ABC of antithrombotic therapy

Venous thromboembolism: pathophysiology, clinical features, and prevention

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Venous thromboembolism is a common complication among hospital inpatients and contributes to longer hospital stays, morbidity, and mortality. Some venous thromboembolisms may be subclinical, whereas others present as sudden pulmonary embolus or symptomatic deep vein thrombosis. Ultrasonic Doppler and venographic techniques have shown deep vein thrombosis of the lower limb to occur in half of all major lower limb orthopaedic operations performed without antithrombotic prophylaxis. Deep vein thrombosis of the lower limb is also seen in a quarter of patients with acute myocardial infarction, and more than half of patients with acute ischaemic stroke.

Deep vein thrombosis of the lower limb normally starts in the calf veins. About 10-20% of thromboses extend proximally, and a further 1-5% go on to develop fatal pulmonary embolism. Appropriate antithrombotic measures can reduce this complication. Until recently, some clinicians were reluctant to provide such prophylaxis routinely. As unfounded fears of major bleeding complications from anticoagulant regimens wane, preventive treatments are used more often with medical and surgical patients. However, the risk of bleeding can be serious and this has particular bearing in postoperative patients.

Venous thromboembolism can also arise spontaneously in ambulant individuals particularly if they have associated risk factors such as thrombophilia, previous thrombosis, or cancer. However, in over half of these patients, no specific predisposing factors can be identified at presentation.

Pathophysiology

Thrombus formation and propagation depend on the presence of abnormalities of blood flow, blood vessel wall, and blood clotting components, known collectively as Virchow's triad. Abnormalities of blood flow or venous stasis normally occur after prolonged immobility or confinement to bed. Venous obstruction can arise from external compression by enlarged lymph nodes, bulky tumours, or intravascular compression by previous thromboses. Increased oestrogens at pharmacological levels, as seen with oral contraceptive use and with hormone replacement therapy in postmenopausal women, have been associated with a threefold increased risk in the small initial risk of venous thromboembolism. Cancers, particularly adenocarcinomas and metastatic cancers, are also associated with increased venous thromboembolism. Indeed, on presentation, some idiopathic venous thromboembolisms have revealed occult cancers at follow up. Both oestrogens at pharmacological levels and cancer can also activate the clotting system.

Clinical presentation and diagnosis

Deep vein thrombosis
Deep vein thrombosis commonly presents with pain, erythema, tenderness, and swelling of the affected limb. Thus, in lower limb deep vein thrombosis, the affected leg is usually swollen with the circumference of the calf larger than the unaffected side. Other causes of leg swelling, erythema, and tenderness include a ruptured Baker's cyst and infective cellulitis. The
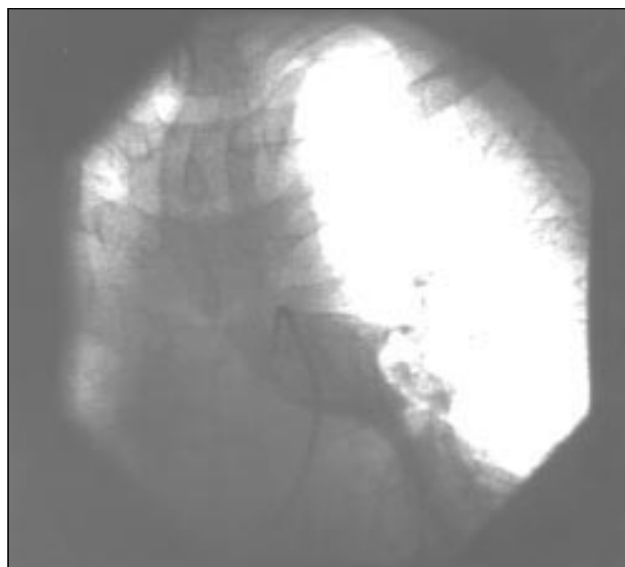
Pulmonary angiography showing large pulmonary embolus in left pulmonary artery

> **Venous thromboembolism often manifests clinically as deep vein thrombosis or pulmonary embolism, and is possibly one of the preventable complications that occur in hospitalised patients**

Risk factors and conditions predisposing to venous thromboembolism

- History of venous thromboembolism
- Prolonged immobility
- Prolonged confinement to bed or lower limb paralysis
- Surgery, particularly lower limb orthopaedic operations, and major pelvic or abdominal operations
- Trauma—For example, hip fractures and acute spinal injury
- Obesity
- Major medical illnesses such as acute myocardial infarction, ischaemic stroke, congestive cardiac failure, acute respiratory failure
- Oestrogen use in pharmacological doses—For example, oral contraception pills, hormone replacement therapy
- Cancer, especially metastatic adenocarcinomas
- Age >40 years
- Aquired hypercoaguable states—Lupus anticoagulant and antiphospholipid antibodies, hyperhomocysteinaemia, dysfibrinogenaemia, myeloproliferative disorders such as polycythaemia rubra vera
- Inherited hypercoaguable states—Activated protein C resistance (factor V Leiden mutation), protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin gene mutation

diagnosis of deep vein thrombosis is therefore more likely when risk factors are present and less so if there are features suggesting alternative diagnoses. For example, ruptured Baker's cysts commonly appear in the context of osteoarthritis and rheumatoid arthritis. Infective cellulitis is unlikely to be bilateral, with clearly demarcated areas of erythema extending proximally. Breaks in the skin, particularly between the toes, and coexistent fungal infection are additional clues to cellulitis.

Objective diagnosis of venous thromboembolism is important for optimal management. Although the clinical diagnosis of venous thromboembolism is imprecise, various probability models based on clinical features have proved to be practical and reliable (interobserver reliability, $\kappa = 0.85$) in predicting the likelihood of venous thromboembolism. These models should be used in conjunction with objective diagnostic tests.

Compression ultrasonography remains the non-invasive investigation of choice for the diagnosis of clinically suspected deep vein thrombosis. It is highly sensitive in detecting proximal deep vein thrombosis although less accurate for isolated calf deep vein thrombosis. In patients with suspected thrombosis and a negative compression ultrasound result, the test should be repeated in seven days because studies have shown that patients with two or more negative tests over a week who are untreated have a less than 2% risk of proximal extension or subsequent deep vein thrombosis.

Impedance plethysmography is slightly less specific and sensitive than ultrasonography but may still have a role in pregnant women and suspected recurrent deep vein thrombosis. The gold standard is invasive contrast venography, which is still used when a definitive answer is needed. Newer imaging techniques are being developed, and tools such as magnetic resonance venography or computed tomography could possibly detect pelvic vein thromboses, but further testing is needed to establish their role in the diagnosis of deep vein thrombosis.

Blood tests such as fibrin D-dimer add to the diagnostic accuracy of the non-invasive tests. In one study, the sensitivity and specificity of a D-dimer concentration of >500 µg/l for the presence of pulmonary embolism were 98% and 39%, respectively, which give positive and negative predictive values of 44% and 98%. The sensitivity of the test even remained high at three and seven days after presentation (96% and 93%).

Modified pretest probability for deep vein thrombosis

Clinical feature	Score
Tenderness along entire deep vein system	1.0
Swelling of the entire leg	1.0
Greater than 3 cm difference in calf circumference	1.0
Pitting oedema	1.0
Collateral superficial veins	1.0
Risk factors present:	
Active cancer	1.0
Prolonged immobility or paralysis	1.0
Recent surgery or major medical illness	1.0
Alternative diagnosis likely (ruptured Baker's cyst in rheumatoid arthritis, superficial thrombophlebitis, or infective cellulitis)	-2.0

Score >3 = high probablility; 1-2 = moderate probability <0 = low probability
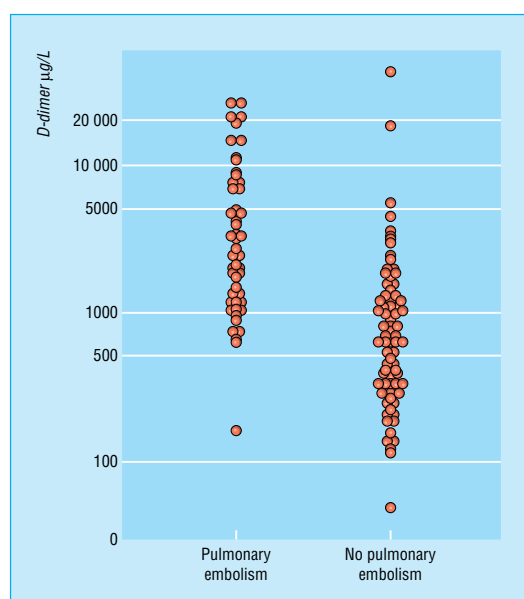
Plasma D-dimer concentrations on day of presentation according to final diagnosis

Investigations for suspected venous thromboembolism by pretest clinical probability

Pretest probability	Fibrin D-dimer	Other investigations	Comment
Deep vein thrombosis:			
Low	Negative		No further investigations needed
Low or moderate	Positive	Negative ultrasound compression	Consider venography or repeat ultrasound after a week
Moderate or high	Positive	Positive ultrasound compression	Treat with anticoagulants
High	Positive	Negative ultrasound compression	Consider venography to rule out deep vein thrombosis, especially in high risk patients and those with recurrent pulmonary emboli
Pulmonary embolism:			
Low	Negative	No	No further investigation needed
Low or moderate	Positive	Proceed to ventilation-perfusion scan	If non-diagnostic ventilation-perfusion scan consider serial compression ultrasound over two weeks to rule out venous thromboembolism
High	Positive	Proceed to ventilation-perfusion scan (or ultrasound)	If non-diagnostic ventilation-perfusion scans, proceed to venography or pulmonary angiography as needed

Pulmonary embolism

Patients presenting with acute pulmonary embolism often complain of sudden onset of breathlessness with haemoptysis or pleuritic chest pain, or collapse with shock in the absence of other causes. Deep vein thrombosis may not be suspected clinically, but its presence, along with thrombotic risk factors, will make the diagnosis of pulmonary embolism more likely. A similar clinical probability model to that for deep vein thrombosis has been developed for pulmonary embolism.

Pulmonary angiography is the gold standard investigation for pulmonary embolism, but it is invasive and associated with 0.5% mortality. A ventilation-perfusion scan using technetium DTPA (ditriaminopentaric acid) is more widely used. However this investigation is non-specific, and is diagnostic in only 30% of cases. Spiral computed tomography scans are more reliable but diagnosis is limited to emboli in larger vessels only. Measurement of fibrin D-dimer levels, used for deep vein thrombosis, is helpful, as is compression ultrasound in the detection of occult deep vein thrombosis.

Prevention strategies

An appropriate strategy for the prevention of venous thromboembolism include pharmacological or physical methods. To optimise treatment, patients should be stratified into risk categories to allow the most appropriate prophylactic measure to be used.

Prophylactic drugs include unfractionated heparin, low molecular weight heparin, oral anticoagulants (such as coumarins), thrombin inhibitors (such as hirudin), and specific factor Xa inhibitors (such as fondaparinux). The recently approved fondaparinux reduces the risk of venous thromboembolism after orthopaedic surgery by more than half compared with low molecular weight heparin and seems likely to become the treatment of choice after universal availability.

Prophylactic physical methods include the use of compression elastic stockings, intermittent pneumatic compression (which provides rythmic external compression at 35-40 mm Hg for about 10 seconds every minute), and early mobilisation to improve venous blood flow in conditions predisposing to venous stasis.

General surgery

Patients at low risk undergoing general surgery do not need specific prophylaxis other than early mobilisation. In moderate risk patients, fixed low doses of unfractionated heparin (5000 IU every 12 hours) or low molecular weight heparin (3400 anti-Xa units or equivalent) once daily is sufficient. Higher doses of low molecular weight heparin (more than 3400 IU anti-Xa daily) should be reserved for high risk general surgery and orthopaedic operations. Compression elastic stockings and intermittent pneumatic compression may protect high risk patients when used with anticoagulants. They are also effective when used alone in moderate risk patients where anticoagulants are contraindicated.

Orthopaedic surgery

In very high risk patients, such as those undergoing major orthopaedic operations, high dose low molecular weight heparin or warfarin is appropriate. The current recommended length of anticoagulant prophylaxis is 7-10 days with low molecular weight heparin or warfarin. Extended use may provide additional benefit. Routine screening with duplex ultrasonography is not helpful. Hirudin seems to be superior to low molecular weight heparin and low dose unfractionated heparin as prophylaxis in patients undergoing elective hip replacements but is still not universally available.

Clinical probability for pulmonary embolism

Clinical feature	Score
Deep vein thrombosis suspected:	
Clinical features of deep vein thrombosis	3.0
Recent prolonged immobility or surgery	1.5
Active cancer	1.0
History of deep vein thrombosis or pulmonary embolism	1.5
Haemoptysis	1.0
Resting heart rate > 100 beats/min	1.5
No alternative explanation for acute breathlessness or pleuritic chest pain	3.0

>6 = high probability (60%); 2-6 = moderate probability (20%); <1.5 = low probability (3-4%)

Thromboembolic risk stratification for surgery patients

- *Low risk*—Uncomplicated surgery in patients aged <40 years with minimal immobility postoperatively and no risk factors
- *Moderate risk*—Any surgery in patients aged 40-60 years, major surgery in patients <40 years and no other risk factors, minor surgery in patients with one or more risk factors
- *High risk*—Major surgery in patients aged >60 years, major surgery in patients aged 40-60 years with one or more risk factors
- *Very high risk*—Major surgery in patients aged >40 years with previous venous thromboembolism, cancer or known hypercoagulable state, major orthopaedic surgery, elective neurosurgery, multiple trauma, or acute spinal cord injury
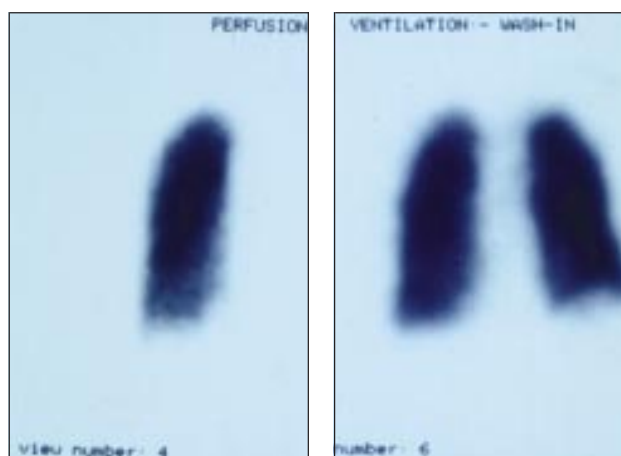
Ventilation-perfusion scan showing massive pulmonary thromboembolism, showing a mismatch between (left) perfusion and (right) ventilation scans

Key points

- Understanding Virchow's triad aids treatment of venous thromboembolism
- Numerous situations and risk factors can contribute to venous thromboembolism
- Diagnosis of venous thromboembolism depends upon combination of history, risk factors, and investigations
- Antithrombotic prophylaxis is safe and effective

Neurosurgery, multiple traumas, and spinal cord injuries

Intermittent pneumatic compression is the prophylaxis of choice for elective neurosurgery. Among the low molecular weight heparins, only enoxaparin 30 mg twice daily has been shown to reduce venous thromboembolism without excess bleeding after elective neurosurgery, multiple traumas, or spinal cord injuries and so may be used in these situations. Other low molecular weight heparins have either not been tested or not conclusively shown to be of benefit in this setting.

Medical conditions

In general medical patients including heart failure and respiratory failure patients, both unfractionated heparin and low molecular weight heparin have been shown to be effective in reducing the risk of venous thromboembolism. Low molecular weight heparin has been shown to be more effective than heparin in stroke. Low dose heparin has been shown to be effective in acute myocardial infarction but this is now largely historic because myocardial infarction patients receive therapeutic dose anticoagulants.

Other considerations

Combined approaches using drugs and physical methods may be better at preventing thromboembolism than physical methods alone. However, compression elastic stockings and intermittent pneumatic compression may be used for moderate or high risk patients when anticoagulation is contraindicated or best avoided. Inferior vena cava filter placement should be reserved for patients at very high risk of venous thromboembolism where anticoagulation as well as physical methods are contraindicated. Inferior vena cava filter placement tends to cause a long term increase of recurrent deep vein thrombosis, even though the immediate risk of postoperative pulmonary embolism is reduced.

Further reading

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Evidence based use of antithrombotic prophylaxis

General surgery
- *Low risk*— Early mobilisation
- *Moderate risk*—UH 5000 IU 12 hourly starting two hours before surgery, or low molecular weight heparin <3400 anti-Xa IU daily*, or compression elastic stockings, or intermittent pneumatic compression
- *High risk*—Low molecular weight heparin >3400 anti-Xa IU daily† plus compression elastic stockings, or unfractionated heparin 5000 IU eight hourly starting two hours before surgery plus compression elastic stockings, or intermittent pneumatic compression if anticoagulation contraindicated
- *Very high risk*—Perioperative warfarin (INR 2-3), low molecular weight heparin >3400 anti-Xa IU daily† plus compression elastic stockings, or prolonged low molecular weight heparin therapy plus compression elastic stockings

Major orthopaedic surgery
- *Elective hip replacement*—Recombinant hirudin 15 mg twice daily, unfractionated heparin 3500 IU eight hourly with postoperative adjustments (APTT 1.2-1.5), or low molecular weight heparin >3400 anti-Xa IU daily†, or perioperative warfarin (INR 2-3), or fondaparinux 2.5 mg daily
- *Elective knee replacement*—Low molecular weight heparin >3400 anti-Xa IU daily†, or perioperative warfarin (INR 2-3), or fondaparinux 2.5 mg daily, intermittent pneumatic compression
- *Surgery for hip fracture*—Low molecular weight heparin >3400 anti-Xa IU daily†, or perioperative warfarin (INR 2-3), or fondaparinux 2.5 mg daily

Elective neurosurgery
- Intermittent pneumatic compression, enoxaparin 30 mg twice daily

Acute spinal cord injury
- Enoxaparin 30 mg twice daily

Trauma
- Enoxaparin 30 mg twice daily

Acute myocardial infarction
- Low dose unfractionated heparin 5000 IU twice daily, full dose unfractionated heparin 40 000 IU infusion over 24 hours, elastic stockings, and early mobilisation

Ischaemic stroke
- Low dose unfractionated heparin 5000 IU twice daily

Other medical conditions including congestive heart failure
- Enoxaparin 40 mg once daily or 30 U twice daily, dalteparin 2500 IU daily, low dose unfractionated heparin 5000 IU twice daily

Cancer patients receiving chemotherapy
- Low dose warfarin (INR <2), dalteparin 2500 IU daily

*Dalteparin 2500 IU once daily starting two hours before surgery
Enoxaparin 20 mg once daily starting two hours before surgery
Nadroparin 3100 IU once daily starting two hours before surgery
Tinzaparin 3500 IU once daily starting two hours before surgery
†Dalteparin 5000 IU once daily starting 10-12 hours before surgery
Danaparoid 750 IU twice daily starting one to two hours before surgery
Enoxaparin 40 mg once daily starting 10-12 hours before surgery or 30 mg twice daily starting after surgery
Tinzaparin 50 IU/kg once daily starting two hours before surgery

The box showing evidence based use of antithrombotic prophylaxis is adapted from the 6th ACCP guidelines Geerts WH, et al. *Chest* 2001;119:132-75S. The figure showing Plasma D-dimer concentrations on day of presentation according to final diagnosis is adapted from Bounameaux H, et al. *Lancet* 1991;337:196-200.