CLINICAL REVIEW

Diagnosis and management of pulmonary embolism

S Takach Lapner *research fellow and haematologist*, C Kearon *professor of medicine*

Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Pulmonary embolism is one manifestation of venous thromboembolism, the other being deep vein thrombosis. Pulmonary embolism occurs when a deep vein thrombosis breaks free, passes through the right side of the heart, and lodges in the pulmonary arteries. About 90% of pulmonary emboli come from the legs, with most involving the proximal (popliteal or more central) veins. Prevention of pulmonary embolism therefore requires both prevention of venous thromboembolism and effective treatment of deep vein thrombosis when it occurs. There is a wealth of high quality individual studies and meta-analyses to guide the diagnosis and treatment of pulmonary embolism, and we provide an overview and synthesis of that evidence in this review.

Why is pulmonary embolism important?

Symptomatic venous thromboembolism occurs in 1–2 per 1000 adults each year, with about a third presenting with pulmonary embolism.[1 2] Pulmonary embolism is the most common cause of vascular death after myocardial infarction and stroke, and the leading preventable cause of death in hospital patients.[2] About 10% or more of cases of symptomatic pulmonary embolism are thought to be rapidly fatal, and another 5% of patients die after starting treatment. About a third of patients are left with some residual symptoms, and 2% develop thromboembolic pulmonary hypertension due to unresolved pulmonary embolism.[3]

Who is at risk?

Presentation of venous thromboembolism as pulmonary embolism rather than deep vein thrombosis is more common in elderly people and in those with cardiorespiratory disease, and less common in those with factor V Leiden. Three quarters of venous thromboembolisms are first events, while a quarter are recurrences, mainly after stopping treatment. Incidence doubles with each decade of age, and is about one per 1000 at 60 years. First episodes of venous thromboembolism occur with similar frequency in men and women, except for an increase in younger women associated with oestrogen therapy. Compared with white people, the incidence of venous thromboembolism is about 20% higher with African ethnicity and 33% lower with Asian ethnicity.

Virchow identified hypercoagulability, vessel wall injury, and stasis as the pathogenic triad for thrombosis (box 1). About 25% of patients with venous thromboembolism have no apparent provoking risk factor ("unprovoked" or "idiopathic" venous thromboembolism), 50% have a temporary provoking risk factor such as recent surgery or oestrogen therapy, and 25% have cancer.[1 2] Half of venous thromboembolism episodes are associated with hospitalisation, and about half of these are in surgical patients and half occur after hospital discharge. Therefore, preventive measures in hospitalised patients who are at high risk have the potential to markedly reduce pulmonary embolism.

How does pulmonary embolism present?

The symptoms and signs are non-specific and vary with the extent of pulmonary embolism and underlying cardiopulmonary impairment. Extensive pulmonary embolism may present with syncope, due to acute lowering of cardiac output, and patients may be found to have hypotension, evidence of poor perfusion (such as confusion), and elevated jugular venous pressure. Breathlessness occurs in most patients. Pleuritic chest pain is caused by pulmonary infarction, which occurs more often with non-massive pulmonary embolism and may be associated with haemoptysis. Although symptoms are usually present for days or weeks, they may be longstanding. Less than a quarter of patients have symptoms or signs of deep vein thrombosis, even though deep vein thrombosis is present in most patients with pulmonary embolism. Unexplained tachycardia, tachypnoea, or low arterial oxygen saturation may also suggest pulmonary embolism

With the widespread use of computed tomography, particularly for the assessment of cancer progression, diagnosis of incidental pulmonary embolism has become increasingly common. Incidental pulmonary embolism was reported in 2.6% of thoracic scans in one meta-analysis, with higher prevalence among hospitalised and cancer patients.[4] In retrospect, many of these patients had symptoms such as fatigue or breathlessness.

How is pulmonary embolism diagnosed?

Before describing the specific test results, or combinations of test results, that "rule in" and "rule out" pulmonary embolism,

Correspondence to: C Kearon, Hamilton Health Sciences, Juravinski Hospital Division, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada kearonc@mcmaster.ca

Summary points

Assessment of clinical pre-test probability (CPTP) is the first step in the diagnosis of pulmonary embolism

Combinations of CPTP and test results are usually needed to identify patients who require, and do not require, anticoagulant therapy

Thrombolytic therapy is usually reserved for patients with hypotension and without major risk factors for bleeding

Pulmonary embolism associated with a reversible risk factor is usually treated for three months

Pulmonary embolism associated with active cancer, or a second unprovoked pulmonary embolism, is usually treated indefinitely

The decision to treat an unprovoked pulmonary embolism for three months or indefinitely is sensitive to an individual patient's preference and risk of bleeding

Sources and selection criteria

We searched Medline and the Cochrane Collaboration for up to date systematic reviews, meta-analyses, and high quality randomised controlled trials pertaining to the epidemiology, diagnosis, and treatment of pulmonary embolism. We also drew on the recently published guidelines on diagnosis and treatment of pulmonary embolism from the National Institute for Health and Clinical Excellence (NICE) and on treatment for venous thromboembolism from the American College of Chest Physicians.

Box 1: Risk factors for pulmonary embolism*

Major risk factors

Intrinsic factors

- Previous venous thromboembolism
- Age >70 years

Acquired factors

- Malignancy
- Cancer chemotherapy
- Paralysis
- Major or lower limb trauma
- Lower limb orthopaedic surgery
- General anaesthesia for >30 minutes
- Heparin induced thrombocytopenia
- Antiphospholipid antibodies

Minor risk factors

Intrinsic factors

- Inherited hypercoagulable state

Acquired factors

- Obesity
- Pregnancy or puerperium
- Oestrogen therapy
- Prolonged immobility

*Combinations of factors have at least an additive effect on the risk of venous thromboembolism

we will first quantify the level of diagnostic certainty that is required for each of these goals. The primary goal of diagnostic testing for pulmonary embolism is to identify patients who would benefit from treatment. We suggest that a pulmonary embolism probability of ≥85% is the threshold that "rules in" pulmonary embolism and justifies anticoagulant therapy; this corresponds to a moderate or high clinical suspicion for pulmonary embolism and a "high probability" ventilation-perfusion lung scan.[5] Conversely, the threshold that "rules out" pulmonary embolism and justifies withholding anticoagulant therapy is a ≤2% probability of progressive venous thromboembolism in the next three months.[5][6] We emphasise that the threshold for withholding anticoagulant therapy focuses on the risk of continuing or progressive symptoms from pulmonary embolism, or of a new episode of venous thromboembolism (that is, progressive thrombosis) during follow-up, rather than the probability that pulmonary embolism is present and has been missed; it is acceptable not to treat a patient with test results possibly associated with pulmonary embolism provided we are confident, based on the findings of

previous prospective studies, that patients with those test results have a very low risk for progressive venous thromboembolism. If the probability of pulmonary embolism lies between these two thresholds the patient requires further testing. If, despite further testing, findings remain non-diagnostic, the options are to (*a*) withhold treatment while performing serial ultrasound imaging of the proximal deep veins of the leg over a two week period and to treat only if deep vein thrombosis is detected (usually the preferred option),[5] or (*b*) treat despite a pulmonary embolism probability of <85% (less preferable).

Clinical pre-test probability

Diagnosis of pulmonary embolism starts with an assessment of clinical pre-test probability. This is based on assessment of whether symptoms and signs are typical for pulmonary embolism, if there are risk factors for pulmonary embolism, if pulmonary embolism is thought to be the most likely diagnosis, and if there is evidence of deep vein thrombosis. CPTP assessment is facilitated by use of a clinical prediction rule, of

which the Wells score (table 1⇓) is most widely used and extensively validated.[7 9] Although CPTP alone cannot diagnose pulmonary embolism, and generally does not exclude pulmonary embolism, it guides the selection of diagnostic tests (for example, a confirmatory test with high CPTP, an exclusionary test with low CPTP) and may be diagnostic in combination with these test results (box 2).[5 10] Every patient for whom pulmonary embolism is initially considered does not need to be tested for pulmonary embolism; a convincing alternative diagnosis may subsequently be found.

D-dimer testing

D-dimer is formed when cross linked fibrin is broken down by plasmin. Levels are almost always increased in venous thromboembolism, and consequently a normal D-dimer level helps to rule out pulmonary embolism (that is, it has a high negative predictive value).[7 11] However, because D-dimer levels are commonly increased by other conditions, an abnormal result has low positive predictive value for pulmonary embolism. D-dimer tests vary in terms of the measurement method and the D-dimer level that is used to categorise a test as positive or negative; consequently, negative predictive value differs among D-dimer tests, and this influences how a negative D-dimer result is used to rule out pulmonary embolism in combination with CPTP or other test results. D-dimer tests can be divided into those that are highly, or only moderately, sensitive for venous thromboembolism.

Highly sensitive tests have sensitivity ≥95%, but specificity is only about 40% in outpatients (lower in inpatients, see below). A negative highly sensitive test has very high negative predictive value and therefore rules out pulmonary embolism in patients with low or moderate CPTP (box 2); however, a negative test is obtained in only about 30% of outpatients because of the low specificity.

Moderately sensitive tests have a sensitivity of 80–94%, and a specificity of up to 70% in outpatients. A negative test has lower negative predictive value than a very sensitive D-dimer test and therefore rules out pulmonary embolism only in patients with low CPTP (box 2); however, most outpatients with low CPTP who do not have pulmonary embolism have a negative test, which increases the value of testing.

Specificity of D-dimer testing decreases with age, pregnancy, inflammatory conditions, cancer, trauma, and recent surgery. If it is very probable that a patient will have a positive D-dimer test in the absence of pulmonary embolism, such as after major surgery, D-dimer testing should not be performed. It is also of limited value in patients with high CPTP because about half will have a positive test due to pulmonary embolism and, if a negative test is obtained, its negative predictive value is reduced by the high prevalence of disease. D-dimer testing should not be ordered to "screen out" pulmonary embolism in patients who have yet to be evaluated clinically because the high frequency of false positive results will increase, rather than decrease, the need for additional testing.

Computed tomographic pulmonary angiography

Computed tomographic (CT) pulmonary angiography, which outlines thrombi in the pulmonary arteries with intravenous contrast medium, has become the primary diagnostic test for pulmonary embolism. Its positive predictive value varies with the extent of pulmonary embolism and CPTP: the positive predictive value is (*a*) 97% with main or lobar, 68% with segmental, but only 25% with isolated subsegmental pulmonary

artery abnormalities, and (*b*) 96% with high CPTP, 92% with moderate CPTP, but only 58% with low CPTP (box 2).[12] Management studies have established that it is safe to withhold anticoagulant therapy in patients with a good quality negative CT pulmonary angiogram, with only about 1% of such patients returning with progressive venous thromboembolism during three months of follow-up (box 2).[13 14]

Isolated subsegmental abnormalities, which are reported in 10–20% of CT pulmonary angiograms, may be due to pulmonary embolism that is causing symptoms or incidental pulmonary embolism that is not responsible for the patient's symptoms (such as after knee replacement surgery[15]), or may be false positive findings. Consequently, it is uncertain if patients with these findings should be treated (box 2).[16] We treat patients with isolated subsegmental abnormalities if there is persuasive evidence for pulmonary embolism (clear, usually multiple, defects on CT pulmonary angiography; moderate or high CPTP) and the risk of bleeding is not high,[17] and we conduct serial ultrasound scans of the deep veins of the legs over two weeks in those who we do not treat, similar to how we manage patients with non-diagnostic ventilation-perfusion scans (see below). Less than 10% of CT pulmonary angiograms are technically inadequate.

CT pulmonary angiography can lead to contrast induced nephropathy and is associated with substantial radiation exposure. Its use should therefore be minimised, particularly in women under the age of 40 because of the associated increased risk of breast cancer.

Ventilation-perfusion lung scanning

Ventilation-perfusion lung scanning has largely been supplanted by CT pulmonary angiography. A "high probability scan," in which there is ≥1.5 segmental perfusion defects with normal ventilation ("ventilation-perfusion mismatch"), is associated with a prevalence of pulmonary embolism of ≥85% and is seen in about half of patients with pulmonary embolism (box 2).[5 18] A normal perfusion scan rules out pulmonary embolism, but is found in only 25% of patients. More than half of patients, therefore, have a non-diagnostic scan and require further testing. CT pulmonary angiography can then be performed, but ventilation-perfusion scanning is often done when CT pulmonary angiography is contraindicated (for example, with renal insufficiency). Consequently, it is usually preferable to do venous ultrasound scans of the proximal deep veins of both legs on the day of presentation and twice during the next two weeks, and to treat patients only if deep vein thrombosis is detected. The specificity of ventilation-perfusion scanning is lower if there is respiratory disease, and higher in younger patients.

Diagnosis of pulmonary embolism in pregnancy

Diagnosis of pulmonary embolism is similar in pregnant and non-pregnant patients, although there are some differences, and many diagnostic strategies have not been well validated in pregnant women.[19] Although the specificity of D-dimer testing decreases in later pregnancy, it is expected to retain most of its negative predictive value. Ultrasound scans of the leg veins, particularly if there are leg symptoms, may identify deep vein thrombosis. Ventilation-perfusion scanning with a lower radiation dose and longer imaging period for the perfusion component, or CT pulmonary angiography modified for physiological changes in pregnancy, can be used. Ventilation-perfusion scanning is probably associated with higher fetal radiation that CT pulmonary angiography, but this

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Box 2: Test results that confirm or exclude pulmonary embolism (adapted from Kearon[5])

Diagnostic for pulmonary embolism (≥85% probability of pulmonary embolism)

- Computed tomography (CT) pulmonary angiogram:
  Intraluminal filling defect in a lobar or main pulmonary artery

  Intraluminal filling defect in a segmental pulmonary artery *and* moderate or high CPTP

- Ventilation-perfusion scan: High probability scan* *and* moderate or high CPTP

- Positive diagnostic test for deep vein thrombosis (with a non-diagnostic ventilation-perfusion scan or CT pulmonary angiogram)

Excludes pulmonary embolism (≤2% probability of progressive venous thromboembolism during 3 months' follow-up†)

- CT pulmonary angiogram: Normal

- Perfusion scan: Normal

- D-dimer test:
  Negative test which has high sensitivity (>95%) *and* low or moderate CPTP

  Negative test which has moderately high sensitivity (>85%) *and* low CPTP

- Non-diagnostic ventilation-perfusion scan or suboptimal CT pulmonary angiogram *and* normal venous ultrasound of the proximal veins *and*
  Low CPTP *or*

  Negative D-dimer test which has moderately high sensitivity (≥85%) *or*

  Normal repeat venous ultrasound scans of the proximal veins after 7 and 14 days

CPTP=clinical pre-test probability.
*Presence of two large (each ≥0.75 segments) perfusion defects with normal ventilation.
†Patients should be told there is still a small chance that pulmonary embolism is present and instructed to return for further evaluation if symptoms persist or deteriorate.

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is still below the level considered harmful. CT pulmonary angiography is associated with much higher maternal radiation. Non-diagnostic ventilation-perfusion scans are also much less common during pregnancy (young patients without comorbidity) than in the general population. For these reasons, if imaging is necessary, we usually prefer ventilation-perfusion scanning to CT pulmonary angiography in pregnant patients, and prefer to do serial ultrasound testing rather than CT pulmonary angiography in patients with non-diagnostic ventilation-perfusion scans. CT pulmonary angiography is preferred to ventilation-perfusion scanning in sicker patients and particularly if there is haemodynamic instability or if the results of chest radiography suggest that a ventilation-perfusion scan is likely to be non-diagnostic. Isolated iliac deep vein thrombosis is more common in pregnant patients, which, if the iliac veins are not part of the initial and follow-up examinations, may undermine the role of serial venous ultrasonography.

How is pulmonary embolism treated?

Anticoagulant therapy before diagnostic testing

This decision depends on the probability that pulmonary embolism is present, how soon diagnostic testing can be performed, how sick the patient is, and the patient's risk of bleeding. A pragmatic approach is to start anticoagulant therapy if (*a*) CPTP is high, (*b*) CPTP is moderate and testing will not be completed within four hours, or (*c*) CPTP is low and testing will be delayed for over 24 hours.[17]

Treating patients with incidental pulmonary embolism

Incidental pulmonary embolism, detected on a CT scan that has been done for another reason, is often reported after an outpatient has left the hospital. If it would be difficult for patients to return the same evening, it is usually reasonable to defer further evaluation and treatment until the next day because, if pulmonary embolism is confirmed, it has usually been present for some time.[17] The decision whether to treat long term will be influenced by the certainty that pulmonary embolism is present (addition diagnostic testing, such as dedicated CT pulmonary

angiography, may be required), whether the abnormality has gone unnoticed on previous CT scans, and the patient's risk of bleeding. However, because incidental pulmonary embolism seems to carry a similar risk of recurrence and poor long term prognosis as symptomatic pulmonary embolism, we treat most the same way as symptomatic episodes.

When are thrombolytic therapy and mechanical thrombus removal used?

Active removal of thrombus is mostly reserved for the roughly 5% of patients with pulmonary embolism who have hypotension (systolic blood pressure <90 mm Hg; usually with other features of shock).[3 17] Systemic thrombolytic therapy is most commonly used, often as 100 mg of tissue plasminogen activator given as a two hour infusion.[17] Alternatively, if expertise is available, thrombus removal may be achieved by infusion of lower doses of thrombolytic drug directly into the thrombus, by catheter based fragmentation and aspiration of thrombus, by use of these two modalities together, or by surgical embolectomy.[3 17 20] These techniques may be preferred if there is a high risk of bleeding,[17] a poor response to systemic thrombolysis, or concern that the patient will die before systemic thrombolytic therapy has a chance to work.[17] Surgical embolectomy is indicated if there is impending paradoxical embolism, with thrombus present in a septal defect.

While there is strong evidence from randomised trials that systemic thrombolysis accelerates resolution of pulmonary embolism, its ability to save lives or reduce long term cardiopulmonary impairment remains uncertain.[21] Fewer than 800 patients have been included in trials that have randomised patients with acute pulmonary embolism to receive or not receive thrombolytic therapy, and these trials were usually not designed to assess clinical outcomes, did not follow up patients to assess long term disability, and had other important methodological limitations that undermine confidence in their findings.[8 21] Systemic thrombolytic therapy, however, is known to markedly increase risk of bleeding, and particularly intracranial bleeds.

Use of thrombus removal interventions in patients with pulmonary embolism and hypotension is based on the

expectation that these patients, who otherwise are expected to have a mortality of up to 30%, will derive net benefit.[3 17] Right ventricular dysfunction on echocardiography and elevated biomarkers of right ventricular injury are predictive of short term mortality from pulmonary embolism; two ongoing large trials are testing if, in the absence of hypotension, patients with these findings benefit from systemic thrombolytic therapy (NCT00639743; NCT00680628).

Anticoagulant therapy

Anticoagulant therapy can be divided into two overlapping phases.[17 22] The first is treatment of the presenting episode of pulmonary embolism, which takes about three months. The second, which is optional, is extended therapy designed to prevent new episodes of venous thromboembolism.

Standard initial therapy is with subcutaneous low molecular weight heparin, fondaparinux, or unfractionated heparin, or intravenous unfractionated heparin.[17] There is no strong evidence that any one method is superior. Subcutaneous low molecular weight heparin and fondaparinux do not require intravenous infusion or laboratory monitoring, whereas intravenous unfractionated heparin is preferred if there is shock, severe renal impairment (low molecular weight heparin and fondaparinux are renally excreted), thrombolytic therapy is being considered, or it may be necessary to reverse anticoagulation rapidly. These treatments should be overlapped with a vitamin K antagonist (such as warfarin) and stopped after a minimum of five days provided the international normalised ratio (INR) has been above 2.0 for at least a day.

Alternatively, low molecular weight heparin can be continued long term, a treatment strategy that is generally preferred in patients with cancer associated pulmonary embolism because of superior efficacy of low molecular weight heparin, difficulty in controlling vitamin K antagonist therapy, and greater compatibility of low molecular weight heparin with chemotherapy and the need for invasive procedures.[17 23] Long term low molecular weight heparin is also used to treat venous thromboembolism during pregnancy because vitamin K antagonists are teratogenic. Observational studies and a recent randomised trial have shown that, with appropriate selection (less acutely ill, good social supports, patient preference), about half of outpatients with acute pulmonary embolism can be treated at home.[24 25]

The new oral anticoagulants rivaroxaban and dabigatran (apixaban is at an earlier stage of assessment in the treatment of venous thromboembolism) are as effective as conventional anticoagulant therapy, do not require laboratory monitoring, and are associated with a lower risk of intracranial bleeding but a higher risk of gastrointestinal bleeding.[17 26-30] Dabigatran is preceded by heparin therapy, whereas rivaroxaban does not require initial heparin therapy but requires a higher dose for the first three weeks of treatment. Both are contraindicated if there is severe renal impairment and are contraindicated or must be used cautiously with some drugs, and there is little experience of using them to treat venous thromboembolism in patients with advanced cancer or receiving cancer chemotherapy. The decision to use one of these drugs for the acute or long term treatment of venous thromboembolism is also influenced by local availability and licensing, whether their cost is covered by state or private insurance plans, and patient and physician satisfaction with current therapy. Because they are emerging therapies, these factors differ among jurisdictions and are rapidly changing.

How long should anticoagulant therapy be continued?

When the presenting episode of pulmonary embolism has been effectively treated, there is the option of continuing anticoagulants indefinitely to prevent new episodes of venous thromboembolism. Extended therapy reduces the risk of recurrent venous thromboembolism by over 90% but increases the risk of bleeding twofold to threefold.[17] If anticoagulant treatments are extended and then stopped the risk of recurrent venous thromboembolism is similar to that if they had been stopped at three months, with the highest risk occurring in the first six months after stopping.[22 31] The risk of recurrent venous thromboembolism is similar after a pulmonary embolism or a proximal deep vein thrombosis, but the recurrent episode is about three times as likely to be a pulmonary embolism after an initial pulmonary embolism, so is more likely to be fatal.[32] The decision to treat indefinitely therefore depends on balancing the increased risk of recurrence with stopping therapy against the increased risk of bleeding with continued therapy, while also considering patient preference and associated costs.

Most patients with active cancer or a second unprovoked venous thromboembolism should receive extended therapy because of a high risk of recurrence (table 2⇓).[17] Most patients with pulmonary embolism associated with a reversible provoking risk factor, such as surgery or oestrogen therapy, should stop treatment after three months because of the low risk of recurrence.[17 31] In patients with a first unprovoked pulmonary embolism, who are estimated to have a risk of recurrence of 10% at one year and 30% at five years if they stop treatment, the decision whether to extend treatment is sensitive to patients' preferences and their individual risk of bleeding.[17] There is a lower risk of recurrence in women than in men, and in those who have a normal D-dimer level a month after stopping therapy. Therefore, extended therapy may not be justified in women with a first unprovoked pulmonary embolism who have a negative D-dimer test a month after stopping anticoagulants.[33 34] Thrombophilia testing has little influence on the treatment of venous thromboembolism.[10 35]

Antiplatelet therapy

Results from two recent placebo controlled randomised trials support that aspirin reduces risk of recurrent venous thromboembolism by about a third in patients with a first unprovoked venous thromboembolism who have completed at least three months of anticoagulant therapy.[36] Therefore, if patients are not candidates for extended anticoagulant therapy, this reduction in recurrent venous thromboembolism can be included in the overall assessment of benefit to risk for indefinite aspirin therapy.

Inferior vena cava filters

Vena cava filters block emboli from reaching the lungs.[3 17 37] We limit use of filters to patients with acute proximal deep vein thrombosis or pulmonary embolism who cannot be given anticoagulants. Observational studies, however, suggest that filters may also benefit patients with pulmonary embolism and hypotension who do receive anticoagulants.[38 39] Removable filters can be used in patients with short term contraindications to anticoagulation, but only about 25% are removed and the long term safety of those that remain is uncertain.[17]

Future research questions

Should systemic thrombolytic therapy or other thrombus removal techniques be used to treat pulmonary embolism associated with right ventricular dysfunction?

Which patients with a first unprovoked pulmonary embolism should receive anticoagulant therapy for three months rather than indefinitely?

Do all patients with asymptomatic incidental pulmonary embolism require treatment?

Which patients with CT pulmonary angiography findings suggestive of isolated subsegmental pulmonary embolism should receive anticoagulant therapy?

Tips for non-specialists

Anticoagulant therapy should be started before diagnostic testing if there is high clinical suspicion for pulmonary embolism or if testing will be delayed

Pulmonary embolism is ruled out without further testing by low clinical suspicion for pulmonary embolism (such as Wells pulmonary embolism score ≤4) and a negative D-dimer test

D-dimer testing should not be performed if it is very probable that patients will have a positive result even if pulmonary embolism is not present (such as after major surgery)

Computed tomography (CT) pulmonary angiography is associated with substantial radiation so it should be used selectively, particularly in younger patients (<40 years old)

Anticoagulant therapy is not invariably indicated in patients who have an isolated subsegmental pulmonary embolism on CT pulmonary angiography or an incidental pulmonary embolism on a CT scan that was done for another reason

Low molecular weight heparin is often the preferred long term anticoagulant for patients with cancer

Additional educational resources

Resources for healthcare professionals

National Institute for Health and Clinical Excellence. Venous thromboembolic diseases (clinical guidelines CG144). http://guidance.nice.org.uk/CG144. (No registration required, free resource)

American College of Chest Physicians. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 suppl). http://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=23443. (Registration required, payment may be required)

Resources for patients (no registration required, free resources)

NHS Choices. Pulmonary embolism. http://www.nhs.uk/conditions/pulmonary-embolism/pages/introduction.aspx. (UK National Health Service patient resources)

US Department of Health and Human Services. Your guide to preventing and treating blood clots. www.ahrq.gov/consumer/bloodclots.pdf

Investigators Against Thromboembolism (INATE). About thrombosis. www.inate.org/en/1/2/

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Tables

Table 1| Clinical prediction rule—Wells model for pulmonary embolism

Variables	No of points	Proportion of patients	Prevalence of pulmonary embolism
Clinically suspected deep vein thrombosis	3		
Alternative diagnosis is less likely than pulmonary embolism	3		
Heart rate >100 beats/min	1.5		
Immobilisation or surgery in previous 4 weeks	1.5		
History of venous thromboembolism	1.5		
Haemoptysis	1		
Malignancy or treatment for it in previous 6 months	1		
Score interpretation			
High probability*	≥6.5	10%	60%
Moderate probability*	4.5–6.0	30%	25%
Low probability†	≤4.0	60%	5%

*A score of ≥4.5 (moderate and high probability groups combined) has been termed "pulmonary embolism likely." This group makes up about 40% of patients and has a prevalence of pulmonary embolism of about 33%.

†Has also been termed "pulmonary embolism unlikely." In the original derivation of the Wells pulmonary embolism model, patients were required to have a score of ≤1.5 to be categorised as low probability, but a score of ≤4 has subsequently been used for low probability.[7 8]

Table 2| **Duration of anticoagulant therapy for venous thromboembolism**

Category of VTE	Duration of treatment*
Provoked by a transient risk factor†	3 months
Unprovoked VTE‡	Minimum of 3 months and then reassess
First unprovoked proximal DVT or PE with no or minor risk factors for bleeding	Indefinite therapy with annual review§
Isolated distal DVT as a first unprovoked event	3 months
Second unprovoked VTE	Indefinite therapy with annual review¶
Cancer associated VTE	Indefinite treatment

VTE= venous thromboembolism. DVT=deep vein thrombosis. PE=pulmonary embolism.

*Treatment with a vitamin K antagonist (VKA) or low molecular weight heparin (LMWH) are currently considered first line therapy. VKA therapy is suggested in preference to LMWH in patients without cancer (avoids injection, less costly). LMWH is preferred in patients with cancer (more effective, dosing and reversal more flexible if there is severe thrombocytopenia or invasive procedures are required, VKA is difficult to control in sicker patients). The choice between VKA and LMWH is also sensitive to patient preference. New oral anticoagulants (such as rivaroxaban, dabigitran) are considered second line therapy as they are not yet widely available or approved for extended therapy of VTE, and there is limited post-marketing experience with these agents.[17]

†Transient risk factors include surgery, hospitalisation, or plaster cast immobilisation in the previous three months; oestrogen therapy, pregnancy, prolonged travel (>8 hours), lesser leg injuries, or more recent (≤6 weeks) immobilisations. The greater the provoking reversible risk factor (such as recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

‡Absence of a transient risk factor or active cancer.

§This decision is sensitive to patient preference.

¶Indefinite therapy is suggested if there is moderate risk of bleeding, and three months is suggested if there is a high risk of bleeding; both of these decisions are sensitive to patient preference.