absolute risk is low.64 An absolute risk of VTE of less than 1/10,000 patients/y increased to only 3 to 4/10,000 patients/y during the time oral contraceptives were used.64 The relative risk for VTE in women using oral contraceptives containing 50 mg of estrogen, compared with users of oral contraceptives that contained less than 50 mg was 1.5.65 The relative risk for VTE in women using oral contraceptives containing more than 50 mg of

estrogen, compared with users of oral contraceptives that contained less than 50 mg was 1.7.65 No difference in the risk of VTE was found with various levels of low doses of 20, 30, 40, and 50 mg/d.66 With doses of estrogen of 50 mg/d, the rate of VTE was 7.0/ 10,000 contraceptive users/y and with more than 50 mg/d, the rate of VTE was 10.0/10,000 oral contraceptive users/y.65 However, some found no appreciable difference in the relative risk of VTE in relation to low or higher estrogen doses.67 Reports of the risk of VTE in relation to the duration of use of oral contraceptives are inconsistent. Some showed relative risks increased as the duration of use of estrogen-containing oral contraceptives increased.68 The relative risks were 0.7 in women who used oral contraceptives for less than 1 year, 1.4 for those who used oral contraceptives for 1 to 4 years and 1.8 in those who used it for 5 years or longer.68 Others showed the opposite effect, with a decreasing relative risk with duration of use.66 The relative risk for DVT or PE was 5.1 with use for less than 1 year, 2.5 with use for 1 to 5 years, and 2.1 with use for longer than 5 years.66 Some showed the risk to be unaffected by the duration of use.67 A synergistic effect of oral contraceptives with obesity has been shown.69,71 The odds ratio of DVT in obese women (BMI _30 kg/m2) who were users of oral contraceptives ranged from 5.2 to 7.8 compared with obese women who did not use oral contraceptives37,69,71 and among women with a BMI 35 kg/m2 or higher, the odds ratio was 3.1 compared with similarly obese nonusers of oral contraceptives.71

6. Tamoxifen

Tamoxifen is a selective estrogen-receptor modulator used for treatment of breast cancer and for prevention of breast cancer in high-risk patients.72,74 Among women with breast cancer currently being treated with tamoxifen, compared with previous users or those who never used it, the odds ratio was 7.1.74 Others found a lower odds ratio of 2.7.43 The odds ratio for VTE in women at high risk of breast cancer who received tamoxifen to prevent breast cancer was 2.1.73 Others found a hazard ratio of 1.63.72

7. Hormonal replacement therapy

There is a 2- to 3-fold increased risk of VTE with the use of hormone replacement therapy in postmenopausal women.75,76 Among postmenopausal women who had coronary artery disease and received estrogen plus progestin, the relative hazard of VTE was 2.7 compared with nonusers.77 Review showed that the risk of VTE is highest in the first year of hormone replacement therapy.78 The risk of VTE is increased for oral estrogen alone, oral estrogen combined with progestin, and probably for transdermal hormone replacement therapy.78

8. Congenital hypercoagulable disorders

8.1 Antithrombin deficiency

Antithrombin is a serine protease inhibitor of thrombin and also inhibits factors IXa, Xa, XIa, and XIIa. Thrombin is irreversibly bound by antithrombin and prevents thrombin's action on fi brinogen, on factors V, VIII, and XIII, and on platelets.[79] This anticoagulant is synthesized in the liver and endothelial cells, and has a half-life of 2.8 days.[80] Antithrombin deficiency has a prevalence of 1 : 5000 with more than 100 genetic mutations and an autosomal dominant inheritance pattern.[81] Homozygotes typically die *in utero* whereas heterozygotes typically have an antithrombin level that is 40 to 70% of normal.

Antithrombin deficiency is associated with lower extremity venous thrombosis as well as mesenteric venous thrombosis. The most common presentation in those with antithrombin deficiency is deep venous thrombosis with or without pulmonary embolism.[82]

8.2 Protein C and protein S deficiency

Protein C is a vitamin K dependent anticoagulant protein that, once activated by thrombin, will inactivate factors Va and VIIIa, thereby inhibiting the generation of thrombin.[83] Additionally, activated protein C stimulates the release of t-PA. It is produced in the liver and is the dominant endogenous anticoagulant with an eight-hour half-life. Protein C deficiency has a prevalence of 1 in 200–300 with more than 150 mutations and an autosomal dominant inheritance.[83,84]

Protein S is also a vitamin K dependent anticoagulant protein that is a cofactor to activated protein C. The actions of protein S are regulated by complement C4b binding protein and only the free form of protein S serves as an activated protein C cofactor.[85] Additionally, protein S appears to have independent anticoagulant function by directly inhibiting procoagulant enzyme complexes.[84,86] The prevalence of protein S defi ciency is about 1 : 500 with an autosomal dominant inheritance.

Clinically, protein C and S deficiencies are essentially identical. With homozygous protein C and S defi ciencies, infants typically will succumb to purpura fulminans, a state of unrestricted clotting and fi brinolysis. In heterozygotes, venous thromboses may occur at an early age especially in the lower extremity.[87] Thrombosis may also occur in mesenteric, renal, and cerebral veins.

8.3 Factor V Leiden mutation and activated protein C resistance

Factor V is a glycoprotein synthesized in the liver. With Factor V Leiden, a point mutation occurs when arginine is substituted by glutamine at position 506. This point mutation causes the activated Factor V to be resistant to inactivation by activated protein C thus causing a procoagulant state.

Clinically, patients may present with deep venous thrombosis in the lower extremities, or less commonly in the portal vein, cerebral vein, or superfi cial venous system.

8.4 Prothrombin G20210 polymorphism

Prothrombin (Factor II) is a zymogen synthesized in the liver and dependent on vitamin K. When prothrombin is activated, it forms thrombin (Factor IIa). A single mutation where adenine is substituted for guanine occurs at the 20210 position. The mechanism for increased thrombotic risk is not well understood, but individuals with this genetic variant have supranormal levels of prothrombin. The mutation is inherited as an autosomal dominant trait and is associated with both arterial and venous thrombosis.

Clinically, patients may present with deep venous thrombosis of the lower extremity, cerebral venous thrombosis, as well as arterial thrombosis. The risk of thrombosis increases in the presence of other genetic coagulation defects and with acquired risk factors.[88,84]

8.5 Hyperhomocysteinemia

Homocysteine is an amino acid formed during the metabolism of methionine and may be elevated secondary to inherited defects in two enzymes that are part of the conversion of homocysteine to cysteine. The two enzymes involved are N5,N10–methylene tetrahydrofolate reductase (MTHFR) or cystathionine beta-synthase. Hyperhomocysteinemia has been shown to increase the risk of atherosclerosis, atherothrombosis, and venous thrombosis. Elevated plasma homocysteine levels cause various dysfunctions of endothelial cells leading to a prothrombotic state.

Hypercoagulable syndromes include inherited and acquired thrombophilias. The former is discussed in detail in the article by Weitz in this issue. The latter includes the antiphospholipid syndrome, heparin-induced thrombocytopenia, acquired dysfibrinogenemia, myeloproliferative disorders, and malignancy. Myeloproliferative disorders and malignancy are described elsewhere in this article. Regarding the antiphospholipid syndrome, antiphospholipid antibodies are associated with both arterial and venous thrombosis.[89] The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant antibodies, anticardiolipin antibodies and anti-b2-glycoprotein I antibodies.[90] DVT, the most common manifestation of the antiphospholipid syndrome, occurs in 29% to 55% of patients with the syndrome, and about half of these patients have pulmonary emboli.[91,92] The risk of heparin-associated thrombocytopenia is more duration related than dose related. Heparin-associated thrombocytopenia occurs more frequently with unfractionated heparin when used for an extended duration than with LMWH used for an extended duration.[93] When used for prophylaxis, there was a higher prevalence of heparin-associated thrombocytopenia inthose receiving unfractionated heparin (1.6%, 57 of 3463) than in those receiving LMWH (0.6%, 23 of 3714).[93] However, treatment resulted in only a small difference in the prevalence of heparinassociated thrombocytopenia comparing unfractionated heparin (0.9%, 22 of 2321) with LMWH (0.6%, 18 of 3126).[93] Acquired dysfibrinogenemia occurs most often in patients with severe liver disease.[94] The impairment of the fibrinogen is a structural defect caused by an increased carbohydrate content impairing the polymerization of the fibrin, depending on the degree of abnormality of the fibrinogen molecule.[94]

9. Heart failure

Congestive heart failure (CHF) is considered amajor risk factor for VTE.[13,41,61,95,96] Among patients with established CHF, those with lower ejection fractions had a higher risk of thromboembolic event.[97,98] However, some investigators did not evaluate CHF among the risk factors for VTE.[99] The reported frequency of PE in patients with heart failure has ranged widely from 0.9% to 39% of patients. [13,97,98,100,101] The reported frequency of DVT in patients with CHF also ranged widely from 10% to 59%.[13,41,61] The largest investigation was from the National Hospital Discharge Survey.[102] Among 58,873,000 patients hospitalized with heart failure in short-stay hospitals from 1979 to 2003, 1.63% had VTE (relative risk 5 1.47).[102] The relative risk for VTE was highest in patients less than 40 years old (relative risk 5 6.91). Some showed the lower the ejection fraction, the greater the risk of VTE.[103] Among 755,807 adults older than 20 years with heart failure who died from 1980 to 1998, PE was listed as the cause of death in 20,387 (2.7%).[104] Assuming that the accuracy of death certificates was only 26.7%,[105] the rate of death from PE in these patients may have been as high as 10.1%.

Therefore, the estimated death rate from PE in patients who died with heart failure was 3% to 10%. CHF seems to be a stronger risk factor in women. Dries and colleagues[97] reported a higher proportion of PE in women (24%) compared with men (14%). We too showed a higher relative risk of PE and of DVT in women with CHF than in men.[102] Although these data seemcompelling, multivariate logistic analysis failed to identify CHF as an independent risk factor for DVT or PE.[43] However, it was a risk factor for postmortem VTE that was not a cause of death.[43] In one study of pediatric patients with dilated cardiomyopathy awaiting transplant the incidence of pulmonary embolism was 13.9% [106].

Heart failure is the second most common risk factor for VTE in hospitalized patients, as shown in ENDORSE.[107]

10. COPD

Hospitalized patients with exacerbations of COPD, when routinely evaluated, showed PE in 25% to 29%.[108,109]From 1979 to 2003, 58,392,000 adults older than 20 years were hospitalized with COPD in short-stay hospitals in the United States.[110] PE was diagnosed in 381,000 (0.65%) and DVT in 632,000 (1.08%).[110] The relative risk for PE in adults hospitalized with COPD was 1.92 and for DVT it was 1.30. Among those aged 20 to 39 years with COPD, the relative risk for PE was 5.34. Among patients with COPD aged 40 to 59 years, the relative risk for PE decreased to 2.02, and among patients aged 60 to 79 years the relative risk for PE was 1.23.[110] The relative risk for DVT was also higher in patients with COPD aged 20 to 39 years (relative risk 5 2.58) than in patients aged 40 years or older (relative risk 0.92-1.17, depending on age).[110] In young adults, other risk factors in combination with COPD are uncommon, so the contribution of COPD to the risk of PE becomes more apparent than in older patients. Although these data strongly suggest that COPD is a risk factor for PE and DVT, multivariate logistic analysis did not identify it as an independent risk factor.[43] Others, with univariate analysis, did not identify COPD as a risk factor.[61]

Neuhaus et al. [111] found pulmonary emboli in 27% of 66 autopsies performed in patients who had respiratory failure (not only as a decompensation of COPD) and died after admission to a Respiratory Intensive Care Unit.

The largest study was conducted by Schonhofer and Kohler [112] on a population of 196 patients admitted to a respiratory intensive care unit. The authors found a DVT rate of 10.7% as assessed by US. The majority (86%) of cases were asymptomatic and, interestingly, almost all major clinical variables (such as age, weight, severity of dyspnea, lung function, situation of blood gases) failed to predict patients who were more likely to develop DVT.

11. Stroke

There is considerable evidence that in spinal cord injury patients interruption of neurologic impulses and the ensuing paralysis cause profound metabolic changes in blood vessels accountable for venous thrombosis.

Vascular adaptations to inactivity and muscle atrophy, rather than the effect of a nonworking leg-muscle pump and sympathetic denervation, cause thrombosis, indicating that thrombosis established through venous incompetence cannot be reversed by anticoagulation alone.

Spinal cord injuries with paralysis result in an immobile state with retardation of the blood flow caused by the relaxation of muscle and the atony of blood vessels. It is not surprising that spinal cord injuries are frequently complicated by the development of venous thrombosis, which is inevitably linked to hospitalization, immobilization, vein wall damage, stasis, and hypercoagulability. Deep vein thrombosis and pulmonary emboli remain the major complications in spinal cord injuries below the C2 through T12 vertebrae associated with motor complete or motor nonfunctional paralysis. [113,114,115,116,117,118,119] Two surprising findings set spinal cord injury apart from other risk factors for venous thrombosis: incidence of leg DVT and pulmonary embolism in spinal cord injury is three times higher than in the general population.

Patients with stroke are at particular risk of developing DVT and PE because of limb paralysis, prolonged bed rest, and increased prothrombotic activity.[120] Among 14,109,000 patients with ischemic stroke hospitalized in short-stay hospitals from 1979 to 2003, VTE was diagnosed in 165,000 (1.17%).[121] Among 1,606,000 patients with hemorrhagic stroke, the incidence of VTE was higher (1.93%).

Among patients with ischemic stroke who died from 1980 to 1998, PE was the listed cause of death in 11,101 of 2,000,963 (0.55%).[122] Based on an assumed sensitivity of death certificates for fatal PE of 26.7% to 37.2%,[105,123] the corrected rate of fatal PE was 1.5% to 2.1%. Death rates from PE among patients with ischemic stroke decreased from 1980 to 1998, suggesting effective use of antithrombotic prophylaxis.

12. Cancer

Cancer is a major risk factor of venous thromboembolism (VTE) [124,125] as defined by deep-vein thrombosis (DVT) – including central venous catheter (CVC) related thrombosis – or pulmonaryembolism (PE), which occur in 4 to 20% of cancer patients [126,127].

12.1 Cancer-related factors

12.1.1 Site of cancer

In studies looking at pooled groups of patients with different types of malignancy, the rate of VTE is consistently highest in patients with cancer of the pancreas, stomach, brain, kidney, uterus, lung or ovary [128,129,130,131].

Both large retrospective studies by Stein et al and Chew et al based on discharge claims databases reported the highest rates of VTE in patients with pancreatic cancer (4.3% and 5.3%, respectively). Patients with stomach cancer had the second and third highest risk of developing VTE in these studies [128,132]. In patients with testicular and lung cancer, those with metastases to the liver and brain were shown to have higher rates of VTE compared with patients with other sites of metastases [133,134]. The rates of VTE for specific types of cancer have been reported in many studies.

12.1.2 Cancer stage

Multiple studies have shown an increased risk of VTE in patients with advanced-stage cancer. In a retrospective study of over 500 000 patients from the California Cancer Registry, patients with metastatic cancer stage were twice as likely to have developed VTE in the year

prior to diagnosis of cancer [135]. In a population-based case–control study of patients with newly diagnosed VTE, including 389 patients with cancer, those with distant metastases had a higher risk of VTE (OR 19.8, CI 2.6–149) [136].

A multicentre retrospective study of VTE in hospitalized cancer patients reported an incidence of 10.3% in patients with advanced-stage cancer compared with 5.6% in patients with localized disease (P < 0.0005, OR 1.92, CI 1.21–3.04) [137], and these findings have been supported by other large studies in hospitalized cancer patients [138]. Other studies in ovarian, colorectal, pancreatic, lung and breast cancer support the finding that advanced-stage disease increases the risk of cancer- associated VTE [139,140,141,142,143,144].

12.2 Histology

In certain types of cancer, higher rates of VTE are found in some histological subtypes compared with others. For example, in patients with non-small-cell lung cancer, 9.9% of those with adenocarcinoma subtype develop VTE in the first 6 months after diagnosis compared with 7.7% with squamous cell carcinoma (HR 1.9, CI 1.7–2.1) [141].Inbreast and colon cancer patients, the type of histology does not predict for the incidence of cancer-associated VTE, but VTE-associated mortality rates are higher in patients with certain histological subtypes [141,143].

12.3 Time after diagnosis

Several studies have demonstrated that the risk of VTE is highest in the initial time period following cancer diagnosis. In a population-based study of patients with thrombosis, the risk of developing VTE was highest in the first few months following the initial diagnosis of malignancy. A retrospective analysis of over 200 000 cancer patients from the California Cancer Registry revealed that the rate of VTE per patient-year in the first year after diagnosis of cancer was 3.3, compared with 0.8 in the second year after diagnosis [145]. The rate of VTE in patients with colon cancer during the first 6 months after diagnosis is 5.0/100 patient-years, but this drops off dramatically to 1.4/100 patient-years in the next 6- month period [143].

12.4 Chemotherapy

Chemotherapy is one of the most important factors in VTE risk stratification of cancer patients. Large population-based studies in groups of pooled cancer patients have demonstrated a significantly increased risk in patients receiving chemotherapy. Heit et al used a population-based study of patients with a new diagnosis of VTE, 23% of which had a diagnosis of active malignancy, to demonstrate a significantly increased risk of VTE in those on chemotherapy (OR 6.5, CI 2.11–20) [146].

Studies in specific types of cancer and with specific antineoplastic agents have also supported the role of chemotherapy in predicting the risk of cancer-associated VTE. Two prospective studies of breast cancer patients demonstrated that the risk of VTE in patients receiving chemotherapy in addition to tamoxifen or surgery increased two- to seven-fold [147,148]. A recent meta-analysis of breast cancer patients revealed that use of adjuvant hormonal therapy was associated with a 1.5–7-fold increased risk of VTE [149].

12.5 Surgery

Surgery is a well-known risk factor for development of VTE in patients without cancer. The incidence of DVT in cancer patients undergoing general surgery is estimated at 37% compared with 20% in patients without cancer [150]. Factors related to immobility, tissue destruction and venous stasis are likely to be related to the increased risk of VTE after surgery.

12.6 Indwelling catheters

Indwelling central venous catheters (CVC) greatly facilitate treatment in cancer patients, but they are also associated with complications including a significant risk of catheter-associated thrombosis. The incidence of symptomatic catheter-related DVT in adult patients ranges from 0.3% to 28%, while the rate of catheter-related DVT assessed by venography is 27–66%[151].

Studies have not consistently demonstrated an association between use of haematopoietic growth factors and risk of cancer-associated VTE. İn a prospective study of ambulatory patients receiving chemotherapy, both the use of white cell growth factors and the use of red cell growth factors or decreased haemoglobin were independent predictors of VTE in multivariate analysis [152]. This association was only significant in types of cancer already known to have high rates of thrombosis, and it is possible that these agents are used more frequently in patients with other markers of poor prognosis or more aggressive disease.

12.7 Platelet and leukocyte counts

The authors' group was the first to identify an elevated prechemotherapy platelet count as a significant risk factor for cancer-associated thrombosis [152]. In a prospective study of outpatients receiving chemotherapy, 21.9% had a platelet count of 350 000/mm3 or more prior to starting chemotherapy. The incidence of VTE was 3.98% (1.66% per month) for these patients, which was significantly higher than the rate of 1.25% (0.52% per month) for patients with a prechemotherapy platelet count of less than 200 000/mm3 (P for trend¼ 0.0003). The distribution of rechemotherapy platelet counts in patients who subsequently developed VTE was significantly higher than that for patients who did not develop VTE (t-test P ¼0.002, Wilcoxon rank sum test P ¼0.0002).

12.8 Tissue factor

Tissue factor (TF), a transmembrane glycoprotein present on subendothelial tissue, platelets and leukocytes, is a key component in the initiation of coagulation and may play a role in cancer- associated thrombosis [153-155]. The authors recently demonstrated a correlation between the level of TF expression in pancreatic tumours and subsequent development of VTE [156]. VTE was four-fold more common (P ¼ 0.04) among patients with high TF-expressing carcinomas (26.5%) than among patients with low TF-expressing carcinomas (5.5%).

From 1979 to 1999, among 40,787,000 patients hospitalized in short-stay hospitals with any of 19 malignancies studied, 827,000 (2.0%) had VTE.[157] This was twice the incidence in patients without these malignancies.[157] The highest incidence of VTE was in patients with

carcinoma of the pancreas (4.3%) and the lowest incidences were in patients with carcinoma of the bladder and carcinoma of the lip, oral cavity, or pharynx (<0.6% to 1.0%). Incidences with cancer were not age dependent.157 Myeloproliferative diseaseand lymphoma were associated with relative risks for VTE of 2.9 and 2.5, respectively157 Leukemia was associated with a lower relative risk (1.7). Based on death certificates from 1980 to 1998 among patients who died with cancer, PE was the listed cause of death in 0.21%.158 Adjustment of the data for the frailty of the diagnosis of fatal PE based on death certificates indicated a likely range of 0.31% to 1.97%.158

13. Pregnancy

Pregnancy-associated DVT based on data from the National Hospital Discharge Survey was diagnosed in 93,000 of 80,798,000 women (0.12%) from 1979 to 1999.151 The rate of pregnancyassociated DVT (vaginal delivery and cesarean section) increased from 1982 to 1999, although the rate of nonpregnancy-associated DVT decreased for most of this period. Some showed the rate of pregnancy-associated DVT was twice the rate of nonpregnancy-associated DVT.159 A 6-fold increase in the rate of thromboembolism during pregnancy and the puerperium compared with nonpregnant women has been reported by others.160 Although the rate of pregnancy-associated DVT was higher than the rate of nonpregnancyassociated DVT, the rate of pregnancyassociated PE was lower than

Pathophysiology of venous thromboembolism during Pregnancy:

Increased venous distensibility and capacity, with a resultant reduction in the velocity of blood flow in the lower limbs, are demonstrable from the first trimester of pregnancy[162,163]. These changes are compounded by a 20–25% increase in the overall circulatory volume during pregnancy[164]. Obstruction of the inferior vena cava by the enlarging gravid uterus may also result in increased stasis[165]. Compression of the left iliac vein by the right iliac artery as they cross [166] may explain the preponderance of left leg DVT during pregnancy [161,167].

Altered levels of coagulation factors have been described both during pregnancy and postpartum. Hypercoagulability is thought to be promoted by increases in coagulation factors such as fibrinogen, von Willebrand factor, and factor VIII:C [168,169-171], as well as by decreases in natural inhibitors of coagulation such as protein S [172] and the development of an acquired resistance to the endogenous anticoagulant, activated protein C [173]. In addition, a reduction in global fibrinolytic activity has been described during pregnancy [174], perhaps as a consequence of increases in the levels of plasminogen activator inhibitor 1 (PAI 1) and plasminogen activator inhibitor 2 (PAI 2) [174-176], the latter being produced by the placenta.

Exogenous risk factors also appear to determine the thrombotic risk associated with pregnancy. In a retrospective cohort study of unselected consecutive patients with confirmed pregnancy-related venous thromboembolism, approximately two-thirds of patients had an identifiable acquired risk factor (for example, age over 35 years, intercurrent illness, immobility, increased parity or caesarean section) [177].

The reason for this difference is unknown and could reflect difference of the natural history of DVT in pregnancy. It also could reflect a reluctance to expose pregnant women to ionizing radiation associated with imaging for PE, resulting in a decreased frequency of diagnosis of PE. The rate of pregnancy-associated DVT was higher among women aged 35 to 44 years than in younger women. The rate of pregnancyassociated DVT among black

women was higher than among white women.159,178,179 DVT was more frequent among women who underwent cesarean section (104/100,000/y) than those who underwent vaginal delivery (47/ 100,000/y).159 VTE in pregnancy is discussed in detail in the article by Marik elsewhere in this issue.

14. Surgery and trauma

In PIOPED, trauma of the lower extremities was a predisposing factor in 10% of patients with PE, and in PIOPED II trauma of the lower extremities or pelvis was a predisposing factor in 14%.180,181 Surgery within 3 months of the acute PE was a predisposing factor in 54% in PIOPED and in 23% in PIOPED II.180,181 The prevalence of VTE following various categories of surgery and trauma has been reviewed in detail by Geerts and colleagues182.

15. Central venous access

The use of long-term venous access is now an integral component of treatment for patients receiving long-term antibiotic administration or hyperalimentation or undergoing chemotherapy. Externalized tunneled catheters were introduced almost 30 years ago, but required daily cleaning and frequent flushing190,191. On average, deep venous thrombosis (DVT) can complicate approximately 2%–6.7% of such port placements192 - 194, although literature reports have ranged from 0% to 26%195-198. In 1991, Monreal et al.199 observed that 4 of 30 consecutive patients with upper extremity deep venous thrombosis (DVT) had PE (13.3%), but more importantly, all these 4 occurred in 20 catheter related DVT patients (20%), while none of 10 patients with primary upper extremity DVT had PE.

16. Medical illnesses

16.1 Inflammatory bowel disease

The incidence of VTE among hospitalized medical patients with ulcerative colitis was 1.9% and the incidence with Crohn disease was lower (1.2%).200 Among medical patients who had neither ulcerative colitis nor Crohn disease the incidence was 1.1%.200 The relative risk of VTE among patients with ulcerative colitis compared with patients who did not have inflammatory bowel disease was 1.9 and with Crohn disease it was 1.2. Among patients younger than 40 years with ulcerative colitis, the relative risk of VTE compared with patients who did not haveinflammatory bowel disease was 2.96 and in patients younger than 40 years with Crohn disease the relative risk was 2.23.200

16.2 Liver disease

Patients with chronic liver disease (both alcoholic and nonalcoholic) seem to have a lower risk of PE than patients without liver disease,43,201 but data are inconsistent.202 Chronic liver disease may result in impaired production of vitamin-K dependent procoagulant factors.203 However, decreased production of vitamin-K dependent endogenous anticoagulants, such as protein C, protein S, and antithrombin III, may counter the hypocoagulability in such patients.203 Other prothrombotic factors may counteract the impaired production of vitamin Kdependent procoagulant factors including lupus anticoagulant, activated protein C resistance, PT20210A mutation, Factor V Leiden, MTHFR

mutation, and increased levels of factor VIII.204 Based on data from the National Hospital Discharge Survey, among 4,927,000 hospitalized patients with chronic alcoholic liver disease from 1979 to 2006, the prevalence of VTE was 0.6% and among 4,565,000 hospitalized patients with chronic nonalcoholic liver disease it was 0.9%.201 The prevalence of VTE was higher in those with chronic alcoholic liver disease than with nonalcoholic liver disease, but the difference was small and of no clinical consequence.201

Both showed a lower prevalence of VTE than in hospitalized patients with most other medical diseases. It may be that both chronic alcoholic liver disease and chronic nonalcoholic liver disease have protective antithrombotic mechanisms although the mechanisms differ.

16.3 Hypothyroidism

Among 19,519,000 hospitalized patients with a diagnosis of hypothyroidism from 1979 to 2005, 119,000 (0.61%) had PE (relative risk 5 1.64).205 DVT was diagnosed in 1.36% of hypothyroid patients (relative risk 5 1.62).205 The relative risk for PE in patients with hypothyroidism was highest in patients younger than 40 years (relative risk 5 3.99) and the relative risk for DVT was also highest in patients younger than 40 years (relative risk 5 2.25). Hyperthyroidism was not associated with an increased risk for VTE (relative risk 5 0.98).

16.4 Rheumatoid arthritis

Rheumatoid arthritis is not generally considered a risk factor for VTE, although abnormalities of coagulation factors have been found in patients with rheumatoid arthritis.206,207 Among 4,818,000 patients hospitalized in short-stay hospitals from 1979 to 2005 with rheumatoid arthritis who did not have joint surgery, the incidence of PE was 2.3%, and the relative risk of VTE compared with those who did not have rheumatoid arthritis was 1.99.208 Among patients younger than 50 years the relative risk was higher (2.13).208

16.5 Diabetes mellitus

Among 92,240,000 patients with diabetes mellitus hospitalized from 1979 to 2005, 1,267,000 (1.4%) had VTE.209 The relative risk for VTE was increased only in patients younger than 50 years and was highest in patients aged 20 to 29 years (relative risk 5 1.73). In patients with diabetes mellitus who did not have obesity, stroke, heart failure, or cancer, compared with those who did not have diabetes mellitus and did not have any of these comorbid conditions, the relative risk for VTE was 1.52 in patients aged 20 to 29 years and 1.19 in patients 30 to 39 years. In older patients, the relative risk of VTE in patients with diabetes mellitus was not increased.209 Among all adults with diabetes mellitus, the relative risk of VTE was 1.05.209

16.6 Human immunodeficiency virus

Among 2,429,000 patients older than 18 years hospitalized in short-stay hospitals from 1990 through 2005 with human immunodeficiency virus (HIV) infection; the prevalence of VTE was 1.7% (relative risk 5 1.21).210 The prevalence of VTE in patients aged 30 to 49 years was also 1.7%, but the relative risk compared with patients who did not have HIV infection was higher (1.65).210

16.7 Nephrotic syndrome

From 1979 to 2005, 925,000 patients were discharged from short-stay hospitals with nephrotic syndrome and 14,000 (1.5%) had DVT (relative risk 5 1.72).211 In patients aged 18 to 39 years the relative risk for DVT was 6.81.211 Renal vein thrombosis was so uncommon that too few were reported to calculate its prevalence. Therefore, PE, if it occurs, is likely to be due to emboli from the lower extremities and not the renal vein.

16.8 Sickle cell disease

Sickle cell disease does not seem to be a risk factor for DVT.212 Among 1,804,000 patients hospitalized in short-stay hospitals with sickle cell disease from 1979 to 2003, 11,000 (0.61%) had a discharge diagnosis of DVT, which was not more than in African Americans without sickle cell disease (0.81%).212 Among patients with sickle cell disease, a discharge diagnosis of PE was made in 0.50% compared with 0.33% who did not have sickle cell disease. Regarding patients younger than 40 years, 0.44% had PE, whereas among patients who did not have sickle cell disease, 0.12% had PE.212 The higher prevalence of apparent PE in patients with sickle cell disease compared with African American patients the same age who did not have sickle cell disease, and the comparable prevalence of DVT in both groups, is compatible with the concept that thrombosis in situ may be present in many.

16.9 Systemic lupus erythematosus

Systemic lupus erythematosus is believed to be independently associated with the risk of developing DVT.61 The odds ratio for DVT in patients with systemic lupus erythematosus, compared with those without it, was 4.3.61

16.10 Behçet disease

Behcet disease is a rare multisystem inflammatory disorder of unknown cause.213 VTE occurs in about one-fifth of patients with Behc¸ et disease.213

16.11 Paroxysmal nocturnal hemoglobinuria

Review of 13 retrospective studies of patients with paroxysmal nocturnal hemoglobinuria showed a 30% prevalence of venous thrombotic events in patients from Western nations.214 The majority was within the hepatic and mesenteric veins.214

16.12 Buerger disease

PE associated with thromboangiitis obliterans (Buerger disease) is rare, and to our knowledge, limited to a case report.215

17. Sepsis

Initiation of coagulation takes place when TF is exposed, such as by fibroblasts, when there is tissue damage or by cytokine-stimulated monocytes and endothelial cells[216], as in sepsis. While TF is the major initiator of coagulation, endotoxin, foreign bodies, and negatively charged particles may initiate coagulation via contact system activation. TF binds to factor

VIIa, and this complex (TF:VIIa) may then activate factor X and factor IX[217]. Factor Xa, associated with factor Va, forms the prothrombinase complex, which subsequently turns prothrombin into thrombin.

The relationship between coagulation and inflammation is complex and, as yet, not completely understood. It is known that blood clotting not only leads to fibrin deposition and platelet activation, but it also results in vascular cell activation, which contributes to leukocyte activation[218]. On the other hand, inflammation can induce TF expression in monocytes, via nuclear factor kappa-B (NF-kB) activation, thus initiating coagulation[216].

Examples of this interaction are readily seen. First, leukocytes are found at relatively high concentrations in venous thrombi, and leukocytes and activated platelets can form rosettes mediated by P-selectin expression on the surface of the activated platelet [219,220].

These microscopic observations are probably elicited from the actions of thrombin, which can activate platelets and endothelium, increasing the surface expression of P-selectin[221,222]. P- electin is the primary initial mediator of leukocyte-endothelial cell rolling and is critical for leukocyte adhesion. Second, TF:VIIa and factor Xa have been shown to activate cells and generate responses similar to those mediated by thrombin[218]. Third, GAG and TM expression on cell surfaces are inhibited by inflammatory cytokines [223,224,225,226] and lipopolysaccharide (LPS)[227], thus blocking the augmentation of AT action by GAG, and APC formation by TM.

18. References

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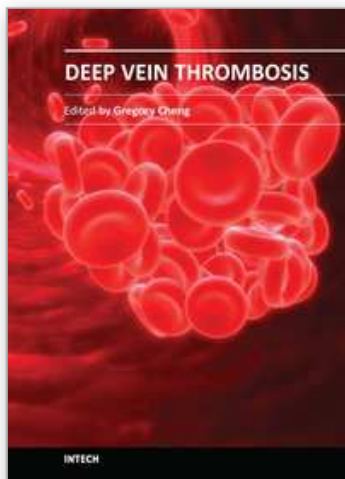[160] Stein PD, Hull RD, Kayali F, et al. Venous thromboembolism in pregnancy: 21 year trends. Am J Med 2004;117:121e5.

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Deep Vein Thrombosis

Edited by Dr. Gregory Cheng

This book provides a comprehensive review of deep vein thrombosis. There are chapters on risk factors for DVT, post thrombotic syndrome and its management, vena cava malformation as a new etiological factor and thrombosis in the upper limbs. DVT is usually seen in patients undergoing major surgeries. The guidelines for thrombo-prophylaxis in orthopaedic patients, radical pelvic surgeries, laparoscopic operations and risks versus benefits in regions with a low prevalence of DVT are thoroughly addressed. Cancer and its treatment are recognized risk factors for VTE and extended prophylaxis in ambulatory cancer patients is reviewed. The role of imaging and endovascular therapies in acute DVT, hypercoagulabilty in liver diseases and the challenges in developing countries are discussed.

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