XVIII VENOUS THROMBOEMBOLISM

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Venous thromboembolism, which involves venous thrombosis and pulmonary embolism, is a leading cause of morbidity and mortality in hospitalized patients and is being seen with increasing frequency in outpatients.[1] This increased incidence of venous thromboembolism in outpatients may be attributable to clinicians' heightened awareness of the importance of this condition and the comparatively recent development of reliable noninvasive tests for its diagnosis.

Risk Factors and Etiology

Most patients with venous thromboembolism have one or more well-recognized clinical risk factors. The most common risk factors are recent surgery, trauma, and immobility, as well as serious illness, including congestive heart failure, stroke, malignancy, and inflammatory bowel disease.[2] The common risk factors in outpatients include hospital admission within the past 6 months,[3] malignancy, presence of antiphospholipid antibody, and familial thrombophilia. Less common risk factors are paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, and polycythemia vera.

Classification

Although venous thrombosis can occur in any vein in the body, it usually involves superficial or deep veins of the legs. Generally benign and self-limiting, thrombosis in a superficial vein of the leg can be serious if it extends from the long saphenous vein into the common femoral vein or if it is associated with deep vein thrombosis that is clinically silent. Superficial thrombophlebitis is easily recognized by the presence of a tender vein surrounded by an area of erythema, heat, and edema. A thrombus can often be palpated in the affected vein. Superficial thrombophlebitis may be associated with deep vein thrombosis. In most cases, superficial disease can be treated conservatively with anti-inflammatory drugs.

Thrombosis involving the deep veins of the leg may be confined to calf veins or may extend into the popliteal or more proximal veins. Thrombi confined to calf veins are usually small and are rarely associated with pulmonary embolism.[2,4] About 20% of calf vein thrombi, however, extend into the popliteal vein and beyond, where they can cause serious complications.[2,4] About 50% of patients with symptomatic proximal vein thrombosis also have silent pulmonary embolism, with high-probability ventilation perfusion lung scans,[4] and about 70% of patients with symptomatic pulmonary embolism have deep vein thrombosis, which is usually clinically silent.[2,5]

Pulmonary embolism is the most serious and most feared complication of venous thrombosis, but the postthrombotic syndrome, which occurs as a long-term complication in 30% to 50% of patients with symptomatic proximal vein thrombosis after 8 years of follow-up,[6,7] is responsible for greater morbidity. Most cases of the postthrombotic syndrome occur within 2 years of the acute thrombotic event.[6,7] Clinically, the postthrombotic syndrome may mimic acute venous thrombosis but typically presents as chronic leg pain that is associated with edema and worsens at the end of the day. Some patients also have stasis pigmentation, induration, and skin ulceration; a smaller number of patients have venous claudication on walking caused by persistent obstruction of the iliac veins. A study has reported that the routine use of compression stockings reduces the incidence of the postthrombotic syndrome by about 50%.[7]

Pathophysiology

Venous thrombi are composed predominantly of fibrin and red blood cells. They usually arise at sites of vessel damage or in the large venous sinuses of the calves or the valve cusp pockets in the deep veins of the calves. Thrombosis occurs when blood coagulation overwhelms the natural anticoagulant mechanisms and the fibrinolytic system. Coagulation is usually triggered when blood is exposed to tissue factor on the surface of activated monocytes that are attracted to sites of tissue damage or vascular trauma. Clinical risk factors that activate blood coagulation include extensive surgery, trauma, burns, malignant disease, myocardial infarction, cancer chemotherapy, and local hypoxia produced by venous stasis. Malignant cells contain a cysteine proteinase that activates factor X, which is a key clotting enzyme. Venous stasis and damage to the vessel wall increase the thrombogenic effect of blood coagulation. Venous stasis is produced by immobility, by obstruction or dilatation of veins, by increased venous pressure, and by increased blood viscosity. The critical role of stasis in the pathogenesis of venous thrombosis is exemplified by the observation that thrombosis occurs with equal frequency in the two legs in paraplegic patients but occurs with greater frequency in the paralyzed limb than in the nonparalyzed limb in stroke patients.[2]

Tissue damage, by stimulating the release of inflammatory cytokines, also results in impaired fibrinolysis. The cytokines induce endothelial cell synthesis of plasminogen activator inhibitor–1 (PAI-1)[8] and, by downregulating the endothelial-bound anticoagulant thrombomodulin,[2] reduce the protective effect of the vascular endothelium.

Increased central venous pressure, which produces venous stasis in the extremities, may explain the high incidence of venous thrombosis in patients with heart failure. Stasis resulting from venous dilatation occurs in elderly patients, in patients with varicose veins, and in women who are pregnant or using supplemental estrogen, perhaps contributing to the increased incidence of thrombosis in these persons. Venous obstruction contributes to the risk of venous thrombosis in patients with pelvic tumors. Increased blood viscosity, which also causes stasis, may explain the risk of thrombosis in patients with polycythemia vera, hypergammaglobulinemia, or chronic inflammatory disorders. Direct venous damage may lead to venous thrombosis in patients undergoing hip surgery, knee surgery, or varicose vein stripping and in patients with severe burns or trauma to the lower extremities.[2]

Table 1 Model for Determining Clinical Suspicion of Deep Vein Thrombosis[32]

Variables	*Points**
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days, or major surgery within the past 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Affected calf 3 cm greater than asymptomatic calf (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Dilated superficial veins (nonvaricose)	1
Alternative diagnosis is at least as likely as that of deep vein thrombosis	-2
Total points	

*Pretest probability is calculated as follows: total points ≤ 0, low probability; 1 to 2, moderate probability; ≥ 3, high probability.

Blood coagulation is modulated by circulating inhibitors or by endothelial cell–bound inhibitors. The most important circulating inhibitors of coagulation are antithrombin (AT), protein C, and protein S.[9,10] An inherited deficiency of one of these three proteins is found in about 20% of patients who have a family history of venous thrombosis and whose first episode of venous thrombosis occurs before 41 years of age.[11] Some types of congenital dysfibrinogenemias can also predispose patients to thrombosis, as can a congenital deficiency of plasminogen.[12] An inherited thrombophilic defect, known as activated protein C (APC) resistance or factor V Leiden, is now established as the most common cause of inherited thrombophilia, occurring in about 5% of whites who do not have a family history of venous thrombosis and in about 20% of patients with a first episode of venous thrombosis.[13,14] The second most common thrombophilic defect is a mutation (G20210A) in the 3′ untranslated region of the prothrombin gene that results in about a 25% increase in prothrombin levels.[13,15] This mutation occurs in about 2% of whites without a family history of venous thrombosis and in about 5% of patients with a first episode of venous thrombosis.[13] Elevated levels of clotting factors VIII[16] and XI[17] and of homocysteine[18] also predispose patients to thrombosis. The risk of thrombosis in patients with activated protein C resistance or the prothrombin gene mutation is increased by estrogen-containing oral contraceptives.[13,19] A randomized trial also found that the administration of estrogens in the doses used for postmenopausal replacement more than doubled the risk of thromboembolism.[20]

Natural History and Prognosis

Most venous thrombi produce no symptoms and are confined to the intramuscular veins of the calf. Many calf vein thrombi undergo spontaneous lysis, but some extend into the popliteal and more proximal veins. Complete lysis of proximal vein thrombosis is less common.[2,21] Most symptomatic pulmonary emboli and virtually all fatal emboli arise from thrombi in the proximal veins of the legs. Extensive venous thrombosis causes valvular damage, which is thought to lead to the postthrombotic syndrome. Patients with a history of venous thrombosis are more likely to experience additional episodes, particularly if they are exposed to high-risk situations.[1]

Untreated or inadequately treated venous thrombosis is associated with a high rate of complications, which can be decreased considerably by adequate anticoagulant therapy. About 20% to 30% of untreated calf vein thrombi extend into the popliteal vein, and about 40% to 50% of untreated proximal vein thrombi also undergo extension.[2,4,22] Patients with proximal vein thrombosis who are inadequately treated have a recurrence rate of about 40%,[22] and patients with symptomatic calf vein thrombosis who are treated with a 5-day course of intermittent intravenous heparin without continuation of oral anticoagulant therapy have a recurrence rate greater than 20% over the following 3 months.[23]

In contrast, fewer than 3% of patients who have proximal vein thrombosis experience a clinically detectable recurrence during the initial period of treatment with high-dose heparin or low-molecular-weight heparin (LMWH), and fewer than 3% of patients experience recurrence during the subsequent 3 months of moderate-intensity oral anticoagulant therapy or moderate-dose subcutaneous heparin therapy.[24] After 3 months of anticoagulant therapy, patients have an annual recurrence rate of about 3% if their thrombosis developed after a reversible provocation, such as surgery, or as high as 15% if their thrombosis is idiopathic or associated with ongoing conditions, such as prolonged immobilization or cancer.[15,25-28] The recurrence rate is significantly higher after a 4- or 6-week course of warfarin treatment, compared with a 3- or 6-month course.[25,27,28] In patients with more than one documented episode of deep vein thrombosis or pulmonary embolism, the recurrence rate in the first year after a 6-month course of anticoagulant therapy is approximately 6%.[27] Additional risk factors for recurrent venous thrombosis include older age, proximal versus isolated distal thrombosis, hyperhomocysteinemia, malignancy, and elevated levels of factor VIII.[29,30]

Diagnosis

VENOUS THROMBOSIS

Clinical Features

The clinical features of venous thrombosis, such as localized swelling, redness, tenderness, and distal edema, are nonspecific and should always be confirmed by objective tests.[4,31]

About 70% of ambulatory patients with clinically suspected venous thrombosis have another cause for their symptoms. The conditions that are most likely to simulate venous thrombosis are ruptured Baker cyst, cellulitis, muscle tear, muscle cramp, muscle hematoma, external venous compression, superficial thrombophlebitis, and the postthrombotic syndrome. Of the 30% of patients who have venous thrombosis, about 85% have proximal vein

thrombosis, and the rest have thrombosis confined to the calf.[4]

Although clinical features cannot unequivocally confirm or exclude a diagnosis of venous thrombosis, careful documentation of the patient's history and of the signs and symptoms at presentation are useful in diagnosis [*see Table 1*].[32] Evidence suggests that patients can be classified as having a high, intermediate, or low probability of venous thrombosis on the basis of (1) the presence or absence of risk factors (such as recent immobilization, hospitalization within the past 6 months, or malignancy), (2) whether the clinical manifestations at presentation are typical or atypical, and (3) whether the patient has an alternative explanation for the symptoms that is at least as likely as deep vein thrombosis.[31-33]

Diagnostic Tests

Three objective tests (venography, impedance plethysmography [IPG], and venous ultrasonography) have been validated for the diagnosis of venous thrombosis.[4] Of these, venography and venous ultrasonography are most widely used.

Venography Venography, which involves the injection of a radiocontrast agent into a distal vein, is the reference standard for the diagnosis of venous thrombosis [*see Figure 1*]. Venography detects both proximal vein thrombosis and calf vein thrombosis. However, it is technically difficult and expensive, can be painful, may produce superficial phlebitis, and is complicated by deep vein thrombosis in 1% to 2% of patients. For these reasons, venography has been replaced by IPG and venous ultrasonography for the diagnosis of most cases of suspected venous thrombosis.[4]

Venous ultrasonography Venous ultrasonography is the noninvasive method of choice for diagnosing venous thrombosis.[4] It is not painful and is easier to perform than venography. The common femoral vein, superficial femoral vein, popliteal vein, and proximal deep calf veins are imaged in real time and compressed with the transducer probe. Inability to fully compress or obliterate the vein is diagnostic of venous thrombosis.[4] Duplex ultrasonography, which combines real-time imaging with pulsed Doppler and color-coded Doppler technology, facilitates the identification of veins.

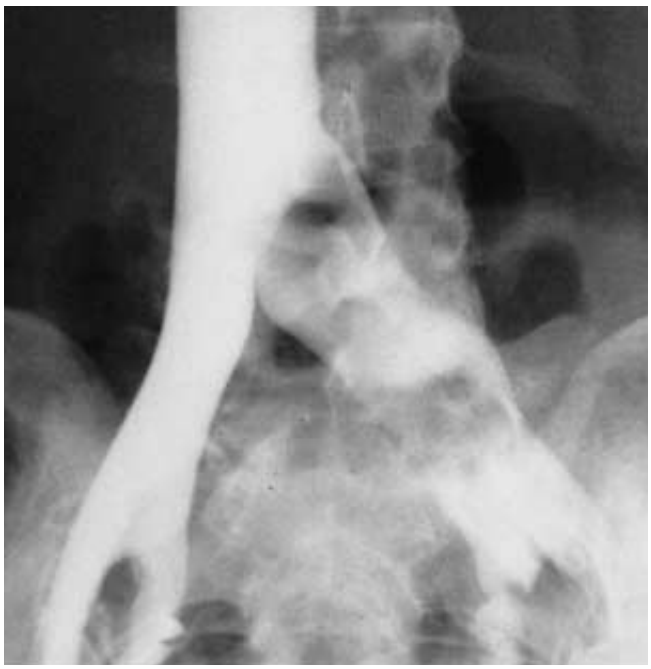

Figure 1 **Filling defects in the left iliac vein, apparent in this venogram, reveal the presence of thrombi.**

Venous ultrasonography is highly accurate for the detection of proximal vein thrombosis in symptomatic patients, with the reported sensitivities and specificities approaching 95%.[4] The sensitivity for symptomatic calf vein thrombosis is approximately 70%.[4] Although venous ultrasonography fails to detect a substantial number of calf vein thrombi and small thrombi of the popliteal vein, this limitation is not critical. If the initial test result excludes proximal deep vein thrombosis, the test can be repeated in 7 days to detect the small number of calf vein thrombi that have extended since initial presentation.[4] If the test remains negative after 7 days, the risk of thrombus extension to the proximal veins is negligible, and it is safe to withhold treatment.[4,34]

In asymptomatic patients who have had elective hip or knee replacement, the sensitivity of real-time ultrasonography or of color Doppler ultrasonography for proximal deep vein thrombosis is about 60%.[4]

Ultrasonography is accurate, provided its results are concordant with clinical assessment; however, its accuracy drops if the results of these two assessments do not agree.[33] Therefore, venography should be considered if the clinical suspicion for deep vein thrombosis is low and the ultrasound is abnormal or if clinical suspicion is high and the ultrasound is normal; in about one quarter of such cases, the results of venography differ from those of the ultrasound.[33] Because the prevalence of deep vein thrombosis (mostly distal) is only about 2% in patients who have a low clinical suspicion of thrombosis and an initial normal proximal venous ultrasound, a follow-up test is not necessary in such patients [*see Table 2*].[4]

D-dimer blood testing D-dimer is formed when cross-linked fibrin in thrombi is broken down by plasmin, so elevated levels of D-dimer can be used to detect deep vein thrombosis and pulmonary embolism. A variety of D-dimer assays are available, and they vary markedly in their accuracy as diagnostic tests for venous thromboembolism.[35]

All D-dimer assays have low positive predictive value for deep vein thrombosis; an abnormal test is nonspecific and cannot be used to diagnose venous thrombosis. However, some D-dimer tests are sensitive for venous thrombosis, and a normal result can be used to exclude venous thromboembolism. In one study, a normal highly sensitive (~ 99%) D-dimer assay that occurred in 27% of consecutive patients was shown to exclude deep vein thrombosis (negative predictive value = 98.4%) [*see Table 2*].[36] Management studies have shown that it is safe to withhold anticoagulant therapy and serial testing in patients who have a normal D-dimer test in combination with a normal impedance plethysmograph (negative predictive value = 98.5%)[37] or a normal venous ultrasound of the proximal veins (negative predictive value = 99.8%)[38] [*see Table 2*].

Table 2 Test Results That Effectively Confirm or Exclude Deep Vein Thrombosis (DVT)

Purpose	*Test*	*Indication for Use*
Diagnostic for first DVT	Venography	Intraluminal filling defect
	Venous ultrasonography	Noncompressible proximal veins at two or more of the common femoral, popliteal, and calf trifurcation sites
Excludes first DVT	Venography	All deep veins seen, and no intraluminal filling defects
	D-dimer	Normal test, which has a very high sensitivity (i.e., ≥ 98%) and at least a moderate specificity (i.e., ≥ 40%)
	Venous ultrasonography or impedance plethysmography	Normal and (1) low clinical suspicion for DVT at presentation, (2) normal D-dimer test, which has a moderately high sensitivity (i.e., ≥ 85%) and specificity (i.e., ≥ 70%) at presentation, or (3) normal serial testing (venous ultrasonography at 7 days; impedance plethysmography at 2 and 7 days)
Diagnostic for recurrent DVT	Venography	Intraluminal filling defect
	Venous ultrasonography	(1) A new noncompressible common femoral or popliteal vein segment or (2) a ≥ 4.0 mm increase in diameter of the common femoral or popliteal vein since a previous test*
	Impedance plethysmography	(1) Conversion of a normal test to abnormal* (2) An abnormal test 1 year after diagnosis*
Excludes recurrent DVT	Venogram	All deep veins seen and no intraluminal filling defects
	Venous ultrasonography or impedance plethysmography	Normal or ≤ 1 mm increase in diameter of the common femoral or popliteal veins on venous ultrasound since a previous test and remains normal (no progression of venous ultrasound) at 2 and 7 days.

*If other evidence is not consistent with recurrent DVT (e.g., venous ultrasonography or impedance plethysmography, clinical assessment, or D-dimer), venography should be considered.

RECURRENT VENOUS THROMBOSIS

The diagnosis of acute recurrent deep vein thrombosis can be difficult.[4] A common approach is to perform venous ultrasonography. If the result is positive and the result of the previous test was negative, a recurrence is diagnosed. This diagnosis can also be made if venous ultrasonography shows more extensive thrombosis than was seen at the initial examination upon which the original diagnosis of deep vein thrombosis was made. If venous ultrasonography continues to show abnormal findings after the initial examination, venography should be performed. If the venogram shows a new intraluminal filling defect or evidence of thrombus extension since the previous venogram, recurrent venous thrombosis is diagnosed. If no new defect is found, however, the diagnosis must be based on clinical features. If venous ultrasonography shows normal findings at presentation, the test should be repeated twice over the next 7 to 10 days [*see Table 2*].

PULMONARY EMBOLISM

Clinical Features

The clinical features of pulmonary embolism, like those of venous thrombosis, are nonspecific, and fewer than one third of symptomatic patients have the diagnosis confirmed by objective tests.[39,40] Although pulmonary emboli may have a subtle presentation and are easily missed, especially in the elderly, it is important to evaluate clinical features carefully in patients with suspected pulmonary embolism. When combined with lung scan findings, the clinical presentation can be extremely useful in diagnosis.

Dyspnea is the most common symptom in patients with pulmonary embolism.[39] Chest pain is also common; it is usually pleuritic but can be substernal and compressing. Hemoptysis is a less frequent feature of pulmonary embolism. Fewer than 25% of patients with symptomatic pulmonary embolism have clinical features of venous thrombosis.[39,41]

Diagnostic Tests

Chest radiography and electrocardiography In patients with pulmonary embolism, chest radiography shows either normal or nonspecific findings. Chest radiography, however, is useful for exclusion of pneumothorax and other conditions that can simulate pulmonary embolism. The electrocardiogram also frequently shows normal or nonspecific findings, but it may be diagnostic of acute myocardial infarction. In the appropriate clinical setting, ECG evidence of right ventricular strain suggests pulmonary embolism.

Ventilation-perfusion lung scanning One of the main diagnostic tests for pulmonary embolism is ventilation-perfusion lung scanning.[5,39] There are two components to lung scanning. In ventilation-perfusion lung scanning, perfusion scanning is performed after intravenous injection of isotopically labeled microaggregates of human albumin [*see Figure 2*]. These particles become trapped in the pulmonary capillary bed, and their distribution reflects lung blood flow, which is recorded with an external photoscanner. Perfusion lung scanning is the pivotal test in the diagnostic process because a normal perfusion scan excludes a diagnosis of pulmonary embolism; an abnormal perfusion scan is nonspecific.[5,39]

During ventilation lung scanning, the patient inhales and exhales either radioactive gases or aerosols while a gamma camera records the distribution of radioactivity within the alveolar gas–exchange units. Ventilation imaging improves

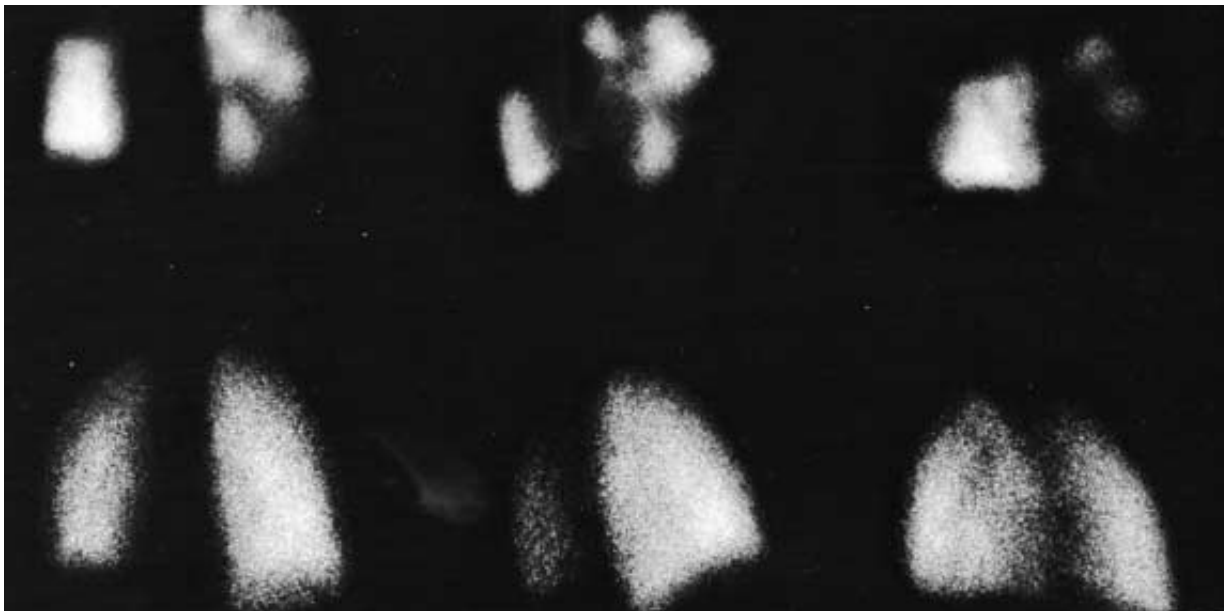

Figure 2 **Posterior, right posterior oblique, and left posterior oblique perfusion scans (top), which were developed by using radiopharmaceutical technetium-99m (^{99m}Tc) microspheres of albumin, show multiple perfusion defects, some relatively large, in both lungs. Three ventilation scans (bottom) made with the patient breathing krypton-81m (^{81m}Kr) were recorded simultaneously with the perfusion scans. The scans were interpreted as showing a marked ventilation-perfusion mismatch, highly suggestive of pulmonary emboli. This diagnosis was confirmed by pulmonary arteriography.**

the specificity of perfusion scanning for the diagnosis of pulmonary embolism, particularly a larger or segmental defect that is not matched by a ventilation scan.[5,39]

Unfortunately, only 40% of patients with pulmonary embolism have a high-probability lung scan.[5,39] The remaining 60% have abnormal perfusion scans that are classified as non–high probability. Patients with non–high-probability findings on lung scanning require pulmonary angiography or objective tests for venous thrombosis. The latter are useful because approximately 70% of patients with proven pulmonary embolism have deep vein thrombosis of the legs.[39]

Pulmonary angiography Pulmonary angiography is the reference standard for establishing the presence or absence of pulmonary embolism [*see Figure 3*].[5,39] Unfortunately, it is invasive, technically difficult, and unavailable in most hospitals. Selective angiography and magnification views improve resolution and reduce the risks associated with the procedure. If the test is performed adequately, a normal pulmonary angiogram excludes the diagnosis of pulmonary embolism; in a patient with a small perfusion defect, however, the diagnosis of a small pulmonary embolism cannot be excluded by pulmonary angiography unless the tertiary pulmonary arteries are visualized.

Arrhythmias, cardiac perforation, cardiac arrest, and hypersensitivity to the contrast medium occur in 3% to 4% of patients undergoing pulmonary angiography.

Computed tomography and magnetic resonance imaging Traditional computed tomography is not suitable for evaluating suspected pulmonary embolism because it is not feasible to opacify the pulmonary arteries with radiographic contrast for the time required to complete imaging (i.e., 3 minutes). Even if the pulmonary arteries could be opacified, motion artifact would interfere with image quality. These problems are overcome by helical CT (also known as spiral or continuous volume CT) because image acquisition can be completed within a single holding of the breath (e.g., 20 seconds). Although it is widely used in clinical practice, the safety of managing patients with suspected pulmonary embolism according to the results of helical CT is not well established. In particular, the safety of withholding further testing and anticoagulation on the basis of a negative study is uncertain. A systematic review of studies that have evaluated the accuracy of helical CT for the diagnosis of pulmonary embolism concluded that the technique has been inadequately evaluated for this purpose.[42]

Current evidence suggests that helical CT has a sensitivity of about 90% or higher for emboli in segmental or larger pulmonary arteries. Sensitivity of isolated subsegmental emboli, which account for about 20% of symptomatic emboli,

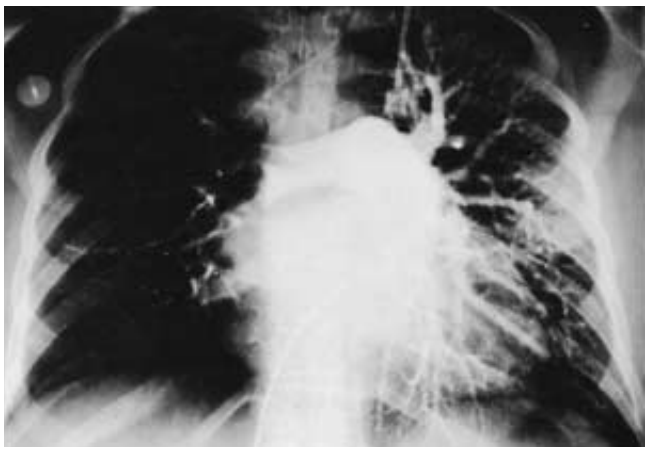

Figure 3 **Pulmonary arteriogram demonstrates nonfilling of pulmonary arterial branches in the right lung, an indication of massive occlusion.**

appears to be much lower. These observations suggest the following:

1. An intraluminal filling defect in a segmental or larger pulmonary artery is likely to be associated with at least a 90% probability of embolism and, therefore, may be interpreted in the same way as a high-probability lung scan.
2. A normal helical CT markedly reduces the probability of pulmonary embolism but does not exclude this diagnosis. It may be reasonable to interpret a normal spiral CT in the same way as a low-probability lung scan.
3. Intraluminal defects that are confined to subsegmental pulmonary arteries are likely to be nondiagnostic and require further investigation (e.g., pulmonary angiography or lung scanning).

Magnetic resonance imaging is less well evaluated than helical CT for the diagnosis of pulmonary embolism but appears to have a similar accuracy. Both helical CT and MRI have the advantage of possibly suggesting an alternative pulmonary diagnosis. MRI does not expose the patient to radiation or radiographic contrast media, and the examination may be extended to look for concomitant deep vein thrombosis.

Compression ultrasonography and D-dimer assay Two noninvasive, relatively inexpensive, complementary approaches can be used to simplify the diagnosis of pulmonary embolism in patients with nondiagnostic lung scan findings. These approaches involve the use of compression ultrasonography and the D-dimer test. Because pulmonary emboli usually arise from mostly asymptomatic thrombi in the deep proximal leg veins, a positive compression ultrasound test result can serve as indirect evidence in making a diagnosis of pulmonary embolism. However, a positive compression ultrasound test result is found in only 5% to 10%[43,44] of patients with nondiagnostic scans. Furthermore, a negative compression ultrasound test result does not exclude a diagnosis of pulmonary embolism in these patients, possibly because either the original thrombus has embolized or the residual thrombus is too small to be detected by compression ultrasonography. A negative ultrasound test result can, however, eliminate the possibility of an associated large proximal vein thrombosis; in most patients with a negative ultrasound test result, treatment can be withheld while further investigations are performed.

Two prospective studies—one utilizing plethysmography[45] and the other utilizing compression ultrasonography[44]—in patients with good cardiopulmonary reserve have reported that patients with non–high-probability lung scan results and a negative noninvasive test result for deep vein thrombosis can be safely managed with serial noninvasive testing for proximal vein thrombosis for 14 days. Both studies reported a very low rate (2%) of confirmed venous thromboembolism over a 6-month follow-up period, provided that the noninvasive test result remained negative.

About 90% of patients with a non–high-probability lung scan have a normal compression ultrasound test; of these, about 80% do not have pulmonary embolism. Therefore, the use of serial ultrasonography in all patients with a non–high-probability lung scan result and a normal compression ultrasound test result would lead to the testing of a large number of patients to identify very few at risk for recurrent pulmonary embolism. The noninvasive diagnostic process has been simplified by introducing two additional components: pretest probability and D-dimer testing.

Table 3 Model for Determining a Clinical Suspicion of Pulmonary Embolism[36]

Variables	*Points**
Clinical signs and symptoms of deep vein thrombosis (minimum leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than pulmonary embolism	3.0
Heart rate > 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous deep vein thrombosis/pulmonary embolism	1.5
Hemoptysis	1.0
Malignancy (treatment ongoing or within previous 6 months or palliative)	1.0
Total points	

*Pretest probability is calculated as follows: total points < 2, low probability; 2 to 6, moderate probability; > 6, high probability.

In a prospective study of 1,177 patients with suspected pulmonary embolism, the D-dimer test (using the SimpliRED whole blood assay) showed a sensitivity of 84% and a specificity of 68%. Of 698 patients with a nondiagnostic lung scan, 668 (96%) had a low or moderate pretest probability and a negative bilateral compression ultrasound test result on presentation. In this group, the D-dimer assay had a negative predictive value of 99.7%. Of all patients, 44% with a nondiagnostic scan had a low pretest probability and a negative D-dimer test result; in this group, the negative predictive value of the D-dimer test was 99%, independent of compression ultrasound findings.[43]

The diagnosis of pulmonary embolism can be safely excluded in patients with nondiagnostic lung scans and either low or moderate pretest probabilities if the presenting bilateral compression ultrasound test result is normal and the D-dimer test result is negative. It is likely that a diagnosis of pulmonary embolism can also be excluded in patients with low pretest probability and nondiagnostic lung scans simply if the D-dimer assay is negative, although this approach requires confirmation before it can be recommended.

Used alone, a rapid enzyme-linked immunosorbent assay (ELISA) for D-dimer has a high sensitivity (99%) and a low-to-moderate specificity (45%) and was found to rule out pulmonary embolism in 36% of consecutive patients with suspected embolism.[36]

Diagnostic Strategy

Until recently, clinical assessment of the probability of pulmonary embolism was not standardized; physicians made the assessment informally on the basis of their experience and the results of initial routine tests (e.g., chest x-ray and electrocardiogram). Two groups have recently published explicit criteria for determining the clinical probability of pulmonary embolism. Clinical probability was used to manage patients in conjunction with perfusion scanning alone in one study,[46] whereas in the other study, clinical probability was used in conjunction with ventilation-

perfusion lung scanning.[44] The latter clinical model, by Wells and colleagues,[44,47] incorporates an assessment of symptoms and signs, the presence of an alternative diagnosis to account for the patient's presentation, and the presence of risk factors for venous thromboembolism. The resulting model enables a patient's clinical probability of pulmonary embolism to be categorized as low (prevalence of 2%), moderate (prevalence of 19%), or high (prevalence of 60%) [*see Table 3*].[40]

The diagnostic approach to pulmonary embolism should take into account pretest clinical probabilities and lung scan findings [*see Figure 4*]. Pulmonary embolism can be excluded in patients with a normal perfusion scan. In patients with high or intermediate pretest clinical probabilities of pulmonary embolism, a diagnosis can be made if there are large perfusion defects (involving one or more segments) and a ventilation mismatch; these patients have a 90% probability of pulmonary embolism. The probability of pulmonary embolism is less than 5% in patients with a low pretest clinical probability of the disease who have a small perfusion defect with a matched ventilation abnormality; in these patients, a diagnosis of pulmonary embolism can be ruled out if noninvasive tests for venous thrombosis show normal findings.

For patients with other combinations of clinical and lung scan findings, including patients with a large ventilation-perfusion mismatch and a low pretest probability and those with perfusion defects—matched or unmatched with ventilatory abnormalities—that are not classified as high-probability defects, the frequency of pulmonary embolism is not sufficiently low to exclude pulmonary embolism or high enough to confirm this diagnosis.[5,39] These patients require further investigation with either pulmonary angiography or objective tests for venous thrombosis. A positive venogram or compression ultrasonogram can be used to make the diagnosis of venous thromboembolism in these patients,[5,39] and treatment with anticoagulants can be started without performing pulmonary angiography. If tests for venous thrombosis are negative, however, pulmonary angiography is required if the clinical probability of pulmonary embolism is high or the perfusion defect is large. In patients with a low pretest likelihood of pulmonary embolism and small defects, anticoagulants can be withheld, and serial ultrasonography or IPG can be used to detect propagating venous thrombosis. As previously described, the negative predictive value of a normal D-dimer test result can supplement this approach.

Prophylaxis and Treatment

PHARMACOLOGY OF ANTITHROMBOTIC AGENTS

Anticoagulants

A less intense anticoagulant effect is required for the prevention of venous thrombosis than is required for its treatment. The anticoagulants in clinical use are heparin and LMWH, which are administered subcutaneously or intravenously, and coumarin compounds, which are given orally. Thrombolytic agents are streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA).

Heparin Heparin is a highly sulfated glycosaminoglycan that produces its anticoagulant effect by binding to AT, markedly accelerating the ability of the naturally occurring anticoagulant to inactivate thrombin, activated factor X (factor Xa), and activated factor IX (factor IXa).[48] At therapeutic concentrations, heparin has a half-life of about 60 minutes. Its clearance is dose dependent. Heparin has decreased bioavailability when administered subcutaneously in low doses but has approximately 90% bioavailability when administered in high therapeutic doses.

Heparin binds to a number of plasma proteins, a phenomenon that reduces the anticoagulant effect of heparin by limiting its accessibility to AT. The concentration of heparin-binding proteins increases during illness, contributing to the variability in anticoagulant response in patients

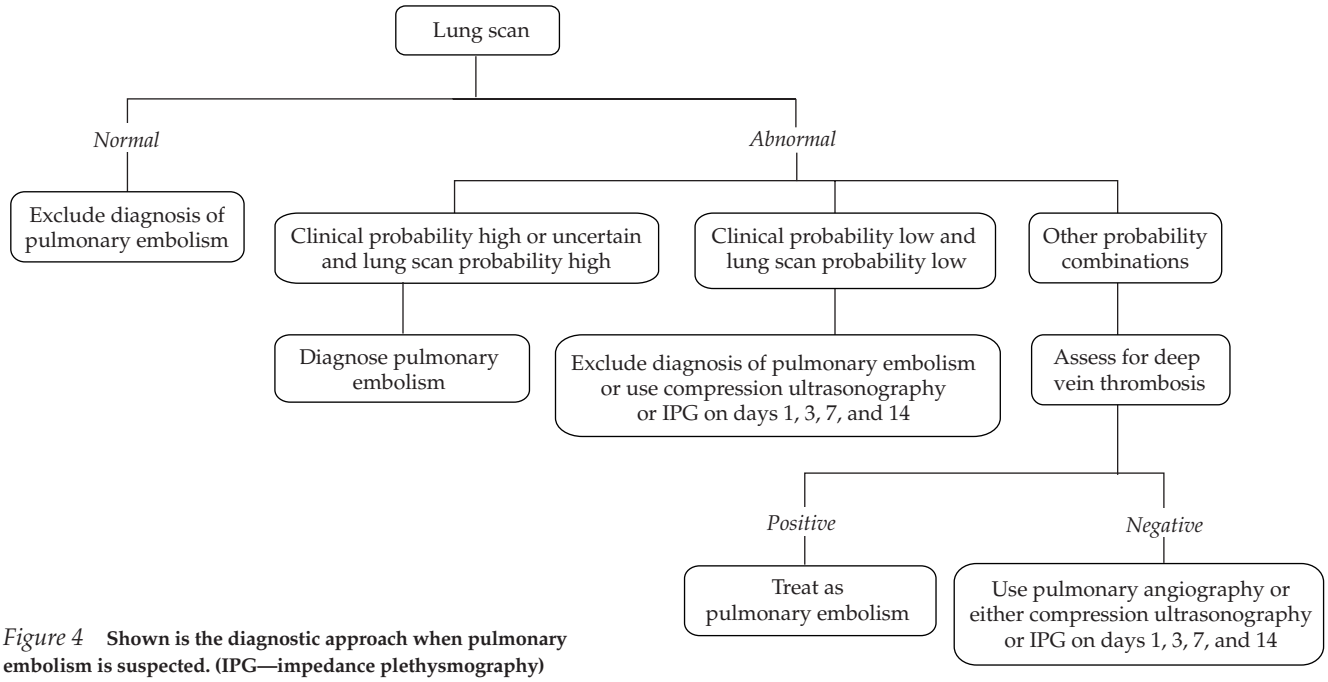

Figure 4 **Shown is the diagnostic approach when pulmonary embolism is suspected. (IPG—impedance plethysmography)**

Table 4 Drug and Food Interactions with Warfarin by Level of Supporting Evidence* and Direction of Interaction[81]

	Antibiotics	*Cardiac*	*Anti-inflammatory*	*Central Nervous System*	*Gastrointestinal*	*Miscellaneous*
Potentiation Level 1	Trimethoprim-sulfamethoxazole, erythromycin, isoniazid, fluconazole, metronidazole, miconazole	Amiodarone, clofibrate, propafenone, propranolol, sulfinpyrazone†	Phenylbutazone,† piroxicam High-dose intravenous methylprednisolone Acetaminophen	Alcohol (with liver disease)	Cimetidine,‡ omeprazole	—
Level 2	Ciprofloxacin, itraconazole, tetracycline	Aspirin, quinidine, simvastatin	Aspirin, dextro-propoxyphene	Chloral hydrate, disulfiram, phenytoin	—	Anabolic steroids, influenza vaccine, tamoxifen
Level 3	Nalidixic acid, norfloxacin, ofloxacin	Disopyramide, lovastatin, metolazone	Topical salicylates, sulindac, tolmetin	—	—	Fluorouracil, ifosfamide
Level 4	Cefamandole, cefazolin, sulfisoxazole	Gemfibrozil, heparin	Indomethacin	—	—	—
Inhibition Level 1	Griseofulvin,* nafcillin, rifampin	Cholestyramine	—	Barbiturates, carbamazepine, chlordiazepoxide	Sucralfate	Foods with a high vitamin K content, enteral nutritional support, large amounts of avocado Ticlopidine
Level 2	Dicloxacillin	—	—	—	—	—
Level 3	—	—	Azathioprine	Trazodone	—	Azathioprine, cyclosporine, etretinate, large amounts of broccoli
No effect Level 1	Enoxacin	Atenolol, bumetanide, felodipine, metoprolol, moricizine	Diflunisal, ketorolac, naproxen	Alcohol, fluoxetine, nitrazepam	Antacids, famotidine, nizatidine, psyllium, ranitidine‡	—
Level 2	Ketoconazole	—	Ibuprofen, ketoprofen	—	—	—
Level 4	Vancomycin	Diltiazem	—	—	—	Tobacco

*Level 1 evidence indicates that the likelihood of an association is very strong; level 2 evidence suggests that a true association is likely; level 3 evidence suggests that a true association is probable; and level 4 evidence suggests that a true association is possible.
†Supporting level 1 evidence was obtained from both patients and volunteers.
‡In a small number of volunteers, an inhibitory drug interaction occurred.

with thromboembolism.[48] Because the clinical effectiveness of heparin is related to its anticoagulant effect, the dose of heparin administered to patients should be monitored by the activated partial thromboplastin time (aPTT) and adjusted to achieve a therapeutic range, which for many aPTT reagents corresponds to an aPTT ratio of 1.5 to 2.5.[48]

LMWHs are effective in the prevention and treatment of venous thrombosis. They are derived from standard commercial-grade heparin by chemical depolymerization to yield fragments approximately one third the size of heparin.[49] Depolymerization of heparin results in a change in its anticoagulant profile, bioavailability, and pharmacokinetics and in a lower incidence of heparin-induced thrombocytopenia and of osteopenia.[50,51]

The plasma recoveries and pharmacokinetics of LMWHs differ from those of heparin because LMWHs bind much less avidly to heparin-binding proteins than does heparin. This property of LMWHs contributes to their superior bioavailability at low doses and their more predictable anticoagulant response. LMWHs also exhibit less binding to macrophages and endothelial cells than does heparin, a property that accounts for their longer plasma half-life, which is approximately 3 hours, and their dose-independent clearance. These potential advantages over heparin permit once-daily administration of LMWHs without laboratory monitoring. These advantages of LMWHs have been exploited to successfully treat patients with deep vein thrombosis out of hospital[52,53] and to treat patients with acute pulmonary embolism in hospital with once- or twice-daily subcutaneous dosing regimens of three different LMWH preparations.[41,54] Collectively, these four studies, which include over 3,000 patients treated with either once-daily or twice-daily subcutaneous doses of LMWH, establish this class of anticoagulants as a safe, effective, and convenient method of treating venous thrombosis and pulmonary embolism.[24]

Oral anticoagulants Oral anticoagulants are coumarin compounds, the most common being warfarin, that produce their anticoagulant effect through the production of

hemostatically defective vitamin K–dependent coagulant proteins (prothrombin, factor VII, factor IX, and factor X).[55]

The dose of warfarin must be monitored closely because the anticoagulant response varies widely among individuals. Laboratory monitoring is performed by measuring the prothrombin time (PT), a test responsive to depression of three of the four vitamin K–dependent clotting factors (prothrombin and factors VII and X). Commercial PT reagents vary markedly in their responsiveness to warfarin-induced reduction in clotting factors. This problem of variability in the responsiveness of PT reagents has been overcome by the introduction of the international normalized ratio (INR).

The starting dose has been 10 mg, with an average maintenance dose of about 5 mg. However, the dose varies widely among individuals. Elderly patients, for example, have been shown, on average, to require lower doses. Evidence indicates that it might be safer to use a starting dose of 5 mg of warfarin because, compared with 10 mg, the 5 mg starting dose does not delay achieving a therapeutic INR and is associated with a lower incidence of supratherapeutic INR values during the first 5 days of treatment.[56] Some patients receiving warfarin are difficult to manage because of unexpected fluctuations in dose response, which may reflect changes in diet, inaccuracy in PT testing, undisclosed drug use, poor compliance, surreptitious self-medication, or intermittent alcohol consumption. Concomitant medication with over-the-counter and prescription drugs can augment or inhibit the anticoagulant effect of coumarin compounds on hemostasis or interfere with platelet function [*see Table 4*].

Patients receiving coumarin compounds are also sensitive to fluctuating levels of dietary vitamin K, obtained predominantly from leafy green vegetables. The effect of coumarins can be potentiated in sick patients with poor vitamin K intake, particularly if they are treated with antibiotics and intravenous fluids without vitamin K supplementation and in states of fat malabsorption.

Thrombolytic Agents

Pharmacologic thrombolysis is produced by plasminogen activators—including streptokinase, tissue plasminogen activator (t-PA), and urokinase—which convert the proenzyme plasminogen to the fibrinolytic enzyme plasmin.[57]

Streptokinase Streptokinase is a protein produced by β-hemolytic streptococci. In contrast to other plasminogen activators, streptokinase is not an enzyme and does not convert plasminogen directly to plasmin by proteolytic cleavage. Instead, streptokinase binds noncovalently to plasminogen, converting it to a plasminogen-activator complex that acts on other plasminogen molecules to generate plasmin. Streptokinase has a plasma half-life of 30 minutes.

Because streptokinase is a bacterial product, it stimulates antibody production and can prompt allergic reactions. Antistreptococcal antibodies, present in variable titers in most patients before streptokinase treatment, induce an amnestic response that makes repeated treatment with streptokinase difficult or impossible for a period of months or years after an initial course of treatment. Laboratory monitoring of streptokinase can be limited to a thrombin time, which is used as a marker for an effective lytic state. If the thrombin time is not prolonged within the first few hours of commencing treatment, resistance to streptokinase resulting from a high titer of antistreptococcal antibodies should be suspected, and the dose of streptokinase should be increased.

Urokinase Synthesized by endothelial and mononuclear cells, urokinase is a direct activator of plasminogen. Like streptokinase, urokinase is non–fibrin specific. It has a plasma half-life of 10 minutes.

rt-PA, which is fibrin specific, is synthesized by endothelial cells as a single-chain polypeptide. Proteolytic cleavage converts the single-chain form into a two-chain species. Both forms are enzymatically active. rt-PA has a plasma half-life of approximately 5 minutes. However, it is no longer commercially available.

Complications of Antithrombotic Agents

Bleeding is the main complication of antithrombotic therapy.[58] With all antithrombotic agents, the risk of bleeding is influenced by the dose and by patient-related factors, the most important being recent surgery or trauma. Other patient characteristics that increase the risk of bleeding are age, recent stroke, generalized hemostatic defect, a history of gastrointestinal hemorrhage, and serious comorbid conditions. Bleeding is more common and more serious with thrombolytic drugs than with anticoagulants. The risk of bleeding with thrombolytic therapy is just as great with rt-PA as with streptokinase and urokinase, which, unlike rt-PA, lack fibrin specificity. The risk of bleeding increases with the duration of treatment.

With heparin, the incidence of bleeding is influenced by dosage and by means of administration, being higher with intermittent intravenous therapy than with continuous intravenous therapy.[58] Recent trials show that the rates of bleeding are similar for heparin and LMWH.[24] Bleeding that is associated with coumarin anticoagulants is influenced by the intensity of anticoagulant therapy. Such bleeding is reduced to about one third if the targeted range is lowered from between 3.0 and 4.5 to between 2.0 and 3.0. Both heparin-induced bleeding and warfarin-induced bleeding are increased by concomitant use of aspirin, which impairs platelet function and produces gastric erosions. When the INR is less than 3.0, coumarin-associated bleeding frequently has an obvious underlying cause or is caused by an occult gastrointestinal or renal lesion.

Nonhemorrhagic side effects of thrombolytic therapy are limited mainly to allergic reactions to streptokinase. Nonhemorrhagic side effects of heparin include the following: (1) urticaria at sites of subcutaneous injection; (2) thrombocytopenia, which occurs in 2% to 4% of patients treated with high-dose heparin and is complicated by arterial or venous thrombosis in about 0.2% of treated patients; (3) osteoporosis, which occurs with prolonged high-dose heparin use; and, rarely, (4) alopecia, adrenal insufficiency, and skin necrosis.[48] The incidence of thrombocytopenia is lower with LMWHs than with heparin.[49] Similarly, there is evidence that the risk of osteopenia is lower with LMWH than with heparin.[48,51]

The most important nonhemorrhagic side effect of coumarin anticoagulants is skin necrosis, an uncommon complication usually observed on the third to eighth day of

therapy. Skin necrosis is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat. An association has been reported between coumarin-induced skin necrosis and protein C deficiency—and, less commonly, protein S deficiency—but this complication can occur in individuals without these protein deficiencies.

PROPHYLAXIS

The most effective way of reducing the mortality associated with pulmonary embolism and the morbidity associated with the postthrombotic syndrome is to institute primary prophylaxis in patients at risk for venous thromboembolism. On the basis of well-defined clinical criteria, patients can be classified as being at low, moderate, or high risk for venous thromboembolism, and the choice of prophylaxis should be tailored to the patient's risk [*see Table 5*].[59] In the absence of prophylaxis, the frequency of fatal postoperative pulmonary embolism ranges from 0.1% to 0.4% in patients undergoing elective general surgery and from 1% to 5% in patients undergoing elective hip or knee surgery, emergency hip surgery, major trauma, or spinal cord injury. Prophylaxis is cost-effective for most high-risk groups.[59]

Prophylaxis is achieved either by modulating activation of blood coagulation or by preventing venous stasis by using the following proven approaches: low-dose subcutaneous heparin, intermittent pneumatic compression of the legs, oral anticoagulants, adjusted doses of subcutaneous heparin, graduated compression stockings, or LMWHs.[59] Administration of antiplatelet agents, such as aspirin, also prevents venous thromboembolism[60] but probably less effectively than the previously stated methods.[59]

Low-dose heparin is given subcutaneously, at a dose of 5,000 U 2 hours before surgery and 5,000 U every 8 or 12 hours after surgery. In patients undergoing major orthopedic surgical procedures, low-dose heparin is less effective than warfarin, adjusted-dose heparin, and LMWHs. Intermittent pneumatic compression of the legs enhances blood flow in the deep veins and increases blood fibrinolytic activity. This method of prophylaxis is free of clinically important side effects and is particularly useful in patients who have a high risk of serious bleeding. It is the method of choice for preventing venous thrombosis in patients undergoing neurosurgery, it is effective in patients undergoing major knee surgery, and it is as effective as low-dose heparin in patients undergoing abdominal surgery.

Graduated compression stockings reduce venous stasis and prevent postoperative venous thrombosis in general surgical patients and in medical or surgical patients with neurologic disorders, including paralysis of the lower limbs.[59] In surgical patients, the combined use of graduated compression stockings and low-dose heparin is significantly more effective than use of low-dose heparin alone. Graduated compression stockings are relatively inexpensive and should be considered in all high-risk surgical patients, even if other forms of prophylaxis are used.

Moderate-dose warfarin (INR = 2.0 to 3.0) is effective for preventing postoperative venous thromboembolism in patients in all risk categories.[59] Warfarin therapy can be started preoperatively, at the time of surgery, or in the early postoperative period. Although the anticoagulant effect is not achieved until the third or fourth postoperative day, warfarin treatment started at the time of surgery or in the early postoperative period is effective in very high risk patient groups, including patients with hip fractures and those who undergo joint replacement. Prophylaxis with warfarin is less convenient than low-dose heparin or LMWHs, however, because careful laboratory monitoring is necessary.

LMWH is a safe and effective form of prophylaxis in high-risk patients undergoing elective hip surgery, major general surgery, or major knee surgery or experiencing hip fracture, spinal injury, or stroke. LMWH was more effective than standard low-dose heparin in general surgical patients, patients undergoing elective hip surgery, and patients with stroke or spinal injury.

In patients who are undergoing hip or major knee surgery, LMWH is more effective than warfarin but is associated with more frequent bleeding; both of these differences may be caused by a more rapid onset of anticoagulation with postoperatively initiated LMWH than with warfarin.[59,61] It is uncertain whether the superior efficacy of LMWH over warfarin in the prevention of venographically detectable venous thrombosis is mirrored by fewer symptomatic episodes of venous thromboembolism with LMWH.[59,61]

Indications for Prophylaxis

General surgery and medicine Low-dose-heparin prophylaxis is the method of choice for moderate-risk general surgical and medical patients.[59] It reduces the risk of venous thromboembolism by 50% to 70%[41] and is simple, inexpensive, convenient, and safe. If anticoagulants are contraindicated because of an unusually high risk of bleeding, intermittent pneumatic compression of the legs should be used.

Hip surgery LMWH or oral anticoagulants are effective prophylaxis for venous thrombosis in patients who have undergone hip surgery. Aspirin has also been shown to reduce the frequency of symptomatic venous thromboembolism and fatal pulmonary embolism after hip fracture.[60] The relative efficacy and safety of aspirin versus LMWH or oral anticoagulants in patients who have a hip fracture or have undergone hip or knee arthroplasty is not known. However, because studies have shown that aspirin is much less effective than LMWH or oral anticoagulants at preventing venographically detectable venous thrombosis,

Table 5 Risk Categories for Venous Thromboembolism and Recommendations for Prophylaxis

	High Risk	*Moderate Risk*
Calf vein thrombosis	30%–50%	10%–30%
Proximal vein thrombosis	10%–20%	2%–8%
Fatal pulmonary embolism	1%–5%	0.2%–0.7%
Recommended prophylaxis	Low-molecular-weight heparin, oral anticoagulants, or adjusted-dose heparin	Low-dose heparin or external pneumatic compression

aspirin is not recommended as the sole agent for postoperative prophylaxis.[59]

Major knee surgery Both LMWH and intermittent pneumatic compression are effective in preventing venous thrombosis in patients undergoing major knee surgery. LMWH is more convenient and will probably become the treatment of choice.

Genitourinary surgery, neurosurgery, and ocular surgery Intermittent pneumatic compression, with or without static graduated compression stockings, is effective prophylaxis for venous thrombosis and does not increase the risk of bleeding.

TREATMENT

Overview

The objectives of treating patients with venous thromboembolism are to prevent fatal pulmonary embolism, the postthrombotic syndrome, thromboembolic pulmonary hypertension, and recurrent venous thromboembolism and to alleviate the discomfort of the acute event.

Anticoagulants can effectively reduce morbidity and mortality caused by pulmonary embolism.[5] Vena caval interruption, which is usually achieved with an inferior vena caval filter, is also effective but is more complicated, expensive, and invasive and is associated with a doubling of the frequency of recurrent deep vein thrombosis during long-term follow-up.[62] For these reasons, it is used generally only if anticoagulant therapy has failed or is contraindicated because of the risk of serious hemorrhage.[5]

Thrombolytic therapy with streptokinase, urokinase, or rt-PA is more effective than heparin in achieving early lysis of venous thromboembolism and is better than heparin for preventing death in patients with massive pulmonary embolism associated with shock.[63] Thrombolytic therapy is therefore the treatment of choice for patients with life-threatening pulmonary embolism.

Thromboendarterectomy is effective treatment in selected cases of chronic thromboembolic pulmonary hypertension involving proximal pulmonary arterial obstruction.[64] Urgent pulmonary embolectomy is rarely indicated, being reserved for patients with a saddle embolism lodged in the main pulmonary artery or for those with massive embolism whose blood pressure cannot be maintained despite administration of thrombolytic therapy and vasopressor agents or in whom there is an absolute contraindication to thrombolytic therapy.[5]

Administration and Dosage Guidelines

Anticoagulant therapy Anticoagulants are the mainstay of treatment for most patients with venous thromboembolism. In the past, the treatment of choice was heparin administered by continuous intravenous infusion or subcutaneous injection, in doses sufficient to produce an adequate anticoagulant response. Results of recent studies indicate that LMWH administered by subcutaneous injection without laboratory monitoring is as effective and safe as heparin.[24]

The anticoagulant effect of intravenous heparin or LMWH is immediate. With subcutaneous injection, the anticoagulant effect of both anticoagulants is delayed for about an hour; peak levels occur at 2 to 3 hours. The anticoagulant effect of subcutaneous heparin is maintained for about 12 hours with therapeutic doses. LMWH is effective when administered subcutaneously once daily.[24]

Heparin therapy is usually monitored by the aPTT and less frequently by heparin assays, which measure the ability of heparin to accelerate the inactivation of factor Xa or thrombin by AT. The anticoagulant effect should be monitored carefully, and the dosage should be adjusted to achieve an adequate anticoagulant effect because there is a greater risk of recurrent venous thromboembolism if the anticoagulant effect is suboptimal.[5] The therapeutic range of aPTT should be maintained above a ratio equivalent to a heparin level between 0.35 and 7.0 U/ml as measured by an anti–factor Xa assay.[65] For many aPTT reagents, this range is equivalent to an aPTT ratio of 1.8 to 2.5 times the mean of the normal laboratory control value.[48,65]

LMWH is administered subcutaneously on a weight-adjusted basis at a dosage of either 100 anti-Xa U/kg every 12 hours or 150 to 200 anti-Xa U once daily.[49] It does not require monitoring.

Treatment with heparin or LMWH is usually continued for 5 to 6 days; warfarin therapy is started on the first or second day, overlapping the heparin therapy (or LMWH) for 4 or 5 days, and is continued until an INR of 2.0 is maintained for at least 24 hours.[48] For patients with major pulmonary embolism or extensive deep vein thrombosis, heparin should be given for at least 7 days. A 4- to 5-day period of overlap is necessary because the antithrombotic effects of oral anticoagulants are delayed. The initial course of heparin should be followed by warfarin for about 3 to 6 months to prevent recurrence.[29] Less intense warfarin therapy (INR = 2.0 to 3.0) is just as effective as the high-intensity regimen (INR = 3.0 to 4.5) but produces significantly less bleeding.[55] Adjusted-dose subcutaneous heparin or intermediate-dose LMWH can also be used in the outpatient setting,[29] but they are more expensive and less convenient than warfarin.

Thrombolytic therapy Thrombolytic therapy produces complete lysis of acute venous thrombi in 30% to 40% of cases and causes partial lysis in an additional 30%.[5,18] In contrast, complete lysis of venous thrombi occurs in fewer than 10% of patients treated with heparin.[5,18] The risk of major bleeding, however, is about three times greater with thrombolytic therapy than with heparin. The risk of hemorrhage increases with the duration of thrombolytic infusion and usually occurs at a site of previous surgery or trauma. Intracranial hemorrhage occurs in 1% to 2% of patients with pulmonary embolism who are treated with thrombolytic agents, which is about five to 10 times higher than that seen in patients with pulmonary emobolism who are treated with heparin.[66] Some evidence suggests that the incidence of postthrombotic syndrome is reduced by thrombolytic therapy with streptokinase,[4] but properly designed trials are lacking. The incidence of postthrombotic syndrome appears to be reduced by the early use of graduated compression stockings.[5,7] Accordingly, patients with previous proximal vein thrombosis should be encouraged to wear these stockings at the first sign of leg swelling.

The potential role of thrombolytic therapy in preventing late sequelae of pulmonary embolism is unknown. Selected patients with thromboembolic pulmonary hypertension,

estimated to occur in fewer than 1% of patients with pulmonary embolism, benefit from surgical pulmonary endarterectomy.[64]

Indications for Treatment

Anticoagulant therapy Most patients with proximal vein thrombosis, calf vein thrombosis, or symptomatic pulmonary embolism should be treated first with high-dose heparin or LMWH and then with moderate-intensity oral anticoagulant therapy (INR = 2.0 to 3.0) for 3 to 6 months, as previously described.

Long-term anticoagulant therapy should be considered for patients with recurrent unprovoked episodes of venous thromboembolism and for those with continuing risk factors; deficiency of protein C, protein S, or AT; malignancy; or the antiphospholipid antibody syndrome.[29]

Thrombolytic therapy As previously discussed, thrombolytic therapy is indicated in patients who have major pulmonary embolism with hemodynamic compromise. A regimen of 100 mg of rt-PA administered over 2 hours is probably the method of choice because this regimen produces greater lysis at 2 hours than a 24-hour course of conventional urokinase[67] and, compared with heparin, produces more rapid improvement in pulmonary vascular resistance and right ventricular function.[68] For patients with major pulmonary embolism who are at high risk for bleeding, a short course of rt-PA (0.6 mg/kg over 10 minutes), which accelerates lysis of pulmonary embolism, can also be considered.[69]

The use of thrombolytic therapy in patients who have venous thrombosis is even more controversial. Although there is no rigorous supporting evidence for it and it is not part of our clinical practice, regional or systemic thrombolysis may be considered in patients who have large proximal venous thrombi—particularly if the thrombi are confined to the iliac and femoral veins—if there are no contraindications.

Absolute contraindications to thrombolytic therapy include major surgery within the past 10 days, active internal bleeding, a stroke within the past 3 months, and intracranial disease. Relative contraindications include recent organ biopsy, recent puncture of a noncompressible vessel, recent gastrointestinal bleeding, liver or renal disease, severe arterial hypertension, and severe diabetic retinopathy.

Venous Thromboembolism in Pregnancy

The management of venous thromboembolism during pregnancy is complicated because clinical diagnosis is unreliable, some of the objective diagnostic tests are potentially risky to the fetus, and treatment is more difficult than in the nonpregnant patient because of potential teratogenicity or bleeding in the fetus.[70] Clinical diagnosis of venous thrombosis is unreliable in pregnancy because leg swelling can be caused by compression of the left common iliac vein by the gravid uterus. Unless special precautions are taken, venography exposes the fetus to radiation, and impedance plethysmography can yield false positive results in the latter part of the third trimester of pregnancy.

DIAGNOSIS

In pregnant patients suspected of having venous thrombosis, venous ultrasonography should be used as the initial test.[4] If the result is not normal, a diagnosis of proximal deep vein thrombosis is made, and the patient is treated with anticoagulants. If venous ultrasound results are normal, we perform IPG to exclude an isolated iliac vein thrombosis. If both tests are normal, either a limited venogram can be performed, to exclude isolated calf vein thrombosis, or serial compression ultrasonography can be performed on four or five occasions over the next 14 days.[4]

The diagnostic approach to pulmonary embolism in pregnancy is similar to that used in nonpregnant patients. Lung scanning and pulmonary angiography can be performed, but the techniques should be modified to reduce exposure of the fetus to radiation. Although there is little radiation exposure from perfusion scanning and ventilation scanning, it can be reduced further without a serious loss of resolution by administering 50% of the standard dose of radioactive particles for perfusion lung scanning and by limiting ventilation scanning to patients with an abnormal perfusion scan. The radiation exposure from pulmonary angiography can be reduced by using the brachial route and by shielding the abdomen with a lead-lined apron.

TREATMENT

The treatment of venous thromboembolism is much more complicated in pregnant patients than in nonpregnant patients because oral anticoagulants cross the placenta and, if administered during the first trimester, can cause warfarin embryopathy, which is characterized by nasal hypoplasia and skeletal abnormalities.[70] If warfarin is administered during the second and third trimesters, possible congenital defects include dorsal midline dysplasia, abnormalities of the ventricular system, and optic atrophy.

Heparin, which does not cross the placenta, is much safer than oral anticoagulants during pregnancy. Although there have been reports associating heparin therapy during pregnancy with a high incidence of stillbirth or prematurity, most of the fetal complications occurred in mothers receiving heparin for disorders that are known to be associated with a high rate of fetal loss. Other studies have shown that heparin is safe for the fetus but, when used on a long-term basis during pregnancy, can produce osteoporosis in the mother.[55] The incidence of heparin-induced osteopenia diagnosed by dual-photon absorption x-ray or by conventional x-rays may be as high as 15%, but overt fractures are uncommon, occurring in fewer than 5% of patients. Heparin-induced bleeding is not a common problem during pregnancy, provided that heparin therapy is monitored carefully. The anticoagulant response to heparin can be prolonged if it is administered in high doses just before parturition, so there is the potential for local bleeding during and immediately after delivery.

In pregnant patients with acute venous thromboembolism, continuous intravenous heparin or twice-daily LMWH should be administered for 4 to 7 days, followed by subcutaneous heparin or LMWH, given in adjusted therapeutic doses for the remainder of the pregnancy.[71] The injection site should be rotated over the fatty tissue of the lower abdomen and thighs; the site should be compressed for 5 minutes after injection to prevent local bruising. An

unwanted anticoagulant effect during delivery can be avoided by discontinuing subcutaneous heparin therapy 24 hours before elective induction of labor.

If there is no evidence of excessive postpartum bleeding, heparin therapy can be resumed about 2 hours after delivery and continued until oral anticoagulation is established. The intensity of heparin therapy will depend on the amount of time that has passed since the diagnosis of venous thromboembolism was made: if the diagnosis was made less than 1 month ago, therapeutic doses may be used; if the diagnosis was made more than 1 month ago, prophylactic or intermediate doses of heparin may be used. Warfarin therapy is started at the same time as heparin and is continued for a minimum of 6 weeks and until patients have received a minimum of 3 months of anticoagulation. Warfarin does not enter breast milk and therefore can be administered to nursing mothers.

Miscellaneous Thromboembolic Disorders

THROMBOSIS IN UNUSUAL SITES

Subclavian or Axillary Veins

Thrombosis of the subclavian or axillary veins may be idiopathic or may occur as a complication of local vascular damage.[72] It is now most frequently seen as a complication of chronic indwelling catheter use, but it also occurs as a complication after mastectomy and local radiotherapy for breast cancer. Idiopathic subclavian or axillary vein thrombosis often occurs in muscular young individuals and may be preceded by repetitive, strenuous activity involving the affected arm. Some of these persons have a fixed stenosis of the subclavian vein that is thought to be caused by external compression of the vein as it courses behind the clavicle. Occasionally, subclavian or axillary vein thrombosis can occur in patients with congenital deficiency of AT, protein C, or protein S or in patients with antiphospholipid antibodies. Thrombosis of the axillary or subclavian vein or the superior vena cava is a rare complication of an implantable perivenous endocardial pacing system.

Subclavian or axillary thrombosis causes pain, edema, and cyanosis of the arm. In rare cases, the thrombosis extends into the superior vena cava and causes edema and cyanosis of the face and neck. Definitive diagnosis is made by venography or venous ultrasonography. Subclavian or axillary vein thrombosis is usually treated with anticoagulants. Regional or systemic thrombolytic therapy may be considered in young patients without contraindications, because a substantial number of these patients experience aching and swelling when they exert the affected arm.

Mesenteric Vein

An uncommon disorder, mesenteric vein thrombosis usually occurs in the sixth or seventh decade of life. It generally affects segments of the small bowel, leading to hemorrhagic infarction. Affected patients often have associated disorders, such as inflammatory bowel disease, malignant disease, portal hypertension, or familial thrombophilia or polycythemia vera, or they may have a history of recent abdominal surgery. In about 20% of cases, no underlying cause is found.

The clinical manifestations of mesenteric vein thrombosis include intermittent abdominal pain, abdominal distention, vomiting, diarrhea, and melena. Diagnosis of mesenteric vein thrombosis is often difficult, but the finding of blood-stained ascitic fluid on abdominal paracentesis or peritoneoscopic evidence of hemorrhagic bowel infarction is characteristic of the disorder. Management includes supportive care and surgical resection, followed by anticoagulant therapy. Mortality is about 20%, and recurrence is likely in up to 20% of patients.

Renal Vein

Renal vein thrombosis can be idiopathic or a complication of the nephrotic syndrome. Patients may be asymptomatic or may present with abdominal, back, or flank pain and tenderness. Pulmonary embolism is a relatively common complication of renal vein thrombosis. Anticoagulant therapy results in a gradual improvement in renal function, but patients may have long-standing proteinuria. Thrombolytic agents have been used, but the data are inadequate for critical appraisal of this form of treatment.

THROMBOPHILIA

The term thrombophilia denotes any increased tendency to thrombosis, whether inherited or acquired. Thrombophilia is usually diagnosed on the basis of the clinical findings, because a patient presents with one or more of the following features[13,9,10]: a family history of thrombosis, thrombosis at a young age, idiopathic thrombosis, or recurrent thrombosis; thrombosis that occurs in an unusual site or despite adequate anticoagulant therapy; a combination of venous thrombosis and arterial thrombosis; and thrombophlebitis migrans.

Many patients with clinical features of thrombophilia do not have a recognizable inherited or acquired disorder.[11] The causes of inherited thrombophilia are APC resistance caused by factor V Leiden, the G20210A prothrombin gene mutation, and abnormalities or deficiencies of AT, protein C, protein S, and, much less commonly, plasminogen and fibrinogen.[13,9,10] There is an association between elevated levels of coagulation factors XI and VIII and venous thrombosis.[16,17] It is probable that there is a hereditary component to these elevations in some patients. Current evidence does not support the view that inherited deficiencies of fibrinolysis cause venous thrombosis or recurrent venous thrombosis, nor is there evidence that deficiencies or elevations of coagulation factors, including factor XII, factor V, and factor VII, predispose to venous thrombosis.

The main causes of acquired thrombophilia are antiphospholipid antibody syndrome, collagen vascular disorders, hyperhomocysteinemia, malignancy, and cancer chemotherapy.[2] Less common causes are paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, nephrotic syndrome, and Buerger disease (thromboangiitis obliterans).

Inherited Thrombophilia

The reported prevalence of inherited thrombophilias is highest in patients referred to specialized laboratories for screening studies and lowest in unselected populations of patients with thrombosis. In a study of unselected outpatients referred with symptoms of venous thrombosis whose diagnosis was confirmed by venography, 23 of 277

(8.3%) had inherited deficiencies of AT, protein C, protein S, or plasminogen.[11] The prevalence of the deficiencies was 22% (6 of 27) in patients younger than 41 years who had a family history of thrombosis and 30% (3 of 10) in young patients with a family history of thrombosis who had had a previous episode of venous thromboembolism. The relative odds of having a deficiency were 3.2 when patients who had thrombosis and a family history of thrombosis were compared with patients who had thrombosis but no family history of the condition. The study was performed before the discovery of APC resistance and the G20210A prothrombin gene mutation. Since their discovery, about 50% of young patients with idiopathic venous thrombosis (including idiopathic thrombosis in pregnancy) have been found to have an inherited thrombophilic defect.

Antithrombin, protein S, protein C deficiency, factor V Leiden, and the G20210A prothombin gene mutation are autosomal dominant traits. Venous thrombosis and pulmonary embolism are the most common manifestations of the inherited thrombophilias. Approximately 50% of episodes occur without a clinically obvious provocation.[13] Superficial thrombophlebitis also occurs, particularly in protein C or protein S deficiencies. Arterial thrombosis has been described in all three deficiencies,[73] but it is uncertain whether the association is causal or coincidental. Cerebral arterial thrombosis has been described in case series of factor V Leiden, the G20210A prothrombin gene mutation, and protein S deficiency. Venous thrombosis during pregnancy appears to be particularly common in AT deficiency, but postpartum venous thrombosis is common in all three deficiencies.[13] Patients with AT deficiency may show heparin resistance, those with protein C or protein S deficiency are prone to warfarin-induced skin necrosis, and those with homozygous recessive protein C and protein S deficiency are prone to neonatal purpura fulminans.

The incidence of a first spontaneous thrombosis in AT, protein C, and protein S deficiencies has been estimated to be about 3% a year.[13] The risk of thrombosis in asymptomatic carriers is very low in the first 2 decades of life. Deep vein thrombosis or pulmonary embolism develops in about 50% to 70% of carriers during their lifetime. Because more than 50% of the thromboembolic episodes in deficient individuals occur during or after a reversible provocation such as surgery, these episodes may be prevented by appropriate prophylaxis.

The combined prevalence of factor V Leiden and the G20210A prothrombin gene mutation in the normal population is about 10-fold higher than the combined prevalence of AT, protein C, and protein S deficiencies. However, the risk of thrombosis with factor V Leiden or the G20210A prothrombin gene mutation is about fivefold lower than for that with the other three deficiencies.[9,10,13] The risk of thrombosis with inherited thrombophilia is increased by the use of estrogen-containing oral contraceptives.[9,10,13]

Because 90% to 95% of episodes of venous thromboembolism are not fatal, antithrombotic therapy is not warranted in most asymptomatic carriers of the inherited thrombophilias. Prophylaxis with either adjusted-dose heparin or oral anticoagulants should be used after surgery or during a major medical illness in asymptomatic carriers.

Long-term anticoagulant treatment should be considered for patients with inherited or acquired thrombophilic disorders who have one or more unprovoked episodes of venous thromboembolism.[13] Because AT is a cofactor for heparin, patients with AT deficiency may have heparin resistance, which can usually be overcome by increasing the heparin dose. Infusions of AT concentrate usually are not necessary. Patients with protein C deficiency are theoretically at risk for hypercoagulability during initial warfarin therapy because protein C has a much shorter half-life than three of the four vitamin K–dependent procoagulants. The thrombogenic risk can be reduced by avoiding a loading dose of warfarin and ensuring that heparin therapy begins before warfarin treatment.

Women with inherited thrombophilia should avoid estrogen-containing oral contraceptives and hormone replacement therapy. Pregnancy is a risk factor for thrombosis in inherited thrombophilic patients and in patients with antiphospholipid antibodies.

We recommend prophylactic doses of heparin or LMWH throughout pregnancy in patients with AT deficiency, regardless of whether they have had a previous episode of thrombosis.[13] Women with deficiencies of protein C or S need prophylactic therapy only if they have had a previous episode of thrombosis. It is generally reasonable to withhold prophylaxis in women with factor V Leiden or the G20210A prothrombin gene mutation. Prophylaxis (e.g., warfarin) should be used for about 6 weeks after delivery.[13]

Acquired Thrombophilia

Malignancy An association between cancer and thrombosis has been recognized for over a century. Patients with cancer (especially pancreatic, ovarian, lung, and gastrointestinal carcinoma) may experience unusual forms of thrombosis, including migratory superficial thrombophlebitis, nonbacterial thrombotic endocarditis, and thrombosis in unusual sites, such as renal veins, the inferior vena cava, and the portal and hepatic veins. Venous thrombosis may progress in cancer patients despite apparently adequate oral anticoagulant therapy or, less often, heparin therapy. Migratory thrombophlebitis, characterized by recurrent thrombosis in superficial and deep veins, is a feature of mucin-secreting tumors. The symptoms may be resistant to treatment with oral anticoagulants but generally respond to heparin. Hepatic vein thrombosis may be associated with myeloproliferative disorders, with hepatoma, and with renal cell and adrenal carcinomas.

Evidence suggests that patients who have idiopathic venous thrombosis are at risk for an associated occult malignancy, which is usually expressed clinically during the following 12 months.[26,74] In one study,[26] approximately 70% of such malignancies were in the gastrointestinal tract, the male or female urogenital tract, and the lung.

It is uncertain whether intensive investigation will detect occult malignancy in patients with idiopathic venous thrombosis and, if it does, whether early identification and treatment of occult malignancies improves prognosis. Expensive or invasive investigations for malignant disease probably are not indicated in patients with the first episode of deep vein thrombosis.[74] Initial investigations should include a complete blood count, hepatic biochemistry, a chest radiograph, and testing for fecal occult blood. If malignancy is strongly suspected on clinical grounds because of associated laboratory abnormalities or because of recurrent

idiopathic venous thrombosis or thrombosis refractory to warfarin therapy, further investigations can be performed.

The risk of thrombosis is also increased by cancer chemotherapy. In a study of patients with stage II breast cancer who were treated with chemotherapy, the incidence of thrombosis was 6.8% during the first 3 months of chemotherapy and 4.9% during the next 6 months (in patients randomized to an additional 6 months of chemotherapy); during the 6-month period, the incidence was 0% among those who did not receive additional chemotherapy.[75]

Antiphospholipid antibody syndrome The antiphospholipid antibody syndrome (APLS) is a disorder in persons with antiphospholipid antibodies plus one or more of the following clinical manifestations: venous and arterial thrombosis, fetal wastage, and thrombocytopenia.[76] The antibodies are of the IgG or IgM class and are directed at various phospholipid moieties, including cardiolipin. Some of the antibodies have anticoagulant properties because they bind epitopes on the phospholipid portion of prothrombinase and, as a result, prolong coagulation assays such as the aPTT and kaolin clotting time. These anticoagulants were initially described in patients with systemic lupus erythematosus (SLE) and were termed lupus anticoagulants. Paradoxically, these circulating anticoagulants do not produce abnormal bleeding but are associated with thrombosis. It subsequently became clear that antiphospholipid antibodies occur in persons with disorders other than SLE, including other autoimmune disorders and drug-induced lupus, as well as in otherwise healthy persons.

Antiphospholipid antibodies with or without anticoagulant properties occur in patients with idiopathic venous and arterial thrombosis and are an important marker for acquired thrombophilia. Cross-sectional studies suggest about a twofold increase in the risk of venous thrombosis with an anticardiolipin antibody and a fivefold to 10-fold increase with a lupus anticoagulant in patients with or without SLE.[77,78] The mechanism by which thrombosis occurred in the patients with antiphospholipid antibodies is uncertain. The titer of antibody and the pattern of test positivity can change over time within an individual, and the test may be only transiently positive. No single test has been demonstrated to be the best predictor of thrombosis, and it is not clear whether the level of the antibody titer influences the risk of thrombosis.

The most common thrombotic manifestation of APLS is idiopathic venous thrombosis involving the deep veins of the legs. Other associations with APLS are thrombosis in childhood, a combination of arterial and venous thrombosis, and thrombosis in an unusual site (including the inferior vena cava or hepatic, portal, splenic, axillary, mesenteric, or renal vein). APLS is also associated with arterial thrombotic disease, especially stroke.[76] Antiphospholipid antibodies are associated with an increased risk of infertility, preeclampsia, fetal growth retardation, and fetal wastage[70] in women with APLS. Evidence suggests that low-dose heparin and aspirin are effective at preventing fetal loss, possibly by limiting the extent of placental infarction.[70]

The management of APLS in nonpregnant women is uncertain, but the following guidelines seem reasonable in the light of current evidence. If an antibody is found in the absence of symptoms or a history of thrombosis, long-term anticoagulant treatment is not indicated. Aggressive prophylaxis should be used in high-risk situations, including long airplane flights, confinement to bed because of medical illness, surgery, and after trauma. Patients with antiphospholipid antibodies and unprovoked venous thromboembolism should be treated with long-term warfarin unless they have a high risk of bleeding.

THROMBOANGIITIS OBLITERANS

A rare form of vasculitis called thromboangiitis obliterans (Buerger disease) involves both arteries and veins, especially those of the lower extremities.[79] The incidence of this disorder, which usually occurs in young men who are heavy smokers, is much higher in Israel, Eastern Europe, and the Far East than in the United States. An immune mechanism appears to be responsible for some of the pathologic features. Occasionally, there is migratory thrombophlebitis, associated with tender areas of erythema. Arterial insufficiency often causes claudication of the foot, Raynaud phenomenon, and tropic changes. Cerebral, coronary, and visceral vessels can be affected. Patients should be told to stop smoking; if they do so, the progress of the disease process will be slowed or arrested.

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