Venous thromboembolism

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Venous thrombosis is the process of clot (thrombus) formation within veins. Although this can occur in any venous system, the predominant clinical events occur in the vessels of the leg, giving rise to deep vein thrombosis, or in the lungs, resulting in a pulmonary embolus. Collectively referred to as venous thromboembolism, these have a high prevalence both in the community and in hospitals, and bring a considerable burden of morbidity and possible mortality.

The causes of venous thromboembolism can be hereditary or acquired. A risk factor for thrombosis often can be identified in over 80% of patients, but usually more than one factor is at play in a patient.

Sources and selection criteria

Our information came from a personal collection of published work and searches of Medline using the key words "venous thromboembolism", "deep vein thrombosis," and "pulmonary embolus". We also reviewed recent guidelines on management of venous thromboembolism and identified several relevant Cochrane reviews.

Deep vein thrombosis

A deep vein thrombosis commonly presents with pain, erythema, tenderness, and swelling of the affected limb. Findings on examination include a palpable cord (reflecting a thrombosed vein), warmth, ipsilateral oedema, or superficial venous dilation. Differential diagnoses include a ruptured Baker's cyst, muscle tears or pulls, and infective cellulitis. Objective diagnosis of deep vein thrombosis (as with pulmonary embolism) is important for optimal management, and although the clinical diagnosis is imprecise, models based on clinical features are fairly practical and reliable in predicting the likelihood of an event. Only a minority of patients (less than a third) with suspected deep vein thrombosis of a lower limb actually have the disease.

Compression ultrasonography remains the non-invasive tool of choice for the investigation and diagnosis of clinically suspected deep vein thrombosis. Although such imaging is highly sensitive for detecting proximal deep vein thrombosis, it is less accurate for isolated deep vein thrombosis of the calf. The ideal method, invasive contrast venography, is used when a definitive answer is required.

Newer imaging techniques being developed (for example, magnetic resonance venography, computed tomography) could detect pelvic vein thromboses,

Summary points

Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, are common and treatable in hospital and the community

Major risk factors include age, recent surgery (especially orthopaedic), cancer, and thrombophilia

Established treatments are unfractionated heparin, low molecular weight heparin, fondaparinux, and warfarin

Treatment agents and duration depend on the cause

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although further testing is necessary to establish their role in the diagnosis of deep vein thrombosis. Blood tests such as for fibrin D-dimer, a fibrin degradation product, add to the diagnostic accuracy of the non-invasive tests. D-dimer levels are >500 ng/ml in nearly all patients with venous thromboembolism. Alone, they are insufficient to establish the diagnosis as such levels are non-specific and often can be found in patients admitted to hospital and in those with malignancy or after recent surgery. Thus, a low or normal D-dimer level with a low pretest probability makes a diagnosis of deep vein thrombosis (or pulmonary embolism) unlikely. Figure 1 shows a practical approach to the diagnosis of deep vein thrombosis using the pretest probability model and a clinical approach to diagnosis.

Pulmonary embolism

Pulmonary embolism commonly presents with a sudden onset of breathlessness with haemoptysis, pleuritic chest pain, or collapse with shock, in the absence of other causes. Such patients should be investigated and treated urgently, as pulmonary embolism has a high risk of mortality and morbidity. Most patients with pulmonary embolism have no leg symptoms at diagnosis, with less than a third having signs or

Further details and ongoing research are on bmj.com

Fig 1 Clinical approach to the diagnosis of deep vein thrombosis. Adapted from Ho et al¹

symptoms of a deep vein thrombus. Conversely, many patients with symptomatic deep vein thrombosis may have asymptomatic pulmonary embolism. A similar clinical model to that for deep vein thrombosis has been developed for pulmonary embolism. Figure 2 summarises the clinical approach to the diagnosis of pulmonary embolism.

The most common symptoms of a pulmonary embolus are dyspnoea (73%), pleuritic pain (66%), and cough (37%), whereas the most common signs are tachypnoea (70%), crepitations (51%), and tachycardia (30%).³ In severe cases circulatory collapse and cardiac arrest due to pulseless electrical activity may occur. A sinus tachycardia is the commonest abnormality with pulmonary embolism on a 12 lead electrocardiograph, although less often atrial fibrillation, right bundle branch block, or other features of right heart strain and a $S_1Q_3T_3$ pattern may be seen.³ Measurement of fibrin D-dimer levels, as for deep vein thrombosis, is helpful.^{4,5}

Pulmonary angiography is the ideal investigation for pulmonary embolism, but as this is invasive and associated with 0.5% mortality, a ventilation-perfusion scan is more widely used. A normal perfusion lung scan virtually excludes the diagnosis of pulmonary embolism. Pulmonary emboli can, however, still present in many patients with low or intermediate probability scans, and angiography may be needed for a definitive diagnosis. Spiral computed tomograms using intravenous contrast (computed tomography angiography) are more reliable and gaining increasing acceptance for the diagnosis of pulmonary embolism.

Who is at risk of venous thromboembolism?

Venous thromboembolism occurs in the community but is a more common complication among hospital

inpatients and contributes to longer hospital stays, morbidity, and mortality. In North America each year it occurs for the first time in around 100 people per 100 000. Of these, about one third has a symptomatic pulmonary embolus, the remainder present with a deep vein thrombus. These rates mask a considerable variation according to defined populations, such as elderly people, rising from fewer than five cases per 100 000 children aged less than 15 years to 450-600 cases per 100 000 adults aged 80. For those aged 65 and older, mortality due to pulmonary embolism in hospital and at one year is 21% and 39% respectively, whereas in the under 40 years of age group the corresponding rates for venous thromboembolism are 2% and <10%.⁶ Despite anticoagulant therapy, venous thromboembolism frequently recurs in the first few months after the initial event, with a rate of about 7% at six months, whereas death occurs in around 6% of cases of deep vein thrombosis and 12% of cases of pulmonary embolism within one month of diagnosis. Many of the classic risk factors for arterial thrombosis (diabetes, smoking) are also risk factors for venous thromboembolism.^{7,8}

Early mortality after venous thromboembolism is strongly associated with presentation as pulmonary embolism, advanced age, cancer, and underlying cardiovascular disease. However, lower limb deep vein thrombosis has been documented in half of all major orthopaedic operations carried out without antithrombotic prophylaxis, in a quarter of patients with acute myocardial infarction, and in more than half of patients with acute ischaemic stroke. Around 25% to 50% of patients with first time venous thromboembolism present without a readily identifiable risk factor, although several are recognised and may be classified as being of high, medium, or low risk (box 1). In a community study of 1231 consecutive cases of venous thromboembolism, 96% had one risk factor, 76% had two, and 39% had three, the most common risk factors being aged more than 40 (present in 88% of cases), obesity (38%), a history of venous thromboembolism (26%), and cancer (22%).⁹

Pathophysiology of venous thromboembolism

What is the link between the risk factors for venous thromboembolism and actual disease? As the basis of

Box 1 Risk factors for venous thromboembolism

Strong risk factors

Fracture of the hip, pelvis, or leg; hip or knee replacement; major general surgery, major trauma, spinal cord injury

Moderate risk factors

Arthroscopic knee surgery; central venous lines; malignancy; congestive heart or respiratory failure; hormone replacement therapy; oral contraceptives; paralytic stroke; post partum period; previous venous thromboembolism; thrombophilia

Weak risk factors

Bed rest for more than three days; immobility due to sitting; increasing age; laparoscopic surgery; obesity; antepartum period; varicose veins

venous thromboembolism is inappropriate thrombus formation, then the risk factors would be expected to promote a prothrombotic or hypercoagulable state, as indeed many do.¹⁰ Virchow's triad refers to three abnormalities—abnormal blood constituents, abnormal vessel wall, and abnormal flow—that promote thrombogenesis (thrombus formation). Many predisposing factors alter one or more components of this triad.

Idiopathic venous thromboemboli on presentation often reveal occult cancers at follow-up, such as those of the blood, kidney, ovary, pancreas, stomach, and lung.^{11 12} The risk of venous thromboembolism is also increased by conditions collectively described as thrombophilia, including activated protein C resistance, factor V Leiden, protein C deficiency, protein S deficiency, antithrombin deficiency, and the prothrombin gene mutation 2021A. To these can also be added increased levels of plasma factor VIII, fibrinogen, factor IX, factor XI, prothrombin, hyperhomocysteinaemia, lupus anticoagulant, and antiphospholipid antibodies.^{13 14} Furthermore, risk factors interact. The risk of venous thromboembolism in users of the oral contraceptive pill or hormone replacement therapy is compounded in the presence of factor V Leiden.^{15 16}

Prevention and treatment of venous thromboembolism

To optimise treatment, patients with venous thromboembolism should be stratified into risk categories to allow the most appropriate prophylactic measure to be used (for example, for surgery; box 2). Thus the clinician must choose a pharmacological regimen (unfractionated heparin, low molecular weight heparin, warfarin),^{17–19} and also its duration. Predictably, in the short term, this may be for only as long as the particular (transient) risk factor is present, which may vary from three to six months. Risks of haemorrhage preclude indiscriminate long term use.

Box 2 Risk stratification of thromboemboli for patients undergoing surgery

Low risk

Uncomplicated surgery in patients aged less than 40 years with minimal immobility postoperatively and no risk factors

Moderate risk

Any surgery in patients aged 40–60 years; major surgery in patients aged less than 40 years and no other risk factors; minor surgery in patients with one or more risk factors

High risk

Major surgery in patients aged more than 60 years; major surgery in patients aged 40–60 years with one or more risk factors

Very high risk

Major surgery in patients aged more than 40 years with previous venous thromboembolism, cancer, or known hypercoagulable state; major orthopaedic surgery; elective neurosurgery; multiple trauma or acute spinal cord injury

Fig 2 Clinical approach to the diagnosis of pulmonary embolism. Adapted from Lee et al²

Idiopathic venous thromboembolism is generally treated for six months, but for those with continuing risk (for example, cancer, immobility, multiple risk factors), anticoagulation may be for life. Many reviews, guidelines, and meta-analyses for thromboprophylaxis in high risk groups are available (box 3).^{18–21} A UK National Institute for Health and Clinical Excellence clinical guideline (www.nice.org.uk) on the prevention of venous thromboembolism in patients undergoing orthopaedic surgery and other high risk surgical procedures is due to be published by May 2007. The Scottish Intercollegiate Guidelines Network (SIGN) published their guideline on prophylaxis against venous thromboembolism in 2002 and is awaiting an update (www.sign.ac.uk).

As the pathophysiology of pulmonary embolism and deep vein thrombosis is common they are treated using broadly similar pharmacological methods and protocols. In patients presenting with symptomatic deep vein thrombosis, 50–80% have asymptomatic pulmonary embolism, whereas 80% of patients presenting with pulmonary embolism will also have an asymptomatic deep vein thrombosis.¹⁷ The well known treatment with unfractionated heparin, often in combination with warfarin, is slowly giving way to more effective and safe compounds.

Low molecular weight heparin

The use of low molecular weight heparin in deep vein thrombosis and pulmonary embolism is now firmly established. Many trials and meta-analyses have confirmed their superior efficacy, safer profile, and cost

Box 3 Advantages of low molecular weight heparin over unfractionated heparin

- More reliable dose-response relation
- No need for laboratory monitoring with the activated partial thromboplastin time (although can be monitored with anti-Xa activity)
- No need for dose adjustments
- Lower incidence of thrombocytopenia
- No excess bleeding
- Can be administered by the patient at home
- Economically advantageous

effectiveness over unfractionated heparin. This is partly due to more targeted action: unfractionated heparin acts on both thrombin and factor Xa about equally, whereas low molecular weight heparin is more active against factor Xa. The low molecular weight heparins are, however, different, and trials for one cannot be extrapolated to another. The introduction of low molecular weight heparin has advanced antithrombotic therapy by providing effective anticoagulation without the need for routine monitoring or adjustments, although it can be monitored through an anti-Xa effect. It also allows patients with uncomplicated deep vein thrombosis to be treated in the community, thus saving an average of 4 or 5 days of admission per patient. Low molecular weight heparin has been shown to be more effective than vitamin K antagonists (almost all being warfarin) in preventing deep vein thrombosis after major orthopaedic surgery, with no significant difference in rates of bleeding.²²

Vitamin K antagonists

Traditionally, oral anticoagulants (warfarin being the most widely used) have been the treatment of choice for long term prophylaxis of venous thromboembolism. However, the inappropriate length of time required for the therapeutic international normalised ratio to be stable between 2 and 3 demands immediate thromboprophylaxis, as can be provided by heparin.^{18 19} Once patients are discharged, oral anticoagulation should be maintained for at least three months although longer duration therapy (for example, six months) is necessary in some circumstances. Patients without a readily identifiable risk factor (idiopathic venous thromboembolism) have higher rates of recurrences that can be reduced by prolonged anticoagulation, but this must be balanced against a corresponding increase in bleeding complications. Current recommendations therefore advocate anticoagulation for at least six months for the first presentation of idiopathic venous thromboembolism. Patients with recurrent venous thromboembolism and hypercoagulable states (acquired or inherited) and cancer, should remain receiving anticoagulation therapy for a minimum of one year and perhaps indefinitely.¹⁸

Fondaparinux

Fondaparinux is a precisely engineered pentasaccharide, which binds antithrombin and enhances its activity towards factor Xa but is devoid of activity against thrombin. This brings several advantages, such as a more predictable profile, a long half life (17 hours), and

no activity towards platelets. It is at least as effective as unfractionated heparin in treating pulmonary embolism,^{3 23} at least as effective as a low molecular weight heparin in treating deep vein thrombosis,²⁴ with a benefit over a low molecular weight heparin in risk reduction of venous thromboembolism after orthopaedic surgery.²⁵ In one UK health economics study, fondaparinux was more effective and reduced costs to the healthcare system when compared with a low molecular weight heparin.²⁶ An example of recommended uses of this and other agents in a defined group (mostly after surgery) is shown on bmj.com, although others recommend a different approach in medical patients.²⁷

Thrombolytic therapy

Unlike heparins and warfarin, which prevent extension and recurrence of thrombosis, the thrombolytic agents (for example, streptokinase, urokinase and tissue-plasminogen activator) lyse the thrombi. Indications for this therapy are, however, unclear. Recent guidelines¹⁸ do not recommend thrombolysis or thrombectomy for deep vein thrombosis unless for limb salvage. Similarly, in acute pulmonary embolism these treatments are reserved for the most serious and unstable cases, where there is haemodynamic instability.³ Thrombolytic therapy infusion into the pulmonary artery (after clot disruption using a pigtail catheter manipulated within the pulmonary artery) has been reported.²⁸

Non-drug treatments

Compression stockings and pneumatic compression have been used as prophylactic measures against deep vein thrombosis. Inferior vena cava filters may be used when anticoagulation is contraindicated in patients at high risk of proximal deep vein thrombosis extension or embolisation. The filter is normally inserted through the internal jugular or femoral vein. This approach should be considered in those patients with recurrent symptomatic pulmonary embolism and as primary prophylaxis of thromboembolism in patients at high risk of bleeding. Other mechanical and surgical treatments (for example, embolectomy) are usually reserved for massive pulmonary embolism where drug treatments have failed or are contraindicated.

The future

Since thrombosis is often the final common pathway in cardiovascular disease, cancer, and connective tissue disease, it is not surprising that considerable interest

Venous thromboembolism: first steps

When faced with a patient with suspected or actual venous thromboembolism, relevant sequential steps are to:

1. Confirm diagnosis of deep vein thrombosis or pulmonary embolism
2. Use established and formal guidelines to consider risk stratification
3. Decide on treatment (warfarin or low molecular weight heparin, or both)
4. Decide on treatment duration
5. Consider self management or referral to specialist centre

Additional educational resources

Useful website

Center for Outcomes Research (www.dvt.org)—useful information for professionals, with links to other sites and access to some research papers

Information for patients

Investigators against thromboembolism

(www.inate.org)—useful website for professionals and patients, with links to other sites

www.heartonline.com—useful website for professionals and patients, with information on cardiovascular disease and its risk factors and links to other sites

has been shown in the development of new antithrombotic agents, as shown by the progress from unfractionated heparin to the low molecular weight heparins and thence, fondaparinux and similar agents. Although aspirin and clopidogrel have their place, particularly in arterial thrombosis, development of new anticoagulants focuses on targeting the coagulation pathway—for example, thrombin and factor Xa. As a class, the direct thrombin inhibitors (hirudin, ximelagatran, dabigatran) are beginning to find their place in situations where heparin use is limited, and some may eventually replace warfarin.²⁹ Like fondaparinux, idraparinux is a heparinoid pentasaccharide, but the long half-life of the latter (80 hours) means it may be given once weekly.²⁹

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So, those who can't do it, teach it?

It has been said that "He who can, does. He who cannot, teaches." I have often wondered whether there is any truth behind this frequently quoted expression, which surgical students hear from the early days of their clinical training. To find the answer, one must look at the origin of the phrase itself—back to the Irish playwright George Bernard Shaw (1903). Shaw, however, was referring to revolutionaries, not teachers. The phrase is, therefore, used out of context.

Most of us, looking back over our training, can attribute our choice of specialty to one or more mentors—teachers so enthusiastic and inspirational that they instilled within us the desire to better ourselves and thereby better serve our patients. They taught us to think for ourselves. Most of us will also admit that these inspiring individuals were not just devoted teachers but

had notably inquiring minds and were almost always exceptional clinicians.

Charles H Mayo (1865-1939), one of the founders of the internationally renowned Mayo Clinic, once said: "The safest thing for a patient is to be in the hands of a man involved in teaching medicine. In order to be a teacher of medicine the doctor must always be a student." Therefore, the next time you hear Shaw quoted out of context, perhaps you might respond by quoting Mayo, a man described not only as an inspirational teacher but also as a "surgical wonder."

Perhaps those who don't teach it can't do it as well as they think.

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