BMJ Best Practice

Pulmonary embolism

The right clinical information, right where it's needed

Last updated: Nov 13, 2017

Table of Contents

Summary

- Pulmonary embolism (PE) is a life-threatening condition resulting from dislodged thrombi occluding the pulmonary vasculature; right heart failure and cardiac arrest may ensue if not aggressively treated.
- Virchow's triad of venous stasis, vessel wall damage, and hypercoagulability reflect the underlying pathophysiology.
- Symptoms include chest pain, dyspnoea, and a sense of apprehension. Syncope also sometimes occurs, and is strongly associated with increased clot burden.
- Definitive diagnostic modalities of exclusion/confirmation include D-dimer, multiple-detector computed tomographic pulmonary angiography (CTPA) scan of the chest, and ventilation-perfusion (V/Q) scan.
- Acute treatment includes thrombolysis, surgical embolectomy, venous filter placement, and/or anticoagulation.
- Long-term anticoagulation therapy is indicated to reduce the risk of recurrent events or fatal pulmonary embolism.

Definition

Pulmonary embolism (PE) is a consequence of thrombus formation in distal veins, most commonly those of the deep venous system of the lower extremities. Thrombus formation in the venous system occurs as a result of venous stasis, trauma, and hypercoagulability. These factors are collectively known as Virchow's triad.[1] Approximately 51% of deep venous thrombi will embolise to the pulmonary vasculature, resulting in a PE.[2] Venous thromboembolic disease is the preferred term to describe the spectrum of disease beginning with the risk factors of Virchow's triad, progressing to deep venous thrombosis, and resulting in life-threatening PE.

Epidemiology

PE is one of the most common cardiovascular diseases. In the UK, 47,594 cases were reported in the 1-year period between 2013 and 2014. [Hospital episode statistics, admitted patient care: England 2013-2014] The annual incidence of PE in Scandinavia has been estimated at between 1.6 and 1.8 cases per 1000 population.[6] In Australia, the crude annual incidence of PE is 0.31 per 1000, which is similar to the WHO age-adjusted incidence of 0.21 per 1000.[7]

PE is the third most common cardiovascular disease in the US.[8] In 1999, 140,000 individuals were discharged from hospital with a diagnosis of PE.[9] The incidence has been estimated at 1 case per 1000 people per year. This results in 200,000 to 300,000 hospitalisations per year, with a prevalence estimated at 1%.[5] [9] PE is the underlying cause of death in 10% to 34% of these cases.[9] [10] The incidence and direct mortality from PE increases with age.[11] The rate of diagnosis was similar among black and white people (not adjusted for age), although mortality was higher in black people compared with white people.[12] Mortality rates are 20% to 30% greater in males than in females irrespective of racial background.[9] Overall mortality ranges from 3.5% to 25% and can be as high as 31% to 58% when circulatory shock is present.[13] [14]

Aetiology

Virchow's triad (i.e., venous stasis, vessel wall damage, and hypercoagulability) is still the preferred aetiological model for DVT and PE.[1]

- Vessel wall damage: endothelial cell damage promotes thrombus formation, usually at the venous valves. Damage to the vessel wall can occur after a number of insults including trauma, previous DVT, surgery, venous harvest, and central venous catheterisation.[15]
- Venous stasis: poor blood flow and stasis promote the formation of thrombi. Venous stasis and congestion result in valvular damage, further promoting thrombus formation. Increased venous stasis is associated with age >40 years, immobility, general anaesthesia, paralysis, spinal cord injury, myocardial infarction, prior CVA, varicose veins, advanced CHF, and advanced COPD.
- Hypercoagulability: a number of other conditions (both inherited and acquired) increase the risk of PE. These include cancer, high-oestrogen states (obesity, pregnancy, and hormone replacement), inflammatory bowel disease, nephrotic syndrome, sepsis, blood transfusion, and inherited thrombophilia (factor V Leiden mutation, prothrombin gene mutation, protein C and S deficiency, antithrombin III deficiency, and antiphospholipid antibody syndrome).

Pathophysiology

Thrombi do not develop de novo in the pulmonary vasculature. Clots usually form in the deep venous system of the lower extremities and embolise. The pathophysiology is therefore directly related to that of DVT. DVT in the upper extremities is associated with a lower incidence of pulmonary embolism.[16] Endothelial damage appears to be less important in DVT than in arterial thrombosis.[17]

Unlike platelet-rich arterial thrombi, DVTs are composed mainly of fibrin and entrapped erythrocytes (red clots). Although platelet aggregation is seen, it is not seen at the site of thrombus attachment, suggesting that activation of the coagulation cascade precedes platelet activation.[17] [18]

PE occurs when a thrombus dislodges and becomes trapped in the pulmonary vasculature. This obstruction increases pulmonary vascular resistance (PVR), increasing the work of the right ventricle. The right ventricle compensates by increasing heart rate using the Frank-Starling preload reserve via dilation. Further increases in PVR overcome the right ventricular (RV) compensatory mechanisms, leading to over-distension of the right ventricle, increased RV end-diastolic pressure, and decreased RV cardiac output. Decreased RV output leads to decreased left ventricular (LV) preload. As left ventricle filling and cardiac output decrease, lowered mean arterial pressure progresses to hypotension and shock. In previously healthy individuals, this can occur when as little as 50% of the pulmonary vasculature is occluded.[19]

Primary prevention

Primary prevention is mainly targeted at DVT prophylaxis.

Many studies show that the incidence of venous thromboembolic event can be reduced in patients who undergo certain surgical procedures associated with postoperative thromboembolism. Regular perioperative unfractionated heparin (UFH) or low molecular weight heparin (LMWH) leads to a significant reduction in venous thromboembolic events.[41] Direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are also approved in some countries for prophylaxis of DVT and PE in surgical patients. Early mobilisation reduces risk following total hip replacement.[42] Use of elastic stockings is widespread, but the evidence is weak for preventing venous thromboembolic events when used in isolation.[43] Acutely ill medical patients have an increased risk of venous thromboembolism. Thromboprophylaxis has been demonstrated to be both safe and effective in these patients.[44] [45] [46] [47] There is no consensus for the duration of DVT prophylaxis on discharge for patients not meeting those recommendations for standard-duration prophylaxis. Further guidance should be developed.[48] [49]

There are few or no data about primary prevention of venous thromboembolic events in many other associated diseases where risk of developing the condition is elevated.[50]

Air travellers, regardless of risk, should keep well hydrated and exercise leg muscles frequently. Travellers on a flight of <6 hours, and those with no known risk factors regardless of the duration of the flight, do not warrant DVT prophylaxis. Those with one or more risk factors should consider graduated compression stockings and/or LMWH for flights longer than 6 hours.[51] Currently available evidence suggests that statins can reduce patients' odds of developing VTE.[52] There is no evidence that aspirin reduces the incidence of post-air travel events.

Studies do not support the use of anticoagulants for the prevention of central venous catheter (CVC)-associated thrombosis. Treatment of CVC-associated thrombosis relies on the same principles as those applied in the treatment of established thrombosis in cancer patients.[53]

Despite the addition of a few matched-control studies of prophylactic inferior vena cava filters, the literature is still plagued by a lack of high-quality data, and, therefore, the true efficacy of these filters for prevention of PE in trauma patients remains unclear.[54]

For women who fulfil the laboratory criteria for antiphospholipid antibody (APLA) syndrome and meet the clinical APLA criteria, based on a history of 3 or more pregnancy losses, antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin is recommended. For women with inherited thrombophilia and a history of pregnancy complications, it is suggested to not use antithrombotic prophylaxis. For women with 2 or more miscarriages, but without APLA or thrombophilia, antithrombotic prophylaxis is not recommended.[55] Ideally, these women should be referred to a doctor or clinic that specialises in recurrent pregnancy loss.

Secondary prevention

Secondary prevention with oral anticoagulant therapy is tailored to pre-existing comorbidities. If the patient is treated with warfarin, target INRs depend on the clinical situation.

- PE secondary to provoked, short-term cause: 3 months of anticoagulation with target INR 2.0 to 3.0.3[B]Evidence
- Unprovoked PE: at least 6 to 12 months of anticoagulation is recommended for most people with first event. Lifetime anticoagulation should be considered in low bleeding risk patients. If warfarin is chosen as the method of anticoagulation, it is recommended to titrate conventional doses with target INR 2.0 to 3.0.
- Initial PE with underlying malignancy: low molecular weight heparin (LMWH) for the first 3 to 6 months. After this time, the use of warfarin can be reconsidered and the chosen anticoagulant continued lifelong or until remission of the malignancy has been achieved. The decision between using LMWH

and warfarin should take into account the balance of benefits and risks, and integrate the patient's values and preferences.

- Initial PE with antiphospholipid antibody syndrome or two or more thrombophilic conditions: 12 or more months with consideration of lifelong warfarin with target INR 2.0 to 3.0. High-intensity therapy (INR 3.0 to 4.0) is not recommended for patients with antiphospholipid antibody syndrome.
- Initial PE with one inherited thrombophilic disorder: at least 6 to 12 months of therapy with warfarin with goal INR 2.0 to 3.0 and consideration of lifelong therapy.
- Two or more episodes of PE regardless of underlying risk factors: lifelong therapy with warfarin with target INR 2.0 to 3.0.
- Among patients with an initial unprovoked VTE who received 6 to 18 months of oral anticoagulation therapy, the subsequent daily use of aspirin significantly reduced the rate of recurrent VTE compared with placebo, with no increase in the risk of major bleeding.[144]

If one of the direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) was started, it is continued and the patient is not transitioned to warfarin. Observational evidence and ad-hoc analysis from clinical trials suggest that these agents may be a safe and efficacious alternative for lifelong anticoagulation in patients with thrombophilia, recurrent venous thromboembolism, or cancer; however, there is still no robust prospective randomised clinical trial in these special populations. These drugs are approved for the prevention of PE after completion of treatment in many countries (note: treatment and prevention doses of apixaban differ).

Case history

Case history #1

A 65-year-old man presents to the emergency department with acute onset of SOB of 30 minutes' duration. Initially, he felt faint but did not lose consciousness. He is complaining of left-sided chest pain that worsens on deep inspiration. He has no history of cardiopulmonary disease. A week ago he underwent a total left hip replacement and, following discharge, was on bed rest for 3 days due to poorly controlled pain. He subsequently noticed swelling in his left calf, which is tender on examination. His current vital signs reveal a fever of 38.0°C (100.4°F), heart rate 112 bpm, BP 95/65 mmHg, and an O2 saturation on room air of 91%.

Other presentations

Symptoms that are predictive of PE include chest pain, dyspnoea, and a sense of apprehension. Syncope also sometimes occurs, and is strongly associated with increased clot burden. Important signs include tachypnoea with a respiratory rate >16 breaths per minute, fever >37.8°C (>100.0°F), and heart rate >100 bpm.[3]

Recently, there has been an increasing number of reports of incidental pulmonary embolism (PE) in patients undergoing chest computer tomography (CT) for reasons other than the research of suspected PE.[4] In one study, the diagnosis of PE was unsuspected in 70% of those who ultimately died from the condition. Early recognition is crucial as, among those who died of an unsuspected PE, death occurred within 1 hour in nearly 79% of patients and within 2.5 hours in 93% of patients.[5]

Step-by-step diagnostic approach

History and physical examination alone are rarely sufficient to confirm or rule out the condition. PE is unsuspected in the majority of people who ultimately die from the condition. A high index of suspicion and expeditious management are required as the highest risk of dying is within the first 2 hours of presentation. In one study, the diagnosis of PE was unsuspected in 70% of those who ultimately died from the condition, and among those who died, death occurred within 1 hour in nearly 79% of patients and within 2.5 hours in 93% of patients.[5] Confirmation of PE with a definitive test is important because treatment is associated with a significant risk of bleeding.

History

History usually reveals an acute onset of symptoms. Chest pain and dyspnoea are the most common presenting features. A sense of apprehension is often reported. Haemoptysis and pleuritic chest pain are thought to be more common with pulmonary infarction. Syncope is a less common symptom but suggests a larger clot burden and poorer prognosis.

Risk factors for DVT or PE should be determined. Family history of DVT or PE, or recurrent miscarriage, indicate an underlying inherited thrombophilia.[3] [9] Other strong risk factors include: increasing age; presence of DVT; surgery within the last 2 months; >5 days bed rest; previous venous thromboembolic event; active malignancy; recent trauma or fracture; pregnancy/postnatal period; paralysis of the lower

extremities; factor V Leiden or prothrombin gene mutation; antithrombin III, protein C, or protein S deficiency; and antiphospholipid antibody syndrome.

Physical examination

PE may be completely asymptomatic and be discovered incidentally during diagnostic work-up for another disease or at autopsy. Physical examination is often non-specific with respect to symptoms and signs, as shown in a multicentre, emergency medicine, pulmonary embolism registry.[56] Despite this, when the clinical presentation is suspicious for PE, it should prompt further objective testing to confirm the diagnosis.

In most patients, PE should be suspected based on the presence of dyspnoea, chest pain, presyncope or syncope, and/or haemoptysis.[56] [57] [58] Chest pain is a frequent symptom and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction.[59] In central PE (in which the thrombus is in the main, left, or right pulmonary artery) angina-like chest pain may be present, possibly due to right ventricle ischaemia. This presentation requires differentiation from acute coronary syndrome or aortic dissection. Syncope is infrequent, but may occur regardless of the presence of haemodynamic instability.[59] Other signs include fever, cough, or unilateral swelling/tenderness of a calf if a DVT is present.

Shock (e.g., hypotension, tachycardia, tachypnoea) is a rare, but important, clinical presentation as it indicates central PE and/or a severely reduced haemodynamic reserve. If the PE has caused a cor pulmonale, the patient may present with elevated jugular venous pressure, sternal heave, or accentuated pulmonary component of S2, although this is uncommon.

Clinical decision rules

The modified Wells' score,[60] and the revised Geneva score,[61] are used to assess the clinical probability of PE. Historical and physical examination features are assigned points, and the points are added together to determine whether PE is likely or unlikely. However, miscalculations can occur with these scores as they are based on multiple clinical variables each with different points assigned. Therefore, the scores have been simplified, and these simplified scores have been prospectively validated and have been found to perform similarly to the original scores in the exclusion of PE in combination with a D-dimer result.[62]

Either the original or simplified scores are acceptable to use, and choice depends on physician preference or location.

Wells' score	Original	Simplified
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1

The difference between the scores in the original modified Wells' score and the simplified version

Created by the BMJ Evidence Centre team

Geneva score	Original	Simplified
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Previous PE or DVT	3	1
Heart rate 75-94 bpm ≥95 bpm	3 5	1 2
Unilateral limb pain	3	1
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active cancer	2	1
Age >65 years	1	1
Clinical probability*		
PE unlikely	≤5	≤2
PE likely	>5	>2

* The revised Geneva score was formerly available as 3-category scheme (i.e., 0-3 = low probability of PE; 4-10 = intermediate probability of PE; and ≥11 = high probability of PE), but was recently made into the 2-category scheme shown above.

The difference between the scores in the original revised Geneva score and the simplified version

Created by the BMJ Evidence Centre team

Initial laboratory tests and imaging

Initial tests include CXR, ECG, and ABG; however, none of these tests can definitively establish or eliminate PE as a diagnosis and specific findings may only be suggestive of PE, so further testing is required.

Clinical decision rules and D-dimer

- Clinical decision rules (see above) to determine the clinical probability of PE improve the diagnostic work-up of patients with suspected PE.[62]
- Clinical probability using either the modified Wells' score or revised Geneva score (or their simplified versions) should be calculated,[60] [61] and a D-dimer (a biomarker of active fibrinolysis) level ordered if appropriate, followed by imaging.
- The Pulmonary Embolism Rule-Out Criteria (PERC) may be used in patients identified as very low risk. In patients who meet all of the criteria (age <50 years; initial heart rate <100 bpm; initial oxygen saturation >94% on room air; no unilateral leg swelling; no haemoptysis; no surgery or trauma within last 4 weeks; no history of VTE; no oestrogen use), the risk for PE is considered to be lower than the risk of testing, and so a D-dimer is not indicated. D-dimer should be done for patients who do not meet all of the criteria.[63]
- D-dimer by ELISA has a sensitivity and negative predictive value >95%, regardless of the calculated clinical probability, making it useful to rule out the presence of venous thromboembolism, particularly in patients with a low or intermediate clinical probability assessment.[64] [65]
- If the patient has a low risk for PE and the D-dimer is not elevated, PE is effectively ruled out without further testing. The risk of PE within 3 months is <1% in these patients.[66]
- If the patient has a high-risk clinical probability (i.e., PE likely) or has an abnormal D-dimer, multiple-detector computed tomographic pulmonary angiography (CTPA) scanning of the chest is the imaging study of choice.

Clinical probability score	D-dimer level	Action
PE unlikely	Normal	Diagnosis ruled out; no further testing required
	Abnormal	Imaging required
PE likely	Normal	Imaging required
	Abnormal	Imaging required

Summary of clinical action required based on clinical probability score and D-dimer level result

Created by the BMJ Evidence Centre team

Computed tomographic pulmonary angiography (CTPA)

- Imaging study of choice in patients with an abnormal D-dimer level or a high probability of PE.
- Diagnosis is confirmed by direct visualisation of thrombus in a pulmonary artery, where it appears as a partial or complete intraluminal filling defect.
  [Fig-4]
- The likelihood ratio to rule in a PE with a filling defect in the segmental or subsegmetal branches is 24.1 (range of 12.4-46.7), whereas the likelihood to rule it out is 0.11 (range of 0.06-0.19), which means that CTPA has the best diagnostic accuracy of all the advanced non-invasive imaging methods.[67]

Other imaging

- If there is a contraindication to a CT scan (e.g., contrast allergy, moderate to severe renal failure, or pregnancy), then a ventilation-perfusion (V/Q) scan, preferably using single photon emission computed tomography (SPECT), should be ordered.
- If a V/Q scan cannot be obtained, alternative tests such as magnetic resonance (MR) angiography, trans-oesophageal echocardiography, or digital subtraction angiography (DSA) can be requested.

Special patient populations

- Pregnant women: despite the low-quality evidence, expert opinion recommendations have been outlined to minimise the exposure to radiation usually associated with CTPA. These recommendations include: CXR as the first radiation-associated procedure; lung scintigraphy (which often includes a V/Q scan) as the preferred test in the setting of a normal CXR; CTPA rather than DSA if CXR is abnormal or V/Q scan is non-diagnostic.[68]
- Pre-existing cardiopulmonary disease: although diagnostic tests such as CTPA and V/Q scans can estimate the extent of pulmonary vascular obstruction, these estimates lack validity when pre-existing cardiopulmonary disease is present. In this population, smaller clot burden can result in right ventricular (RV) strain; therefore, direct imaging of the right ventricle is felt to have added prognostic value in these patients.
- Low PE severity indices: CTPA seems to increase the proportion of patients diagnosed with subsegmental PE without lowering the 3-month risk of thromboembolism, suggesting that subsegmental PE may not be clinically relevant.[69]
- Adolescents and young adults: CTPA should be used with discretion, especially if pulmonary embolism can be ruled out by other non-invasive methods with less radiation exposure.[70]

Other investigations

Transthoracic echo is a readily available, non-invasive method for evaluating RV function and pulmonary haemodynamics, particularly among patients with large clot burden or clinical features of haemodynamic compromise.

The definitive confirmatory test with the highest positive and negative pretest value is pulmonary angiography; however, it is now rarely used in clinical practice due to a high incidence of morbidity/mortality. Alternative imaging tests to confirm the diagnosis of PE by direct visualisation of a filling defect include gadolinium-contrast enhanced angiography (Gd-MRA), real time angiography (RT-MRA), and MR-perfusion images.[71]
[Fig-5]

Baseline laboratory tests including PT, aPTT, and INR are important to aid decisions about the safety and type of initial anticoagulation selected.

Thrombophilia screening is not indicated in all cases of incident venous thromboembolic events; however, it may be useful if the site of thrombus is unusual, if there is a large clot burden, or if there are recurrent events. Thrombophilia screening for certain conditions such as protein S, protein C, or antithrombin III deficiency should be repeated after 12 weeks as serum levels may be decreased in the hyperacute phase of thrombus formation or due to the use of anticoagulants such as heparin, low molecular weight heparin, or warfarin.

It should be noted that the interpretation of diagnostic techniques should be done according to clinical probability. Special additional studies should only be done when the clinical picture is not consistent with the diagnostic imaging.[72]

Prognostic stratification

Prognostic stratification may have significant clinical and therapeutic implications. The Pulmonary Embolism Severity Index (PESI), and other simplified versions such as the RIETE (Registro Informatizado de la Enfermedad TromboEmbolica venosa – Computerised registration of venous thromboembolism) score, are commonly used.[73] Patients in the high-risk category have a high short-term (i.e., 30 day) mortality of up to 15%, whereas patients with a low severity index have a short-term mortality of 1% or lower, making early discharge or outpatient treatment a cost-effective therapeutic option.

Very few clinical and laboratory tests have a strong prognosis value.[74] However, increasing evidence suggests that brain natriuretic peptide (BNP)[75] and troponin I and T have useful prognostic significance. High levels of BNP are correlated with RV strain detected on transthoracic echocardiography. Low levels are strongly predictive of uncomplicated hospital course. Age-adjusted D-dimer may have a role in excluding ongoing fibrinolysis as an indirect biomarker of ongoing thrombosis after discontinuation of anticoagulation therapy.

Risk factors

Strong

increasing age

- The incidence and direct mortality from PE increases with age.[11]
- Age-specific mortality rates double for every 10 years starting at age 25.[9]

diagnosis of DVT

- Present in 49% of patients with a diagnosed PE.[20]

surgery within the last 2 months

- Present in 29% confirmed with the condition.[20]

bed rest >5 days

- Present in 28% confirmed with the condition.[20]

previous venous thromboembolic event

- Present in 25% confirmed with the condition.[20]

family history of venous thromboembolism

- An increased incidence of venous thromboembolism (VTE) has been found in patients who have at least one sibling with a history of VTE. This risk increased more than 20-fold in patients with at least two affected siblings, making this one of the strongest risk factors identified for VTE.[21]

active malignancy

- Present in 22% confirmed with the condition.[20]
- Ovarian, uterine, prostate, and brain cancers are most commonly associated with death due to PE.[9]

recent trauma or fracture

- Present in 11% confirmed with the condition.[20]

pregnancy/postnatal period

- There is a 4- to10-fold increased risk of thrombosis throughout gestation and the postnatal period.[22]
- Venous thromboembolic events are responsible for 10% of maternal deaths.[23]

paralysis of the lower extremities

- Venous stasis and prolonged bed rest are known to increase the risk of venous thromboembolic event.[33]

factor V Leiden mutation

- Most common of the inherited thrombophilias, occurring in 5% of the general population of European descent. Present in 11% to 21% of patients with a venous thromboembolic event (combining incident rates of DVT and PE).[36]
- Heterozygous carriers have an estimated risk for venous thromboembolic event that is 7 times higher than those without the mutation. Homozygous carriers are at 80 times higher risk for venous thromboembolic event than non-affected individuals.[37]
- Patients with factor V Leiden are less likely to have a PE than are subjects with other inherited thrombophilias. This paradox highlights the differences that exist between the risk factors for DVT and PE.[38] [39]

prothrombin gene mutation

- This mutation is seen in 2% of the general population.[36]
- Estimated to increase the risk of a venous thromboembolic event by 2 to 5 times that of those without the mutation.[35]

antithrombin III deficiency

- Large variability to the disorder. May not significantly increase the risk of thrombosis in subjects without a concomitant family history. Fifty percent of patients with antithrombin III deficiency and a family history of thrombosis will have a venous thromboembolic event before the age of 40.[35]

protein C deficiency

- Rare inherited thrombophilia. Heterozygotes without a family history of thrombosis are not thought to be at an increased risk for a venous thromboembolic event when compared with those without the mutation. Heterozygotes with a family history of thrombosis have an incidence of venous thromboembolic event of approximately 2.5% per year.[35]

protein S deficiency

- Found in 1% to 2% of patients presenting with DVT.
- The increase in risk associated with this disorder is not well established, with an incidence of venous thromboembolic event of approximately 3.5%/year.[35]

antiphospholipid antibody syndrome

- DVT will occur in about half of patients with this syndrome in the 6 years following diagnosis.[40]

Weak

obesity (BMI ≥29 kg/m^2)

- Present in 29% of patients with a diagnosed PE.[20]

- More likely to be present in patients who die from PE.

cigarette smoking

- Present in 18% confirmed with the condition.[20]

COPD

- Present in 12% confirmed with the condition.[20]

CHF

- Present in 10% confirmed with the condition.[20]

central venous catheterisation

- Seen in 7% confirmed with the condition.[20]

varicose veins

- Valvular incompetence leads to venous stasis in the lower extremities and endothelial damage at valvular sites. Thrombi may form and embolise to the pulmonary vasculature.

recent air travel

- Long-distance flights are a well-documented risk factor for VTE with an estimated risk of between 3% and 12% for long-haul flights. The duration of travel yielded an increased odds ratio of 2.5 in the category of 10 to 15 hours of travel.[24]
- Multiple pathophysiological factors have been attributed to this increase in risk including immobility, relative hypoxia in the pressure-controlled cabin, and dehydration.
- Individual risk factors for air travel-related VTE also play an important role. Age >40 years, female gender, women who use oral contraceptives, people with chronic venous insufficiency and/or varicose veins in the lower limbs, obesity, and genetic thrombophilia are strong modulators of VTE attributed to long-distance flights.[25]

history of spontaneous abortion

- There is a 4- to 10-fold increased risk of thrombosis throughout pregnancy and the postnatal period.[22]
- Acquired thrombophilic factors related to arterial and/or venous thrombosis are associated with recurrent miscarriage. The presence of antiphospholipid antibodies, rather than of the more frequent thrombophilic genetic defects such as factor V Leiden or prothrombin G202010A mutation, in patients with recurrent miscarriage is a key determinant of thrombotic events later in life. The risk appears to be modulated and significantly increased in the presence of other risk factors, especially cardiovascular risk factors such as diabetes, hypertension, and cardiomyopathy.

recent acute MI

- MI is associated with higher than usual risk of VTE, particularly among hospitalised patients with acute MI. The increased risk is comparable with that of moderate-risk general surgical patients in which the overall 30-day risk is 20% overall, but only 2% are symptomatic.[26] With the advent of modern antiplatelet and antithrombotic therapies that are used in the hyperacute phase of acute coronary syndrome, symptomatic and fatal pulmonary embolism is less common. In patients with triple vessel disease requiring CABG, the incidence of asymptomatic VTE is surprisingly high.
- In universal screening ultrasound protocols it has been found that the ratio of isolated calf DVT to proximal leg DVT was approximately 5:1, and the ratio of all DVT to symptomatic PE or DVT exceeded

20:1 with less than a 1% incidence of fatal embolism during the primary admission. However, PE and DVT is the fifth most common cause of readmission within 30 days of discharge, accounting for 6.3% of all readmissions, and is exceeded in frequency only by infections, heart failure, myocardial ischaemia, and arrhythmia.[27]

sepsis

- Endothelial cells are injured during septic shock and generate tissue factor, which activates the coagulation cascade. Acute disseminated intravascular coagulation activates the fibrinolytic system, leading to occlusion of the pulmonary vasculature among other sites.

recent blood transfusion

- Transfusion of red blood cells, platelets, and fresh frozen plasma is associated with an increased risk of venous and arterial thrombotic events and mortality in hospitalised patients with cancer, acute coronary syndrome, or acute bleeding.[28] [29]

oral contraceptive pill

- The oral contraceptive pill is associated with an increased risk of death from a venous thromboembolic event, amounting to 1 to 3 deaths/million women/year.[30] [31] [32]

inflammatory bowel disease

- More likely to be seen in those who die with a PE, with an adjusted mortality ratio double that of unaffected individuals.[9]
- Serological abnormalities found in inactive Crohn's disease and ulcerative colitis, including abnormalities in fibrinolysis, may increase risk of PE.

nephrotic syndrome

- Severe nephrotic syndrome leads to hypercoagulability, resulting in thromboembolism at sites such as the renal and pulmonary vasculature.

Behcet's disease

- Venous thromboembolic events occur in 12.8% of patients with the disease.[34] This association may be linked to hyperhomocysteinaemia.

homocysteinaemia

- Increases the relative risk of venous thromboembolic event by 2.5-fold.[35]

polycythaemia vera

- It is unclear why thrombosis occurs in this condition. It may be related to hyperviscosity and/or leukocytosis.

chest CT

- There have been an increasing number of reports of incidental PE in patients undergoing chest computer tomography (CT) for reasons other than the research of suspected PE.[4]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include: increasing age; presence of DVT; surgery within the last 2 months; >5 days bed rest; previous venous thromboembolic event; family history of venous thromboembolism; active malignancy; recent trauma or fracture; pregnancy/postnatal period; paralysis of the lower extremities; factor V Leiden or prothrombin gene mutation; antithrombin III, protein C, or protein S deficiency; and antiphospholipid antibody syndrome.

chest pain (common)

- Found in between 49% and 88% of patients.[3] [20]
- Usually caused by pleural irritation due to distal emboli causing pulmonary infarction.[59]
- In central PE (in which the thrombus is in the main, left, or right pulmonary artery), angina-like chest pain may present, possibly due to right ventricle ischaemia. This presentation requires differentiation from acute coronary syndrome or aortic dissection.
- Pleuritic chest pain is thought to be more common with pulmonary infarction.

dyspnoea (common)

- Found in between 82% and 84% of patients.[3] [20]

tachypnoea (common)

- Feature of shock.
- >16 breaths per minute in 92% of patients; >20 breaths per minute in 60%.[3] [20]

presyncope or syncope (uncommon)

- Found in 13% of patients.[3] [20]
- Presence suggests a larger clot burden and poorer prognosis.

hypotension (systolic BP <90 mmHg) (uncommon)

- Feature of shock.
- Occurs in 4% of patients.[20]
- Indicates central PE and/or a severely reduced haemodynamic reserve.

Other diagnostic factors

feeling of apprehension (common)

- Found in 59% of patients.[3]

cough (common)

- Found in between 20% and 53% of patients.[3] [20]

tachycardia (common)

- Feature of shock.
- >100 beats per minute in 44% of patients with PE.[3]

fever (common)

- 37.8°C (100.0°F) in 43% of patients; >38.0°C (>100.4°F) in 9% of patients.[3] [20]

haemoptysis (uncommon)

- Found in between 7% and 30% of patients.[3] [20]
- More common with pulmonary infarction.

elevated jugular venous pressure (uncommon)

- A feature elicited if cor pulmonale is present.

sternal heave (uncommon)

- A feature elicited if cor pulmonale is present.

accentuated pulmonary component of S2 (uncommon)

- A feature elicited if cor pulmonale is present.

unilateral swelling/tenderness of calf (uncommon)

- A feature elicited if DVT is present.

Diagnostic tests

1st test to order

Test	Result
ECG • May show tachycardia (37%); new right axis deviation (5%); new right bundle branch block (11%); S wave in lead I, Q wave with T-wave inversion in lead III (12%).[61] [76] [77] [78] • Findings are suggestive of PE; however, they are not specific and could be associated with any other lung abnormality that results in pulmonary hypertension and right ventricle overload (e.g., acute bronchospasm, pneumothorax, volume overload).[77]	**atrial arrhythmias, right bundle branch block, inferior Q waves, precordial T-wave inversion, and ST segment changes suggest poor prognosis**
CXR • May show Fleischner sign/prominent central pulmonary artery (20%); Westermark sign/oligaemia in PE's area of distribution (11%); Hampton hump/pleural-based areas of increased opacity corresponding to the distribution of the PE (27%).[61] [76] [77] [78] • Findings are only suggestive of PE.[79] Not diagnostic as a single test. • In pregnant women, despite the low-quality evidence, expert opinion recommendations have been outlined to minimise the exposure to radiation usually associated with computed tomographic pulmonary angiography (CTPA), and include CXR as the first radiation-associated procedure.[68]	**band atelectasis, elevation of hemidiaphragm, prominent central pulmonary artery, oligaemia at site of embolism**

Test	Result
ABG • Not suggestive of PE: PaO2 80 mmHg or more; PaCO2 35 mmHg or more; arterial-alveolar O2 gradient [P(A-a)O2] <20 mmHg. • Suggestive of PE: PaO2 <80 mmHg; PaCO2 <35 mmHg; P(A-a)O2 20 mmHg or more. • However, in patients with no cardiopulmonary disease, PE will be present in 38% of patients with all 3 normal findings on ABG.[78] • In pre-existing cardiopulmonary disease, PE will be present in 14% of patients with all 3 normal findings on ABG. • Findings are only suggestive of PE. Not diagnostic as a single test.[78]	**hypoxia and hypocapnia are suggestive**
Wells' score • Should be calculated in all patients with suspected PE. • Historical features and physical examination can determine pretest probability of PE using the Wells' score. Either this score or the Geneva score can be used depending on physician preference/ location. • A simplified version of the score has been prospectively validated.[62]	**original score: ≤4 = PE unlikely and >4 = PE likely; simplified score: ≤1 = PE unlikely and >1 = PE likely**

Wells' score	Original	Simplified
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1

The difference between the scores in the original modified Wells' score and the simplified version
Created by the BMJ Evidence Centre team

- 8% of patients with a PE unlikely score (original version) will have a PE.[60]
- Clinical probability score alone is not enough to diagnose or exclude the condition. It must be combined with additional tests.

Test	Result
Geneva score • Should be calculated in all patients with suspected PE. • Historical features and physical examination can determine pretest probability of PE using the Geneva score. Either this score or the Wells' score can be used depending on physician preference/ location. • The revised Geneva score was formerly available as 3-category scheme (i.e., 0-3 = low probability of PE; 4-10 = intermediate probability of PE; and ≥11 = high probability of PE) but was recently made into the 2-category scheme. • According to the 3-category scheme: 10% of patients with a low probability score will have a PE; 38% of patients with an intermediate score will have a PE; and 81% of patients with a high probability score will have a PE.[76] • A simplified version of the score has been prospectively validated.[62]	**original score: ≤5 = PE unlikely and >5 = PE likely; simplified score: ≤2 = PE unlikely and >2 = PE likely**
Pulmonary Embolism Rule-Out Criteria (PERC) • The Pulmonary Embolism Rule-Out Criteria (PERC) may be used in patients identified as very low risk. In patients who meet all of the criteria (age <50 years; initial heart rate <100 bpm; initial oxygen saturation >94% on room air; no unilateral leg swelling; no haemoptysis; no surgery or trauma within last 4 weeks; no history of VTE; no oestrogen use), the risk for PE is considered to be lower than the risk of testing, and so a D-dimer is not indicated. D-dimer should be done for patients who do not meet all of the criteria.[63]	**positive score**

Geneva score	Original	Simplified
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Previous PE or DVT	3	1
Heart rate 75-94 bpm ≥95 bpm	3 5	1 2
Unilateral limb pain	3	1
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active cancer	2	1
Age >65 years	1	1
Clinical probability*		
PE unlikely	≤5	≤2
PE likely	>5	>2

* The revised Geneva score was formerly available as 3-category scheme (i.e., 0-3 = low probability of PE; 4-10 = intermediate probability of PE; and ≥11 = high probability of PE), but was recently made into the 2-category scheme shown above.

The difference between the scores in the original revised Geneva score and the simplified version
Created by the BMJ Evidence Centre team

• Clinical probability score alone is not enough to diagnose or exclude PE. It must be combined with the results of additional tests.

DIAGNOSIS

Test	Result
D-dimer • Should be ordered in intermediate-risk patients, or low-risk patients with a positive PERC score. • Sensitivity and negative predictive value depends on the type of laboratory technique used to measure D-dimer. D-dimer sensitivity is acceptable for screening and diagnosis. A low specificity is a concern, particularly among patients with other causes of D-dimer elevation including overwhelming infection, renal disease, or liver disease. • A D-dimer by the VIDAS® rapid quantitative ELISA has a sensitivity of >95% regardless of the calculated clinical probability.[64] [65] • Normal rapid quantitative ELISA D-dimer combined with an intermediate- or low-probability Geneva score rules out PE, with a 0% risk of venous thromboembolic event in the following 3 months.[67] • Normal rapid quantitative ELISA D-dimer combined with a PE unlikely modified Wells' score rules out PE, with a 0.5% to 0.7% risk of a venous thromboembolic event in the following 3 months.[80] • Can safely rule out PE as a diagnosis in 32% to 44% of patients without further work-up or imaging.[67] [80] • Age-adjusted D-dimer may have a role in excluding ongoing fibrinolysis as an indirect biomarker of ongoing thrombosis after discontinuation of anticoagulation therapy.	**elevated**
multiple-detector computed tomographic pulmonary angiography (CTPA) of chest • The recommended initial imaging test in patients with a high probability or PE likely clinical probability score, or an abnormal D-dimer test.[80] [Fig-4] • Specificity is 96%.[81] • Among patients with low pulmonary embolism severity indices, CTPA seems to increase the proportion of patients diagnosed with subsegmental PE without lowering the 3-month risk of thromboembolism, suggesting that subsegmental PE may not be clinically relevant.[69] • Three-month incidence of a subsequent venous thromboembolic event with a negative CT scan is only 1.3% to 1.7%.[67] [80] • CT scans are contraindicated in approximately 25% of patients due to pregnancy or renal insufficiency.[81] However, when used appropriately, CT (and MRI) can be valuable tools in imaging pregnant and lactating women; risks and benefits always should be considered and discussed with patients.[82] • CTPA should be used with discretion in adolescents and young adults, especially if pulmonary embolism can be ruled out by other non-invasive methods with less radiation exposure.[70]	**diagnosis is confirmed by direct visualisation of thrombus in a pulmonary artery; appears as a partial or complete intraluminal filling defect**

Test	Result
ventilation-perfusion scan (V/Q scan) • Normal reading is the most sensitive of all the imaging tests for excluding PE; negative predictive value of 96% regardless of clinical probability.[10] • Low-probability reading with a low clinical probability has a negative predictive value of 96%.[10] • High-probability reading with a high clinical probability has a positive predictive value of 96%.[10] • Intermediate reading will occur in 39% of patients and requires further work-up; 32% of this group will have a PE.[10] • Single photon emission CT improves the accuracy of the V/Q scan and may eliminate the intermediate reading.[83] [84] [85]	**normal, low, intermediate, and high probability; PE likely when an area of ventilation is not perfused**
lung scintigraphy • In pregnant women, despite the low-quality evidence, expert opinion recommendations have been have been outlined to minimise the exposure to radiation usually associated with CTPA and include use of lung scintigraphy (which often includes a V/Q scan) as the preferred test in the setting of a normal CXR.[68]	**ventilation-perfusion mismatch**

Other tests to consider

Test	Result
digital subtraction angiography (DSA) • Can be useful when there is a contraindication to CT scanning (e.g., contrast allergy, moderate to severe renal failure, or pregnancy) and a ventilation-perfusion (V/Q) scan also cannot be obtained.	**may show arterial occlusion corresponding to the PE**
transthoracic echocardiography (TTE) • A readily available, non-invasive method for evaluating RV function and pulmonary haemodynamics, particularly among patients with large clot burden or clinical features of haemodynamic compromise. • 40% to 53% of patients will present with RV dysfunction on TTE.[20] [86] • 58% of patients with RV dysfunction on TTE are haemodynamically stable with a systolic BP >100 mmHg.[86] • Mortality for haemodynamically stable patients with RV dysfunction on echo ranges from 2% to 5%.[14] [86] [87] • Poor discriminator of those at high risk of immediate mortality, with a positive predictive value of 5%.[88] • Haemodynamically stable patients without RV dysfunction have a very low mortality in the presence of anticoagulation therapy, ranging from 0% to 3%.[86] [87] [89] Thrombolytic therapy has not been shown to improve survival in haemodynamically stable patients with evidence of RV strain.[87] [90]	**helpful in identifying right ventricular (RV) strain/dysfunction; important prognostic considerations**

Test	Result
MR angiography • Three different techniques: gadolinium-contrast enhanced angiography (Gd-MRA), real time angiography (RT-MRA), and MR-perfusion images.[71] [Fig-5] • High specificity (91% to 98%) allows for accurate diagnosis. • Low sensitivity (75% to 93%) cannot reliably exclude PE with a negative test.[71] • Gadolinium contrast, used in Gd-MRA and MR perfusion studies, is relatively contraindicated in pregnancy.	**diagnosis is confirmed by direct visualisation of thrombus in a pulmonary artery; appears as a partial or complete intraluminal filling defect**
trans-oesophageal echocardiography • Not well studied. Visualisation of thrombus can be treated with confidence as indicator of condition. • Cannot be used to reliably exclude the condition.	**may visualise thrombus in the main pulmonary artery or thrombus-in-transit**
coagulation studies • INR, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should be ordered. • Required to establish baseline prior to commencing anticoagulation. • Aids decisions about the safety and type of initial anticoagulation to prescribe.	**baseline values; establishing correct therapeutic range**
thrombophilia screen • Not indicated in all cases of incident venous thromboembolic events; however, it may be useful if the site of thrombus is unusual, if there is a large clot burden, or if there are recurrent events. • Best performed at the end of the appropriate treatment period, although many clinicians frequently test patients for antithrombin (AT) deficiency and perform tests to diagnose antiphospholipid syndrome during the acute treatment period. • Screening for certain conditions such as protein S, protein C, or antithrombin III deficiency should be repeated after 12 weeks as serum levels may be decreased in the hyperacute phase of thrombus formation or due to the use of anticoagulants such as heparin, low molecular weight heparin, or warfarin.	**positive in inherited thrombophilias; repeat after 12 weeks**
brain natriuretic peptide (BNP) • Non-specific, non-sensitive diagnostic test for PE. • Peptide is secreted in both left and right ventricular strain. • Useful as a prognostic marker in PE.[75] • Normal reference range is <75 nanograms/L (<75 picograms/mL), found in 94% of patients without RV strain.[91] Negative predictive value for uncomplicated hospital course is >93%.[92] • Abnormal level is >90 nanograms/L (>90 picograms/mL):[91] [93] 64% of patients with RV strain will have BNP level >90 picograms/mL.[91] Positive predictive value for RV strain is 94%.[91] Positive predictive value for death is only 13%.[93] Positive predictive value for complicated hospital course (including death) is 53%.[93]	**may be elevated or normal; insensitive/non-specific for diagnosis; useful for prognosis**

Test	Result
troponin I • Divided into normal, moderate elevation, and high elevation. • Elevated in 41% of patients presenting with acute PE.[94] • Positive predictive value for death or complicated hospital course is 37%. • Normal is <0.07 micrograms/L (<0.07 nanograms/mL); 9.6% of patients with normal troponin I will have RV strain on echo. Strongly predictive of patients who will have an uncomplicated hospital course, with a negative predictive value of 92%. • Moderate is 0.07 to 1.5 micrograms/L (0.07 to 1.5 nanograms/mL): 43% of patients with moderate elevation of troponin I will have RV strain present on echo. Moderate elevations in troponin I are not predictive of mortality or complicated hospital course. • High is >1.5 micrograms/L (>1.5 nanograms/mL): 50% of patients with a high troponin I will have RV strain on echo.	**elevation not useful diagnostically; prognostically valid**
troponin T • Elevated in 37% of patients presenting with acute PE.[94] • Elevated in 28% of patients who have an uncomplicated hospital course. • Positive predictive value for death or complicated hospital course is 41%. • Divided into normal, moderate elevation, and high elevation. • Normal is ≤0.04 micrograms/L (≤0.04 nanograms/mL): 18% of patients with normal troponin T will have RV strain on echo. Strongly predictive for uncomplicated hospital course, with a negative predictive value of 93%. • Moderate is 0.04 to 0.1 micrograms/L (0.04 to 0.1 nanograms/mL): 20% of patients with moderate elevation of troponin T will have RV strain present on echo. Moderate elevations in troponin T are not predictive of mortality or complicated hospital course. • High is >0.1 micrograms/L: (>0.1 nanograms/mL): 48% of patients with a high level of troponin T will have RV strain on echo.	**elevation not useful diagnostically; prognostically valid**
pulmonary angiography • Considered the definitive test for diagnosis/exclusion, but is rarely used in clinical practice due to the increased risk of mortality/ morbidity. • Negative predictive value is as high as 99%.[10] • Invasive test with morbidity of 3% to 6% and a mortality of 0.2% to 0.5%.[95] [96] • Involves the use of contrast and is generally contraindicated in pregnancy and renal failure.	**diagnosis made by visualisation of a complete or incomplete filling defect in the pulmonary artery**
prognostic stratification • The Pulmonary Embolism Severity Index (PESI) and other simplified versions such as the RIETE (Registro Informatizado de la Enfermedad TromboEmbolica venosa – Computerised registration of venous thromboembolism) score are commonly used. • Patients in the high-risk category have a high short-term (i.e., 30 day) mortality of up to 15%, whereas patients with a low severity index have a short-term mortality of 1% or lower, making early discharge or outpatient treatment a cost-effective therapeutic option.	**higher severity index indicates higher short-term mortality**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Angina, unstable	• Typical cardiac chest pain is described as a retrosternal pressure or heaviness radiating to the jaw, arm, or neck. • Pain may be intermittent or persistent. • Differentiating risk factors include long-standing hypertension, diabetes, or hypercholesterolaemia. • Can be difficult to differentiate from PE on the basis of signs and symptoms alone.	• ST segment depression in contiguous leads on ECG. • Normal troponin I or T. These tests may be elevated in PE. Negative diagnostic imaging study for PE. • Critical stenosis of a coronary artery on coronary angiography.
Myocardial infarction, non-ST elevation (NSTEMI)	• Part of acute coronary syndrome spectrum. • Presents with central chest pain that is classically heavy in nature, like a sensation of pressure or squeezing. • Examination findings are variable and range from normal to a critically unwell patient in cardiogenic shock. • Often difficult to differentiate from PE in acute setting.	• ECG does not show ST-elevation, but serum levels of cardiac biomarkers are raised. • ECG may show non-specific ischaemic changes such as ST depression or T wave inversion. • May see bilateral increased pulmonary vascular congestion on chest radiograph consistent with CHF. • Elevated troponin I or T. These may also be elevated in the setting of PE. • Regional wall motion abnormality of the left ventricle on echo.
Myocardial infarction, ST-elevation (STEMI)	• Presents with central chest pain that is classically heavy in nature, like a sensation of pressure or squeezing. • Examination findings are variable and range from normal to a critically unwell patient in cardiogenic shock. • Often difficult to differentiate from PE in acute setting.	• STEMI is diagnosed by persistent ST segment elevation in 2 or more anatomically contiguous ECG leads in a patient with a consistent clinical history. • Elevated troponin I or T, can also be raised in PE. • Regional wall motion abnormality of the left ventricle on echo. • Critical stenosis of a coronary artery on coronary angiography.

Condition	Differentiating signs / symptoms	Differentiating tests
Pneumonia, community-acquired	• May be difficult to differentiate on the basis of signs and symptoms. • Cough productive of purulent sputum. • Fever above 39.0°C (102.2°F); generally higher than in PE.[97]	• WBC count normally >11 x 10^9/L (>11,000/microlitre). • CXR may show a focal opacity and other features of pneumonic consolidation. This can also be seen with PE. • Sputum culture grows an organism known to cause pneumonia. • Negative diagnostic imaging study for PE.
Bronchitis, acute	• More insidious, subacute onset of symptoms than PE. • Diffuse wheezes/rhonchi on pulmonary auscultation. • Cough productive of purulent sputum.	• Normal CXR. This can also be seen in PE. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.
COPD, acute exacerbation	• History of previous/ongoing tobacco use. • Diffuse wheezes on pulmonary auscultation. • Diffuse decrease in breath sounds on pulmonary auscultation. • Increased expiratory phase of the respiratory cycle. • PE may be present in 6% to 25% of patients with a COPD exacerbation of unknown cause.[98] [99]	• Evidence of hyperinflation, flattened diaphragms, and increased retrosternal air on CXR. • Incompletely reversible reduction in FEV1 and FEV1/FVC on spirometry. • Normal troponin I and T. Normal brain natriuretic peptide (BNP). • Normal right and left ventricular function on echo. • Right ventricular (RV) strain with decreased RV function can be seen on echo in patients with pulmonary hypertension secondary to COPD. This can also be seen in PE. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.
Asthma, acute exacerbation	• Previous history of asthma/ atopy. • Diffuse wheezes on pulmonary auscultation. • Diffusely decreased breath sounds on pulmonary auscultation. • Prolonged expiratory phase of the respiratory cycle.	• Normal chest radiograph. This can also be seen with PE. • Reversible reduction in peak flow measurement (peak expiratory flow or FEV1). • Normal troponin I and T and normal BNP. • D-dimer, CT pulmonary angiogram, and V/Q scan normal.

Condition	Differentiating signs / symptoms	Differentiating tests
CHF, acute exacerbation	• May be difficult to differentiate solely on the basis of signs and symptoms. • More insidious, subacute onset of symptoms than those generally seen with PE. • Orthopnoea, paroxysmal nocturnal dyspnoea, and documented weight gain are common. • Increased bilateral lower extremity swelling. • Diffuse crackles on pulmonary auscultation. • Elevated jugular venous pressure. • Features of right-sided heart failure can occur in PE.	• Increased pulmonary vascular congestion on chest radiograph with enlarged cardiac silhouette. • Bilateral alveolar infiltrates on chest radiograph. • Elevated BNP. This can also be seen in PE, but PE rarely results in BNP levels >1000 nanograms/L (>1000 picograms/mL).[91] • Decreased LV function with a decreased ejection fraction on echo. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.
Pericarditis	• May be difficult to differentiate on the basis of signs and symptoms. • Chest pain improves when sitting up and worsens when supine.	• ST segment elevation in all leads on ECG. • Electrical alternans on ECG. • Normal chest radiograph. May see an enlarged cardiac silhouette. • Elevated troponin I or T. This may also be seen with PE. • Pericardial effusion on echo. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.
Tamponade, cardiac	• Difficult to differentiate on the basis of signs and symptoms. • The Beck's triad of hypotension, muffled heart sounds, and elevated jugular venous pressure are classic features, although are not always present. • Patients often complain of dyspnoea and chest pain.	• Normal CXR. May see an enlarged cardiac silhouette. • Pericardial effusion on echo with evidence of tamponade physiology is diagnostic. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.

Condition	Differentiating signs / symptoms	Differentiating tests
Pulmonary HTN due to chronic thromboembolic disease	• History of PE; bruits over the lung fields (pulmonary flow murmurs) are present in 30% of cases. • More insidious, subacute onset of symptoms than those generally seen with PE. • Documented weight gain. • Bilateral lower extremity swelling.	• ECG findings can show right axis deviation, p-pulmonale, and/or possible right bundle branch block. • Normal D-dimer/CXR. • Ventilation-perfusion lung scintigraphy: one or more segmental-sized or larger unmatched perfusion defects. • Pulmonary angiography: vascular webs or band-like narrowing, intimal irregularities, pouch defects, abrupt and angular narrowing, and proximal obstruction.
Pneumothorax	• May be difficult to differentiate on the basis of signs and symptoms. • History of recent trauma to the chest. • Decreased breath sounds unilaterally on pulmonary auscultation. • Hyperresonance on percussion of affected side. • Deviation of the trachea away from the affected lung.	• Loss of lung markings in the periphery with evidence of lung collapse on CXR. • May see evidence of pneumothorax associated with a rib fracture on CXR. • Normal D-dimer in the correct clinical setting or a negative diagnostic imaging study for PE.
Costochondritis	• Presents with insidious onset of anterior chest-wall pain exacerbated by certain movements of the chest and deep inspiration. • Point tenderness on palpation of costochondral joints (particularly the second to the fifth).	• No specific diagnostic tests. • Normal D-dimer or a negative diagnostic imaging study for PE.
Panic disorder	• Sudden-onset anxiety, feeling faint, and palpitations. • Recurrent, discrete period of intense fear/discomfort. • Sense of apprehension can be manifested as fear of death or life-threatening illness.	• Clinical diagnosis requiring formal psychiatric assessment. • Normal D-dimer or a negative diagnostic imaging study for PE.

Diagnostic criteria

Clinical decision rules

The modified Wells' score[60] and the revised Geneva score[61] are used to assess the clinical probability of PE. Historical and physical examination features are assigned points, and the points are added together to determine whether PE is likely or unlikely. However, miscalculations can occur with these scores as they are based on multiple clinical variables each with different points assigned. Therefore, the scores have been simplified, and these simplified scores have been prospectively validated and have been found to perform similarly to the original scores in the exclusion of PE in combination with a D-dimer result.[62]

Either the original or simplified scores are acceptable to use, and choice depends on physician preference or location.

Wells' score	Original	Simplified
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1

The difference between the scores in the original modified Wells' score and the simplified version
Created by the BMJ Evidence Centre team

Geneva score	Original	Simplified
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Previous PE or DVT	3	1
Heart rate 75-94 bpm ≥95 bpm	3 5	1 2
Unilateral limb pain	3	1
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active cancer	2	1
Age >65 years	1	1
Clinical probability*		
PE unlikely	≤5	≤2
PE likely	>5	>2

* The revised Geneva score was formerly available as 3-category scheme (i.e., 0-3 = low probability of PE; 4-10 = intermediate probability of PE; and ≥11 = high probability of PE), but was recently made into the 2-category scheme shown above.

The difference between the scores in the original revised Geneva score and the simplified version
Created by the BMJ Evidence Centre team

DIAGNOSIS

Pulmonary Embolism Rule-Out Criteria (PERC)

The Pulmonary Embolism Rule-Out Criteria (PERC) may be used in patients identified as very low risk. In patients who meet all of the criteria (age <50 years; initial heart rate <100 bpm; initial oxygen saturation >94% on room air; no unilateral leg swelling; no haemoptysis; no surgery or trauma within last 4 weeks; no history of VTE; no oestrogen use), the risk for PE is considered to be lower than the risk of testing, and so a D-dimer is not indicated. D-dimer should be done for patients who do not meet all of the criteria.[63]

Step-by-step treatment approach

Risk of pulmonary embolism (PE) can be assessed on the basis of haemodynamic stability (systolic BP >90 mmHg or systolic BP <90 mmHg), and high (>4 points) or low (<4 points) probability according to the original modified Wells' criteria.[60] Due to high mortality in the early stages of PE,[13] aggressive treatment is necessary in the case of high-risk patients (modified Wells' score >4, systolic BP <90 mmHg). Hypoxaemia with systolic BP <90 mmHg suggests massive PE, which has a high mortality.1[B]Evidence

In all patients undergoing diagnostic evaluation awaiting confirmation of PE, supportive therapies and empirical anticoagulation (unless contraindicated) should be instituted without delay.[101]The data on exclusive outpatient management of acute symptomatic pulmonary embolism are limited, but the existing evidence supports the feasibility and safety of this approach in carefully selected low-risk patients.[102]

Supportive therapies

Respiratory support

- Supplemental high-flow oxygen should be administered.
- Mechanical ventilation may be necessary for patients with severe hypoxaemia/respiratory failure.

[VIDEO: Tracheal intubation animated demonstration]

Intravenous fluids

- If systolic BP is <90 mmHg, intravenous fluids should be given. Acute right ventricular failure with resulting low systemic output is the leading cause of death in patients with PE.
- Studies indicate that aggressive volume expansion is of no benefit, and may even worsen right ventricular function by causing mechanical overstretch, or by reflex mechanisms that depress contractility. However, modest fluid challenge (i.e., 500 mL) may help to increase cardiac index in patients with PE, a low cardiac index, and normal BP.[105]
- Local resuscitation protocols should be followed.

Vasopressors

- If systolic BP is <90 mmHg, vasopressors should be given. Use of vasopressors is often necessary in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment.
- Noradrenaline (norepinephrine) appears to improve right ventricular function via a direct positive inotropic effect, while also improving right ventricular coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. However, its use should probably be limited to hypotensive patients.
- Dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.[106]
- Adrenaline (epinephrine) combines the beneficial properties of noradrenaline and dobutamine, without the systemic vasodilatory effects of the latter.

Bed rest

- A systematic recommendation of bed rest as part of the early management of patients with DVT, PE, or both, is not supported by available evidence.[107]

Initial anticoagulation

Anticoagulation should be instituted immediately in all patients who present with suspected PE, unless contraindicated.[101] If PE is subsequently excluded, anticoagulation can be discontinued. In patients with confirmed PE, anticoagulation should continue for at least 3 months.[101]

Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low-molecular weight heparin (LMWH).[101] Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition.

In haemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. These agents have the advantage of requiring no monitoring, having a rapid onset of action, and being short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility, although dabigatran can be reversed with idarucizumab. Randomised clinical trials have demonstrated non-inferiority for efficacy and safety in patients with haemodynamically stable PE.[108] Rivaroxaban and apixaban are used as single agents for treatment, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are started. Because of this, rivaroxaban and apixaban are often the preferred treatments in haemodynamically stable patients.

When a patient has been started on warfarin, it is usually appropriate to stop administration of the parenteral anticoagulant once a therapeutic INR of 2.0 to 3.0 has been established.

Fondaparinux is generally not recommended in haemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols.[109] No difference in thromboembolism recurrence, haemorrhage, or overall mortality has been demonstrated between the different drugs in this class. UFH is recommended for patients in whom primary reperfusion is being considered, as well as for those with serious renal impairment (i.e., creatinine clearance <30 mL/min), or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine.

In pregnant women, LMWH instead of UFH is recommended for prevention and treatment.[55] For pregnant women with acute PE, it is suggested that anticoagulants be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55] Warfarin is contraindicated in pregnant women and the safety of other anticoagulants is not well established in this population.

LMWH is recommended in patients with active malignancy.[110]

Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

Thrombolytic therapy

In patients with haemodynamic compromise (shock or systolic BP <90 mmHg) or right-sided heart strain (as assessed by transthoracic echocardiogram), thrombolytic treatment is recommended as this patient group has a high mortality rate.[101]

Choice of intervention will vary according to local provision: systemic thrombolysis[101] or catheter-directed thrombolysis,[111] [112] [100] [113] although current guidelines from the American College of Chest Physicians recommend systemic thrombolytic therapy using a peripheral vein over catheter-directed thrombolysis.[101] Whichever technique is employed, a delay in treatment can be life-threatening. [114]

Thrombolytic treatment of acute PE restores pulmonary perfusion more rapidly than anticoagulation with UFH alone. The early resolution of pulmonary obstruction leads to a prompt reduction in pulmonary artery pressure and resistance, with a concomitant improvement in right ventricular function. The haemodynamic benefits of thrombolysis are confined to the first few days; in survivors, differences are no longer apparent at 1 week after treatment.[89] [115] [116] With thrombolysis, risk of major bleeding is 22%. In the case of thrombolysis, intracranial haemorrhage risk is 1% to 3% when compared with 0.3% with heparin alone.[94]

Absolute contraindications for thrombolysis include:[117] [118]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury (in the preceding 3 weeks)
- Gastrointestinal bleeding within the last month
- Known bleeding risk.

Relative contraindications for thrombolysis include:[117] [118]

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within 1 week postnatal
- Traumatic resuscitation (in relation to this episode of PE)
- Refractory hypertension (systolic BP >180 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer.

When patients are excluded on the basis of these criteria, incidence of intracranial haemorrhage in the remaining treated patients has been shown to be negligible.[90]

In patients with confirmed PE, deciding whether to initiate thrombolysis or to continue with anticoagulation should be made on a case-by-case basis according to clinical presentation and pre-existing morbidity. This tends to vary according to local expertise and centre provision.

Surgical intervention

In high-risk patients unable to receive thrombolytic therapy because of bleeding risk, or when there is insufficient time for effective systemic thrombolytic therapy, or such therapy fails, surgical pulmonary embolectomy or one of the following interventional options should be considered, depending on

local availability: thrombus fragmentation with pigtail or balloon catheter; rheolytic thrombectomy with hydrodynamic catheter devices; or suction thrombectomy with aspiration catheters and rotational thrombectomy.[119]

A meta-analysis of non-randomised trials of these less invasive procedures revealed a clinical success rate of 87% with an associated risk of major and minor complications of 2% and 8%, respectively.[114] 2[C]Evidence However, for patients without absolute contraindications to thrombolysis, catheter-directed thrombolysis or pharmacomechanical thrombolysis are preferred.

Concomitant placement of an inferior vena cava (IVC) filter should be performed with surgical embolectomy to prevent recurrent PE. If bleeding risk resolves, subsequent anticoagulation should be given.

Venous filters

Venous filters are indicated in patients with acute PE who have absolute or relative contraindications to anticoagulants.[122] In some cases with objectively confirmed recurrent PE despite adequate anticoagulation treatment, filter placement may be considered as a last resort to prevent a fatal event. Other relative indications may include massive pulmonary embolism with residual deep venous thrombus in a patient at risk for further PE, free-floating iliofemoral or inferior vena cava thrombus, severe cardiopulmonary disease and DVT (e.g., cor pulmonale with pulmonary hypertension).[123] Placement should take place as early as possible if it is the only treatment that can be initiated. There is little evidence available to suggest the ideal time for placement. However, the highest risk of dying is within the first 2 hours of presentation,[100] which might indicate that this is a reasonable timeframe for filter placement. Observational studies suggest that insertion of a venous filter might reduce PE-related mortality rates in the acute phase with the benefit possibly coming at the cost of an increased risk of recurrence of venous thromboembolism.[124] [125]

Complications associated with permanent IVC filters are common, although they are rarely fatal.[125] Overall, early complications (which include insertion-site thrombosis) occur in approximately 10% of patients. Late complications are more frequent and include recurrent DVT (approximately 20% of patients) and post-thrombotic syndrome (up to 40% of patients).[126] [127] Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation.[127]

Post-filter anticoagulation should be considered on a case-by-case basis according to the profile of relative and absolute contraindications.[128] Anticoagulation should be initiated if the contraindication resolves or if a risk/benefit analysis suggests this to be a reasonable course.[101]

Filters should also be considered in patients where recurrent venous thromboembolism occurs despite conventional anticoagulant therapy or where risk of subsequent PE is high.

Long-term (extended) anticoagulation

Recommendations for continuation of anticoagulant therapy beyond 3 months vary by patient group. In patients who receive extended anticoagulation therapy, there is usually no need to change the choice of anticoagulant.[101]

Anticoagulation for 3 months only is generally recommended for patients with a PE related to surgery or to a transient, non-surgical risk factor.[101] There is usually no need for extended anticoagulation beyond 3 months.

For patients with a PE as part of a first VTE that is unrelated to any risk factors who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date). For those patients with a high bleeding risk, 3 months' treatment only is recommended. For patients with a second unprovoked episode of VTE who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date) over 3 months. In patients with a high bleeding risk, 3 months' treatment only is recommended.[101]

In all patients who receive extended anticoagulant therapy, its continued use should be reassessed at periodic intervals (such as annually).[101]

Bleeding risk:

- When assessing bleeding risk, the following factors should be considered:[101] age >65 years, previous bleeding, cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes mellitus, anaemia, antiplatelet therapy, poor anticoagulant control, comorbidity with reduced functional capacity, recent surgery, frequent falls, alcohol abuse, use of non-steroidal anti-inflammatory drugs.
- Patients with none of these risk factors are considered low risk; one risk factor renders a patient moderate risk; and two or more risk factors renders a patient high risk.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Presumptive (summary)

Patient group	Tx line	Treatment
systolic BP <90 mmHg	1st	oxygen ± mechanical ventilation
systolic BP <90 mmHg	plus	intravenous fluids
systolic BP <90 mmHg	adjunct	anticoagulation
systolic BP <90 mmHg	adjunct	vasopressor therapy
systolic BP ≥90 mmHg	1st	oxygen
systolic BP ≥90 mmHg	adjunct	anticoagulation

Acute (summary)

Patient group	Tx line	Treatment
no excessive risk of bleeding	1st	oxygen ± mechanical ventilation
no excessive risk of bleeding	plus	intravenous fluids

Acute (summary)

no excessive risk of bleeding	plus	thrombolysis
no excessive risk of bleeding	plus	anticoagulation
no excessive risk of bleeding	adjunct	vasopressors
excessive risk of bleeding or failed thrombolysis	1st	oxygen ± mechanical ventilation
excessive risk of bleeding or failed thrombolysis	plus	intravenous fluids
excessive risk of bleeding or failed thrombolysis	plus	inferior vena cava (IVC) filter placement
excessive risk of bleeding or failed thrombolysis	adjunct	surgery
excessive risk of bleeding or failed thrombolysis	adjunct	vasopressors
excessive risk of bleeding or failed thrombolysis	adjunct	post-intervention anticoagulation
no anticoagulation contraindication	1st	anticoagulation
no anticoagulation contraindication	adjunct	oxygen
anticoagulation contraindication, complication, or failure	1st	inferior vena cava (IVC) filter placement
anticoagulation contraindication, complication, or failure	adjunct	oxygen
anticoagulation contraindication, complication, or failure	adjunct	post-intervention anticoagulation

Ongoing (summary)

Patient group	Tx line	Treatment
no underlying malignancy (non-pregnant)	1st	oral anticoagulant
underlying malignancy (non-pregnant)	1st	low molecular weight heparin (LMWH) for at least 3-6 months

Ongoing		(summary)
pregnant	1st	low molecular weight heparin (LMWH) for at least 6 weeks postnatal
confirmed PE post-stabilisation: anticoagulation contraindication or failure, or risk of fatal PE	1st	inferior vena cava (IVC) filter placement

Treatment options

Presumptive

Patient group	Tx line	Treatment
systolic BP <90 mmHg	1st	**oxygen ± mechanical ventilation** » Local resuscitation protocols should be followed. » Supplemental high-flow oxygen should be administered. » Mechanical ventilation may be necessary for patients with severe hypoxaemia/respiratory failure. Careful monitoring for hypotension during mechanical ventilation should be observed. **[VIDEO: Tracheal intubation animated demonstration]**
systolic BP <90 mmHg	plus	**intravenous fluids** » Local resuscitation protocols should be followed. » Studies indicate that aggressive volume expansion is of no benefit, and may even worsen right ventricular function by causing mechanical overstretch, or by reflex mechanisms that depress contractility. However, modest fluid challenge (i.e., 500 mL) may help to increase cardiac index in patients with PE, a low cardiac index, and normal BP.[105]
systolic BP <90 mmHg	adjunct	**anticoagulation** » Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low-molecular weight heparin (LMWH).[101] Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In haemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. These agents have the advantage of requiring no monitoring, having a rapid onset of action,

Presumptive

Patient group	Tx line	Treatment
		and being short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility. Randomised clinical trials have demonstrated non-inferiority for efficacy and safety in patients with haemodynamically stable PE.[108] Rivaroxaban and apixaban are used as single agents for treatment, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are started. Because of this, rivaroxaban and apixaban are often the preferred treatments in haemodynamically stable patients. » Fondaparinux is generally not recommended in haemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols.[109] No difference in thromboembolism recurrence, haemorrhage, or overall mortality has been demonstrated between the different drugs in this class. » UFH is recommended for patients in whom primary reperfusion is being considered, as well as for those with serious renal impairment (i.e., creatinine clearance <30 mL/min) or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine. » In pregnant women, LMWH instead of UFH is recommended for prevention and treatment.[55] For pregnant women with acute PE, it is suggested that anticoagulants be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55] » LMWH is recommended in patients with active malignancy.[110] » Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients. » Warfarin is started at the same time as either UFH or LMWH and is continued until the INR is between 2 and 3 for 2 consecutive days, at which point the UFH or LMWH can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants. Warfarin is contraindicated in pregnant women.

Primary options

Presumptive

Patient group	Tx line	Treatment
		» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily
		OR
		Primary options
		» apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily
		OR
		Primary options
		» edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant
		OR
		Primary options
		» dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant
		OR
		Primary options
		» enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» fondaparinux: body weight <50 kg: 5 mg subcutaneously once daily; body weight 50-100 kg: 7.5 mg subcutaneously

Presumptive

Patient group	Tx line	Treatment
		once daily; body weight >100 kg: 10 mg subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban
systolic BP <90 mmHg	**adjunct**	**vasopressor therapy** » Use of vasopressors is often necessary in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment in haemodynamically unstable patients. » Noradrenaline (norepinephrine) appears to improve right ventricular function via a direct positive inotropic effect, while also improving right ventricular coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. However, its use should probably be limited to hypotensive patients. » Dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.[106] » Adrenaline (epinephrine) combines the beneficial properties of noradrenaline and dobutamine, without the systemic vasodilatory effects of the latter.

Presumptive

Patient group	Tx line	Treatment
		Primary options » noradrenaline: 0.5 to 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-12 micrograms/min, maximum 30 micrograms/min **OR** **Primary options** » dobutamine: 0.5 to 1 microgram/kg/min intravenously initially, adjust according to response, usual dose range 2 to 20 micrograms/kg/min, maximum 40 micrograms/kg/min **OR** **Primary options** » adrenaline: 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-10 micrograms/min
systolic BP ≥90 mmHg	**1st**	**oxygen** » Supplemental high-flow oxygen should be provided if oxygen saturation in room air is <92%, and vital signs should be monitored in case of decompensation.
systolic BP ≥90 mmHg	**adjunct**	**anticoagulation** » Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low-molecular weight heparin (LMWH).[101] Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In haemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. These agents have the advantage of requiring no monitoring, having a rapid onset of action, and being short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility.

Presumptive

Patient group	Tx line	Treatment

Randomised clinical trials have demonstrated non-inferiority for efficacy and safety in patients with haemodynamically stable PE.[108] Rivaroxaban and apixaban are used as single agents for treatment, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are started. Because of this, rivaroxaban and apixaban are often the preferred treatments in haemodynamically stable patients.

» Fondaparinux is generally not recommended in haemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols.[109] No difference in thromboembolism recurrence, haemorrhage, or overall mortality has been demonstrated between the different drugs in this class.

» UFH is recommended for patients in whom primary reperfusion is being considered, as well as for those with serious renal impairment (i.e., creatinine clearance <30 mL/min), or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine.

» In pregnant women, LMWH instead of UFH is recommended for prevention and treatment.[55] For pregnant women with acute PE, it is suggested that anticoagulants be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55]

» LMWH is recommended in patients with active malignancy.[110]

» Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

» Warfarin is started at the same time as either UFH or LMWH and is continued until the INR is between 2 and 3 for 2 consecutive days, at which point the UFH or LMWH can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants. Warfarin is contraindicated in pregnant women.

Primary options

» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily

Presumptive

Patient group	Tx line	Treatment
		OR **Primary options** » apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily **OR** **Primary options** » edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant **OR** **Primary options** » dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant **OR** **Primary options** » enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » fondaparinux: patients <50 kg body weight: 5 mg subcutaneously once daily; patients 50-100 kg body weight: 7.5 mg subcutaneously once daily; patients >100 kg body weight: 10 mg subcutaneously once daily **-and-**

Presumptive

Patient group	Tx line	Treatment
		» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban

Acute

Patient group	Tx line	Treatment
no excessive risk of bleeding	**1st**	**oxygen ± mechanical ventilation** » Local resuscitation protocols should be followed. » Supplemental high-flow oxygen should be administered. » Mechanical ventilation may be necessary for patients with severe hypoxaemia/respiratory failure. Careful monitoring for hypotension during mechanical ventilation should be observed. **[VIDEO: Tracheal intubation animated demonstration]**
no excessive risk of bleeding	**plus**	**intravenous fluids** » Local resuscitation protocols should be followed. » Studies indicate that aggressive volume expansion is of no benefit, and may even worsen right ventricular function by causing mechanical overstretch, or by reflex mechanisms that

Acute

Patient group	Tx line	Treatment
		depress contractility. However, modest fluid challenge (i.e., 500 mL) may help to increase cardiac index in patients with PE, a low cardiac index, and normal BP.[105]
no excessive risk of bleeding	**plus**	**thrombolysis** » Systemic thrombolysis is recommended in haemodynamically unstable patients as mortality rate is high in these patients.[129] [130] » Absolute contraindications: haemorrhagic stroke or stroke of unknown origin at any time; ischaemic stroke in the preceding 6 months; central nervous system damage or neoplasms; recent major trauma/surgery/head injury (in the preceding 3 weeks); gastrointestinal bleeding within the last month; known bleeding risk. » Relative contraindications: transient ischaemic attack in the preceding 6 months; oral anticoagulant therapy; pregnancy, or within 1 week postnatal; traumatic resuscitation (in relation to this episode of PE); refractory hypertension (systolic BP >180 mmHg); advanced liver disease; infective endocarditis; active peptic ulcer. » Choice of intervention will vary according to local provision: systemic thrombolysis or catheter-directed thrombolysis.[111] [112] [100] [113] [114] Neither technique has been proven to be superior over the other, but whichever technique is employed, a delay in treatment can be life-threatening.[114] Systemic thrombolysis (i.e., with alteplase or reteplase administered via a peripheral vein) is preferred to catheter-directed thrombolysis.[101] With thrombolysis, risk of major bleeding is 22%. In the case of thrombolysis, intracranial haemorrhage risk is 1% to 3% when compared with 0.3% with heparin alone.[94] » Catheter-directed thrombolysis usually involves a combination of mechanical fragmentation and thrombolysis using alteplase. » Modern catheter-directed thrombolysis is a relatively safe and effective treatment for acute massive PE. At experienced centres, this should be considered as a first-line treatment for patients with massive PE.[111] [131] **Primary options**

Acute

Patient group	Tx line	Treatment
		» alteplase: 100 mg intravenously given over 2 hours **OR** **Primary options** » reteplase: 10 units intravenously initially, followed by second dose of 10 units 30 minutes later
no excessive risk of bleeding	**plus**	**anticoagulation** » Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low-molecular weight heparin (LMWH).[101] Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In haemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. These agents have the advantage of requiring no monitoring, having a rapid onset of action, and being short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility. Randomised clinical trials have demonstrated non-inferiority for efficacy and safety in patients with haemodynamically stable PE.[108] Rivaroxaban and apixaban are used as single agents for treatment, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are started. Because of this, rivaroxaban and apixaban are often the preferred treatments in haemodynamically stable patients. » Fondaparinux is generally not recommended in haemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols.[109] No difference in thromboembolism recurrence, haemorrhage, or overall mortality has been demonstrated between the different drugs in this class. » UFH is recommended for patients in whom primary reperfusion is being considered, as well as for those with serious renal impairment (i.e.,

Acute

Patient group

Tx line

Treatment

creatinine clearance <30 mL/min) or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine.

» In pregnant women, LMWH instead of UFH is recommended for prevention and treatment.[55] For pregnant women with acute PE, it is suggested that anticoagulants be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55]

» LMWH is recommended in patients with active malignancy.[110]

» Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

» Warfarin is started at the same time as either UFH or LMWH and is continued until the INR is between 2 and 3 for 2 consecutive days, at which point the UFH or LMWH can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants. Warfarin is contraindicated in pregnant women.

Primary options

» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily

OR

Primary options

» apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily

OR

Primary options

» edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant

OR

Primary options

Acute

Patient group	Tx line	Treatment
		» dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant
		OR
		Primary options
		» enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» fondaparinux: patients <50 kg body weight: 5 mg subcutaneously once daily; patients 50-100 kg body weight: 7.5 mg subcutaneously once daily; patients >100 kg body weight: 10 mg subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options
		» heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Secondary options

Acute

Patient group	Tx line	Treatment
		» argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban
no excessive risk of bleeding	**adjunct**	**vasopressors** » Use of vasopressors is often necessary in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment in haemodynamically unstable patients. » Noradrenaline (norepinephrine) appears to improve right ventricular function via a direct positive inotropic effect, while also improving right ventricular coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. However, its use should probably be limited to hypotensive patients. » Dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.[106] » Adrenaline (epinephrine) combines the beneficial properties of noradrenaline and dobutamine, without the systemic vasodilatory effects of the latter. **Primary options** » noradrenaline: 0.5 to 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-12 micrograms/min, maximum 30 micrograms/min **OR** **Primary options** » dobutamine: 0.5 to 1 microgram/kg/min intravenously initially, adjust according to response, usual dose range 2 to 20 micrograms/kg/min, maximum 40 micrograms/kg/min **OR** **Primary options**

TREATMENT

Acute

Patient group	Tx line	Treatment
		» adrenaline: 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-10 micrograms/min
excessive risk of bleeding or failed thrombolysis	1st	**oxygen ± mechanical ventilation** » Local resuscitation protocols should be followed. » Supplemental high-flow oxygen should be administered. » Mechanical ventilation may be necessary for patients with severe hypoxaemia/respiratory failure. Careful monitoring for hypotension during mechanical ventilation should be observed. **[VIDEO: Tracheal intubation animated demonstration]**
excessive risk of bleeding or failed thrombolysis	plus	**intravenous fluids** » Local resuscitation protocols should be followed. » Studies indicate that aggressive volume expansion is of no benefit, and may even worsen right ventricular function by causing mechanical overstretch, or by reflex mechanisms that depress contractility. However, modest fluid challenge (i.e., 500 mL) may help to increase cardiac index in patients with PE, a low cardiac index, and normal BP.[105]
excessive risk of bleeding or failed thrombolysis	plus	**inferior vena cava (IVC) filter placement** » Venous filters are indicated in patients with acute PE who have absolute or relative contraindications to anticoagulants. In some cases with objectively confirmed recurrent PE despite adequate anticoagulation treatment, filter placement may be considered as a last resort to prevent a fatal event. » Observational studies suggest that insertion of a venous filter might reduce PE-related mortality rates in the acute phase with the benefit possibly coming at the cost of an increased risk of recurrence of venous thromboembolism.[124] [125] » Complications associated with permanent IVC filters are common, although they are rarely fatal.[125] Overall, early complications (which include insertion-site thrombosis) occur in approximately 10% of patients. Late

Acute

Patient group	Tx line	Treatment
		complications are more frequent and include recurrent DVT (approximately 20% of patients) and post-thrombotic syndrome (up to 40% of patients).[126] [127] Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation.[127]
excessive risk of bleeding or failed thrombolysis	**adjunct**	**surgery** » In patients unsuitable for thrombolytic therapy because of bleeding risk, or when there is insufficient time for effective systemic thrombolytic therapy, or such therapy fails, surgical pulmonary embolectomy or one of the following interventional options should be considered, depending on local availability: thrombus fragmentation with pigtail or balloon catheter; rheolytic thrombectomy with hydrodynamic catheter devices; or suction thrombectomy with aspiration catheters and rotational thrombectomy.[119] » A meta-analysis of non-randomised trials of these less invasive procedures revealed a clinical success rate of 87% with an associated risk of major and minor complications of 2% and 8%, respectively.[114] 2[C]Evidence On the other hand, for patients without absolute contraindications to thrombolysis, catheter-directed thrombolysis or pharmacomechanical thrombolysis are preferred. » Concomitant placement of an inferior vena cava filter should be performed with surgical embolectomy to prevent recurrent PE. » If bleeding risk resolves, subsequent anticoagulation should be given.
excessive risk of bleeding or failed thrombolysis	**adjunct**	**vasopressors** » Use of vasopressors is often necessary in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment in haemodynamically unstable patients. » Noradrenaline (norepinephrine) appears to improve right ventricular function via a direct positive inotropic effect, while also improving right ventricular coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP. However, its use should probably be limited to hypotensive patients.

Acute

Patient group	Tx line	Treatment
		» Dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.[106] » Adrenaline (epinephrine) combines the beneficial properties of noradrenaline and dobutamine, without the systemic vasodilatory effects of the latter. **Primary options** » noradrenaline: 0.5 to 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-12 micrograms/min, maximum 30 micrograms/min **OR** **Primary options** » dobutamine: 0.5 to 1 microgram/kg/min intravenously initially, adjust according to response, usual dose range 2 to 20 micrograms/kg/min, maximum 40 micrograms/kg/min **OR** **Primary options** » adrenaline: 1 microgram/min intravenously initially, adjust according to response, usual dose range 2-10 micrograms/min
excessive risk of bleeding or failed thrombolysis	**adjunct**	**post-intervention anticoagulation** » Anticoagulation following placement of an inferior vena cava filter should be considered on a case-by-case basis according to the profile of relative and absolute contraindications.[128] » Anticoagulation should be initiated if the contraindication resolves or if a risk/benefit analysis suggests this to be a reasonable course.[101]
no anticoagulation contraindication	**1st**	**anticoagulation** » Therapeutic anticoagulation can be achieved with dabigatran, rivaroxaban, apixaban, or edoxaban, which are recommended over vitamin K antagonist (VKA) therapy (usually

Acute

Patient group	Tx line	Treatment
		warfarin), which is in turn recommended over low-molecular weight heparin (LMWH).[101] Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In haemodynamically stable patients, direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) are considered to be an acceptable therapeutic intervention. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors. These agents have the advantage of requiring no monitoring, having a rapid onset of action, and being short-acting. They also do not interact with food; however, they do undergo drug interactions and have limited reversibility. Randomised clinical trials have demonstrated non-inferiority for efficacy and safety in patients with haemodynamically stable PE.[108] Rivaroxaban and apixaban are used as single agents for treatment, whereas dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant for 5 to 10 days before they are started. Because of this, rivaroxaban and apixaban are often the preferred treatments in haemodynamically stable patients. » Fondaparinux is generally not recommended in haemodynamically unstable patients. LMWHs can be used interchangeably, in accordance with local protocols.[109] No difference in thromboembolism recurrence, haemorrhage, or overall mortality has been demonstrated between the different drugs in this class. » UFH is recommended for patients in whom primary reperfusion is being considered, as well as for those with serious renal impairment (i.e., creatinine clearance <30 mL/min), or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring, and its rapid reversal by protamine. » In pregnant women, LMWH instead of UFH is recommended for prevention and treatment.[55] For pregnant women with acute PE, it is suggested that anticoagulants be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55] » LMWH is recommended in patients with active malignancy.[110]

Acute

Patient group	Tx line	Treatment

» Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

» Warfarin is started at the same time as either UFH or LMWH and is continued until the INR is between 2 and 3 for 2 consecutive days, at which point the UFH or LMWH can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants. Warfarin is contraindicated in pregnant women.

Primary options

» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily

OR

Primary options

» apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily

OR

Primary options

» edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant

OR

Primary options

» dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant

OR

Primary options

» enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily
-and-
» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)

OR

Acute

Patient group	Tx line	Treatment
		Secondary options » dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » fondaparinux: patients <50 kg body weight: 5 mg subcutaneously once daily; patients 50-100 kg body weight: 7.5 mg subcutaneously once daily; patients >100 kg body weight: 10 mg subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban
no anticoagulation contraindication	**adjunct**	**oxygen** » Supplemental high-flow oxygen should be provided if oxygen saturation in room air is <92%, and vital signs should be monitored in case of decompensation.
anticoagulation contraindication, complication, or failure	**1st**	**inferior vena cava (IVC) filter placement** » Venous filters are indicated in patients with acute PE who have absolute or relative

Acute

Patient group	Tx line	Treatment
		contraindications to anticoagulants. In some cases with objectively confirmed recurrent PE despite adequate anticoagulation treatment, filter placement may be considered as a last resort to prevent a fatal event. » Observational studies suggest that insertion of a venous filter might reduce PE-related mortality rates in the acute phase with the benefit possibly coming at the cost of an increased risk of recurrence of venous thromboembolism.[124] [125] » Complications associated with permanent IVC filters are common, although they are rarely fatal.[125] Overall, early complications (which include insertion-site thrombosis) occur in approximately 10% of patients. Late complications are more frequent and include recurrent DVT (approximately 20% of patients) and post-thrombotic syndrome (up to 40% of patients).[126] [127] Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation.[127]
anticoagulation contraindication, complication, or failure	**adjunct**	**oxygen** » Supplemental high-flow oxygen should be provided if oxygen saturation in room air is <92%, and vital signs should be monitored in case of decompensation.
anticoagulation contraindication, complication, or failure	**adjunct**	**post-intervention anticoagulation** » Anticoagulation following placement of an inferior vena cava filter should be considered on a case-by-case basis according to the profile of relative and absolute contraindications.[128] » Anticoagulation should be initiated if the contraindication resolves or if a risk/benefit analysis suggests this to be a reasonable course.[101]

Ongoing

Patient group	Tx line	Treatment
no underlying malignancy (non-pregnant)	**1st**	**oral anticoagulant** » Following diagnosis, anticoagulant therapy is given for 3, 6, or 12 months, or for life based on

Ongoing

Patient group	Tx line	Treatment
		an assessment of the patient's risk factors and the underlying cause.[132] [133] [101] » If the patient is started on warfarin, once a therapeutic INR has been established, it is usually appropriate to stop administration of the parenteral anticoagulant. » If the patient was initially started on one of the direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) the patient should remain on this drug and is not transitioned to warfarin. Observational evidence and ad-hoc analysis from clinical trials suggest that these agents may be a safe and efficacious alternative for lifelong anticoagulation in patients with thrombophilia, recurrent venous thromboembolism, or cancer; however, there is still no robust prospective randomised clinical trial in these special populations. » The following may be used as a guide for duration of treatment for patients on warfarin: » PE secondary to provoked short-term cause: 3 months of anticoagulation with target INR 2.0 to 3.0.3[B]Evidence » Unprovoked PE: at least 6 to 12 months of anticoagulation is recommended for most people with first event. Lifetime anticoagulation should be considered in low bleeding risk patients. If warfarin is chosen as the method of anticoagulation, it is recommended to titrate conventional doses with target INR 2.0 to 3.0. » Initial PE with antiphospholipid antibody syndrome or two or more thrombophilic conditions: 12 or more months with consideration of lifelong warfarin with target INR 2.0 to 3.0. High-intensity therapy (INR 3.0 to 4.0) is not recommended for patients with antiphospholipid antibody syndrome. » Initial PE with one inherited thrombophilic disorder: at least 6 to 12 months of therapy with warfarin with goal INR 2.0 to 3.0 and consideration of lifelong therapy. » Two or more episodes of PE regardless of underlying risk factors: lifelong therapy with warfarin with target INR 2.0 to 3.0. **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
		OR
		Primary options
		» apixaban: 5 mg orally twice daily; 2.5 mg orally twice daily after completing at least 6 months treatment
		OR
		Primary options
		» rivaroxaban: 20 mg orally once daily; 10 mg orally once daily after completing at least 6 months treatment
		OR
		Primary options
		» edoxaban: body weight >60kg: 60 mg orally once daily; body weight ≤60 kg: 30 mg orally once daily
		OR
		Primary options
		» dabigatran: 150 mg orally twice daily
underlying malignancy (non-pregnant)	**1st**	**low molecular weight heparin (LMWH) for at least 3-6 months** » Patients with PE and underlying malignancy should be treated with LMWH for at least 3 to 6 months as LMWH has improved efficacy over warfarin in this patient group.[134] [110] After this time, the use of warfarin can be reconsidered and the chosen anticoagulant continued lifelong or until remission of the malignancy has been achieved. The decision between using LMWH and warfarin should take into account the balance of benefits and risks, and integrate the patient's values and preferences. **Primary options** » enoxaparin: 1 mg/kg subcutaneously every 12 hours; or 1.5 mg/kg subcutaneously once daily **OR** **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» dalteparin: 200 units/kg subcutaneously once daily, maximum 18,000 units/dose; or 100 units/kg subcutaneously every 12 hours **OR** **Secondary options** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)
pregnant	**1st**	**low molecular weight heparin (LMWH) for at least 6 weeks postnatal** » For pregnant women with acute VTE, anticoagulation with LMWH is recommended as warfarin is contraindicated in pregnant women and the safety of other anticoagulants is not well established in this population. » Anticoagulants should be continued for at least 6 weeks postnatal (for a minimum duration of therapy of 3 months).[55] **Primary options** » enoxaparin: 1 mg/kg subcutaneously every 12 hours; or 1.5 mg/kg subcutaneously once daily **OR** **Primary options** » dalteparin: 200 units/kg subcutaneously once daily, maximum 18,000 units/dose; or 100 units/kg subcutaneously every 12 hours
confirmed PE post-stabilisation: anticoagulation contraindication or failure, or risk of fatal PE	**1st**	**inferior vena cava (IVC) filter placement** » In patients where anticoagulant therapy is not possible because of active bleeding or the risk of bleeding, placement of an IVC filter is recommended. However, although deployment of IVC filters seems of theoretical benefit, their clinical efficacy and adverse-event profile is unclear.[101] [122] 4[C]Evidence » Filters should also be considered in patients where recurrent VTE occurs despite conventional anticoagulant therapy or where risk of subsequent PE is high. » Anticoagulation should be given when the risk of bleeding resolves.

Emerging

Andexanet alfa

Andexanet alfa is a specific reversal agent designed to neutralise the anticoagulant effects of both direct and indirect factor Xa inhibitors. It has been used in healthy older participants without evidence of clinical toxic effects.[135]

FOLLOW UP

Recommendations

Monitoring

Absence of right ventricular (RV) dysfunction and reference range levels of cardiac biomarkers suggest excellent prognosis, with mortality nearing 0% and predictive values for uncomplicated course of >93%.

Despite these values, RV strain and elevated cardiac biomarkers should not be used to justify escalation of therapy (thrombolysis, etc.) in the absence of haemodynamic instability.

For patients on IV heparin, activated partial thromboplastin time (aPTT) is measured:

- 6 hours after initiation of the infusion
- 6 hours after each adjustment in the dose
- At least once daily thereafter.

Target values for aPTT are based on the local laboratory's standardised aPTT values, which should correspond to a heparin level between 0.4 u/mL and 0.8 u/mL. Platelet counts are measured at baseline, day 3, and every other day thereafter.

During follow-up, frequent INR monitoring of patients who are treated with oral anticoagulant therapy is required. This should be done by experts or specialised anticoagulation clinics whenever possible.

Patients who discontinue warfarin do not need to be followed or monitored, unless they have ongoing symptoms or signs of post-phlebitic syndrome.

Direct-acting oral anticoagulants (i.e., apixaban, edoxaban, rivaroxaban, dabigatran) do not require routine monitoring with coagulation assays; however, monitoring of renal function prior to the initiation of therapy, as clinically indicated, and at least annually is suggested with these medications.

Patients with PE should be evaluated clinically over time to determine if they have unresolved PE with evidence of chronic thromboembolic pulmonary hypertension, which may occur in up to 4% of the patients.[140]

Patient instructions

Patients must be instructed carefully about the proper use of warfarin and the need for regular follow-up and monitoring of their INR. Patients must understand the following:

- Warfarin makes the blood more difficult to clot (it 'thins' the blood).
- The effect of the drug is not based on the size of the warfarin dose but, instead, it depends on the value of a blood clotting test called the INR.
- Warfarin dose frequently changes over time, and dosing that varies with the day of the week is very common (e.g., 4 mg on Monday, Wednesday, Friday, and Sunday; 5 mg on Tuesday, Thursday, and Saturday).
- The desired or target INR values are generally between 2 and 3 or 2.5 and 3.5.
- Many drugs interact with warfarin, so the physician/healthcare provider who oversees the warfarin treatment must be notified whenever a new medicine is started for the first time, or when a current medication is stopped.

- Diet changes can affect the INR, especially the intake of foods with high amounts of vitamin K; eating any amount of vegetables or greens is acceptable, so long as the intake is consistent from week to week.
- The INR must be checked (monitored) frequently, with blood tests sometimes several times a week and at least once a month.
- If a warfarin dose is missed in the morning or evening, it can and should be taken as soon as the mistake is recognised.
- Planned daily doses should be written down in a log book, and a note or check made after the dose is taken.
- A pill organiser can help.
- A portable monitor (point-of-care device) for the management of patients on oral anticoagulation allows self-testing by patients at home and can improve the quality of their oral anticoagulation therapy.[143]

Complications

Complications	Timeframe	Likelihood
acute bleeding during treatment	**short term**	**medium**
Most episodes result from a previously unrecognised pathological lesion, such as duodenal ulcer, angiodysplasia in the colon, microvascular disease (such as a striatal intracerebral bleed in a patient with hypertension), or rare conditions such as amyloid angiopathy in the CNS. Fresh frozen plasma (FFP) should be given promptly together with intravenous vitamin K. The effect of the FFP can be assessed immediately by measuring the INR. Repeat FFP administration might be necessary if the INR remains >1.5 and if the patient can tolerate the volume load. A small dose of activated factor VIIa should be considered if there is intracranial bleeding or massive GI bleeding. This dose reverses the effect of warfarin almost immediately and the effect lasts up to an hour. Prothrombin complex concentrates normalise coagulation in studies in normal volunteers given high-dose rivaroxaban or apixaban. It is not known whether this is the case with edoxaban, and it is not so for dabigatran; however, 60% of dabigatran can be removed by dialysis and dabigatran can be reversed with idarucizumab.[141]		
pulmonary infarction	**short term**	**low**
Localised necrosis of lung tissue, due to obstruction of the arterial blood supply. Pulmonary infarction is uncommon when emboli obstruct central arteries, but is frequent when distal arteries are occluded.		
cardiac arrest/death	**short term**	**low**
Cardiac arrest and death can result from ventricular collapse due to massive embolism and occlusion of the pulmonary vasculature. Mortality risk depends on haemodynamic stability and presence of right ventricular (RV) dysfunction on transthoracic echocardiography.1[B]Evidence		

FOLLOW UP

Complications	Timeframe	Likelihood
chronic thromboembolic pulmonary hypertension	**long term**	**low**
Occurs in approximately 1.5% of cases 2 years after presentation.[139] Two-year incidence of 4% in patients with either an initial or recurrent PE.[140] Minimal evidence exists that treatment modalities such as anticoagulation, systemic thrombolysis, catheter-directed thrombolysis, or surgical embolectomy affect the probability of developing this complication.		
heparin-associated thrombocytopenia	**long term**	**low**
The risk of heparin-associated thrombocytopenia is more duration-related than dose-related, and higher with unfractionated heparin (UFH) when used for an extended duration. The literature suggests that although heparin-associated thrombocytopenia is uncommon, the incidence can be minimised by use of a low molecular weight heparin or fondaparinux.[142]		
recurrent venous thromboembolic event	**variable**	**medium**
60% of recurrent venous thromboembolic events are PE in patients who have initially presented with PE. Only 20% of recurrent venous thromboembolic events are PE in patients who initially present with DVT.[137] Individuals with PE are 4 times more likely to die from recurrent venous thromboembolic events than individuals who presented with DVT alone.[138]		

Prognosis

Prognostic stratification may have significant clinical and therapeutic implications. The Pulmonary Embolism Severity Index (PESI) and other simplified versions such as the RIETE (Registro Informatizado de la Enfermedad TromboEmbolica venosa – Computerised registration of venous thromboembolism) score are commonly used.[73] Patients in the high-risk category have a high short-term (i.e., 30 day) mortality of up to 15%, whereas patients with a low severity index have a short-term mortality of 1% or lower, making early discharge or outpatient treatment a cost-effective therapeutic option. Very few clinical and laboratory tests have a strong prognosis value.

Mortality is often due to cardiogenic shock secondary to right ventricular (RV) collapse. The size of embolus required to cause RV strain and decrease cardiac output varies based on pre-existing cardiopulmonary status. In those without pre-existing cardiopulmonary disease, 25% to 30% of the pulmonary vasculature needs to be obstructed to cause an increase in mean pulmonary artery pressure.[19] A decrease in cardiac output is not seen in this population until over 50% of the pulmonary vasculature is obstructed. RV dysfunction has been shown to be a predictor of adverse outcomes and increased mortality in PE.[14] [20] [86]

Absence of RV dysfunction and reference range levels of cardiac biomarkers suggest excellent prognosis with mortality nearing 0% and predictive values for uncomplicated course of >93%.[87] [100]

Mortality rates in PE

- Haemodynamically unstable patients with a systolic BP <90 mmHg have a significantly increased mortality of 31% to 58% despite treatment.[13]

- A further subset of patients who are haemodynamically stable with evidence of RV dysfunction on transthoracic echo have an increased mortality that ranges from 2.2% to 8.7% when treated with anticoagulation alone.[20] [87] [90]
- In patients with acute PE, elevated D-dimer is associated with increased short-term and 3-month mortality, suggesting the potential of using this test for risk stratification as well as for diagnosis.[136]
- Haemodynamically stable patients with a systolic BP >90 mmHg have a low mortality, between 1% and 3%.[87] [100]

Diagnostic guidelines

Europe

Guidelines on the diagnosis and management of acute pulmonary embolism

Published by: European Society of Cardiology **Last published:** 2014

Clinical guidelines for testing for heritable thrombophilia

Published by: British Committee for Standards in Haematology **Last published:** 2010

EANM guidelines for ventilation/perfusion scintigraphy - Part 1 and Part 2

Published by: European Association of Nuclear Medicine **Last published:** 2009

Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis

Published by: Health Technology Assessment NHS R&D HTA Programme **Last published:** 2006

Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis

Published by: Health Technology Assessment NHS R&D HTA Programme **Last published:** 2006

North America

Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline

Published by: Interdisciplinary Expert Panel on Iliofemoral Deep Vein Thrombosis (InterEPID) **Last published:** 2015

Summary: This guideline provides a comprehensive overview of the diagnostic approach for this condition.

Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians

Published by: American College of Physicians **Last published:** 2015

Summary: This guideline provides a comprehensive overview of the diagnostic approach for this condition.

North America

An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy

Published by: American Thoracic Society; Society of Thoracic Radiology **Last published:** 2011

Summary: These evidence-based guidelines make strong recommendations for three specific scenarios (despite the low-quality evidence): performance of chest radiography (CXR) as the first radiation-associated procedure; use of lung scintigraphy as the preferred test in the setting of a normal CXR; and performance of computed tomographic pulmonary angiography (CTPA) rather than digital subtraction angiography (DSA) in a pregnant woman with a non-diagnostic ventilation-perfusion (V/Q) result.

Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians

Published by: American Academy of Family Physicians; American College of Physicians **Last published:** 2007

Summary: Provides diagnostic guidance on VTE including PE.

Treatment guidelines

Europe

Thrombosis and embolism in pregnancy and the puerperium: reducing the risk (Green-top guideline no. 37a)

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

Thrombosis and embolism in pregnancy and the puerperium: acute management (Green-top guideline no. 37b)

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

Venous thromboembolism: reducing the risk for patients in hospital

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: The guideline provides detailed recommendations for reducing the risk of deep vein thrombosis and PE in patients admitted to hospital.

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: For patients with PE and haemodynamic instability, unfractionated heparin (UFH) should be offered and thrombolytic therapy considered.

Europe

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Published by: National Institute for Health and Care Excellence **Last published:** 2014

Antithrombotics: indications and management

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2013

The investigation, management and prevention of venous thrombosis in children

Published by: British Committee for Standards in Haematology **Last published:** 2011

Summary: Provides recommendations for the investigation, management, and prevention of venous thrombosis in children.

EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients

Published by: European Academy of Neurology (European Federation of Neurological Societies) **Last published:** 2010

2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer

Published by: French National Federation of Cancer Centres **Last published:** 2009

Safety indicators for inpatient and outpatient oral anticoagulant care

Published by: British Committee for Standards in Haematology; National Patient Safety Agency **Last published:** 2007

Summary: Provides comprehensive recommendations for the safe use of oral anticoagulants.

Guidelines on the use of vena cava filters

Published by: British Committee for Standards in Haematology **Last published:** 2006

Summary: The guideline recommends the use of vena cava filters in PE as follows: 1. To prevent PE in patients with venous thromboembolism who have contraindications to anticoagulation. 2. Vena cava filters can be used in selected patients with PE who are receiving anticoagulation. 3. No particular type of filter is superior to another.

Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis

Published by: Health Technology Assessment NHS R&D HTA Programme **Last published:** 2005

International

Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH

Published by: International Society on Thrombosis and Haemostasis **Last published:** 2012

Summary: Provides guidance on deciding the duration of anticoagulation after a first episode of an unprovoked pulmonary embolus and/or deep vein thrombosis, defined as those occurring in the absence of an antecedent (within 3 months) surgical or non-surgical risk factor. The guidance does not apply to patients with an unprovoked thrombosis in unusual sites, such as the splanchnic or intracerebral veins, or cancer-associated venous thrombosis.

North America

Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report

Published by: American College of Chest Physicians **Last published:** 2016

Summary: Provides a comprehensive overview of the management of PE.

NCCN clinical practice guidelines in oncology: cancer-associated venous thromboembolic disease

Published by: National Comprehensive Cancer Network **Last published:** 2015

Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014

Published by: American Society of Clinical Oncology **Last published:** 2015

ACR-SIR practice guideline for the performance of inferior vena cava (IVC) filter placement for the prevention of pulmonary embolism

Published by: American College of Radiology; Society of Interventional Radiology **Last published:** 2014

Summary: Evidence-based guidelines for the performance of IVC filter placement for the prevention of PE.

Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Comprehensive guidelines that review the evidence and provide weighted recommendations on a range of practical management issues. Strong recommendations include targeting an international normalised ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy and not routinely using pharmacogenetic testing for guiding doses of vitamin K antagonist. Weak recommendations address issues such as loading doses, initiation overlap, monitoring frequency, vitamin K supplementation, patient self-management, weight and renal function adjustment of doses, dosing decision support, drug interactions to avoid, and prevention and management of bleeding complications.

North America

VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed.

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides recommendations for prevention and treatment of VTE in pregnant women and prevention of VTE in women with antiphospholipid antibody syndrome. For women with inherited thrombophilia and a history of pregnancy complications, or with two or more miscarriages but without APLA or thrombophilia, antithrombotic prophylaxis is not recommended.

Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed.

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides recommendations for prevention and treatment of VTE in neonates and children.

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension

Published by: American Heart Association **Last published:** 2011

Summary: This scientific statement makes recommendations for management and optimal medical decision-making incorporating other factors, including patient wishes, quality of life, and life expectancy based on age and comorbidities.

Quality improvement guidelines for the performance of inferior vena cava filter placement for the prevention of pulmonary embolism

Published by: Society of Interventional Radiology Standards of Practice Committee **Last published:** 2011

Summary: These guidelines have been compiled for use in quality improvement programmes for assessment of inferior vena cava (IVC) filter placement procedures. The most important parts of patient care include: patient selection, performing the procedure, and monitoring the patient. The outcome measures or indicators for these processes are indications, success rates, and complication rates. Outcome measures are assigned threshold levels.

Venous thromboembolism prophylaxis in hospitalized patients

Published by: American College of Physicians **Last published:** 2011

Summary: Evidence-based guideline providing clinical recommendations on prophylaxis of venous thromboembolism for hospitalised non-surgical patients (medical patients and patients with acute stroke).

North America

An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy

Published by: American Thoracic Society; Society of Thoracic Radiology **Last published:** 2011

Summary: Despite the low-quality evidence, strong recommendations were made for three specific scenarios: performance of chest radiography (CXR) as the first radiation-associated procedure; use of lung scintigraphy as the preferred test in the setting of a normal CXR; and performance of computed tomographic pulmonary angiography (CTPA) rather than digital subtraction angiography (DSA) in a pregnant woman with a non-diagnostic ventilation-perfusion (V/Q) result.

Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty

Published by: American Academy of Orthopaedic Surgeons **Last published:** 2011

Summary: Provides guidance on the prevention of VTE and PE in orthopaedic patients undergoing elective hip or knee arthroplasty.

Diagnostic evaluation and management of chronic thromboembolic pulmonary hypertension: a clinical practice guideline

Published by: Canadian Thoracic Society **Last published:** 2010

Summary: Provides evidence-based recommendations including screening for, diagnosis of, and treatment of chronic thromboembolic hypertension.

Practice parameters for the prevention of venous thrombosis

Published by: American Society of Colon and Rectal Surgeons **Last published:** 2006

Guidelines for deep venous thrombosis prophylaxis during laparoscopic surgery

Published by: Society of American Gastrointestinal and Endoscopic Surgeons **Last published:** 2006

Online resources

1. Hospital episode statistics, admitted patient care: England 2013-2014 *(external link)*

Evidence scores

1. Mortality rates in PE: there is medium-quality evidence for these findings. Haemodynamically stable patients with a systolic BP >90 mmHg have a low mortality, between 1% and 3%.[87] [100] Haemodynamically unstable patients with a systolic BP <90 mmHg have a significantly increased mortality of 31% to 58%.[13] A further subset of patients who are haemodynamically stable with evidence of right ventricular (RV) dysfunction on transthoracic echo have an increased mortality that ranges from 2.2% to 8.7% when treated with anticoagulation alone.[20] [87] [90]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

2. Mortality rates and embolectomy: there is poor-quality evidence that supports consistent reduction in mortality with this intervention. Mortality rates vary from 16% to 57% in haemodynamically unstable people according to centre.[120] [121]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

3. Recurrence of venous thromboembolism: there is medium-quality evidence that prolonged anticoagulation (6-9 months) may not reduce recurrence of venous thromboembolism compared with shorter anticoagulation (3 months) in pulmonary embolism.
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

4. z`Venous thromboembolism (VTE), future morbidity, and inferior vena cava (IVC) filters: there is poor-quality evidence for this intervention, which has mainly been studied with concomitant anticoagulation.[128]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

REFERENCES

Key articles

- Wood KE. The presence of shock defines the threshold to initiate thrombolytic therapy in patients with pulmonary embolism. Intensive Care Med. 2002;28:1537-1546. Abstract
- Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e691S-e736S. Full text Abstract
- Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200-1208. Full text Abstract
- Baglin T, Bauer K, Douketis J, et al; SSC of the ISTH. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. J Thromb Haemost. 2012;10:698-702. Full text Abstract
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e419S-e494S. Full text Abstract

References

1. Cervantes J, Rojas G. Virchow's legacy: deep vein thrombosis and pulmonary embolism. World J Surg. 2005;29(Suppl 1):S30-S34. Abstract
2. Huisman MV, Büller HR, ten Cate JW, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest. 1989;95:498-502. Full text Abstract
3. Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. Am J Med. 1977;62:355-360. Abstract
4. Dentali F, Ageno W, Becattini C, et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. Thromb Res. 2010;125:518-522. Abstract
5. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest. 1995;108:978-981. Full text Abstract
6. Nordstrom M, Lindblad B, Bergqvist D, et al. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232:155-160. Abstract
7. Ho WK, Hankey GJ, Eikelboom JW. The incidence of venous thrombembolism: a prospective, community-based study in Perth, Western Australia. Med J Aust. 2008;189:144-147. Abstract

8. Stein PD, Hull RD, Ghali WA, et al. Tracking the uptake of evidence: two decades of hospital practice trends for diagnosing deep vein thrombosis and pulmonary embolism. Arch Intern Med. 2003;163:1213-1219. Full text Abstract

9. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch Intern Med. 2003;163:1711-1717. Full text Abstract

10. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA. 1990;263:2753-2759. Abstract

11. Stein PD, Huang HI, Afzal A, et al. Incidence of acute pulmonary embolism in a general hospital: relation to age, sex, and race. Chest. 1999;116:909-913. Full text Abstract

12. Stein PD, Hull RD, Patel KC, et al. Venous thromboembolic disease: comparison of the diagnostic process in blacks and whites. Arch Intern Med. 2003;163:1843-1848. Full text Abstract

13. Wood KE. The presence of shock defines the threshold to initiate thrombolytic therapy in patients with pulmonary embolism. Intensive Care Med. 2002;28:1537-1546. Abstract

14. Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation. 1997;96:882-888. Full text Abstract

15. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. BMJ. 1992;305:567-574. Full text Abstract

16. Levy MM, Albuquerque F, Pfeifer JD. Low incidence of pulmonary embolism associated with upper-extremity deep venous thrombosis. Ann Vasc Surg. 2012;26:964-972. Abstract

17. Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. J Clin Pathol. 1974;27:517-528. Full text Abstract

18. Paterson JC, McLachlin J. Precipitating factors in venous thrombosis. Surg Gynec Obstet. 1954;98:96-102. Abstract

19. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol. 1971;28:288-294. Abstract

20. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-1389. Abstract

21. Zöller B, Li X, Sundquist J, et al. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation. 2011;124:1012-1020. Abstract

22. Martínez-Zamora MÁ, Cervera R, Balasch J. Thromboembolism risk following recurrent miscarriage. Expert Rev Cardiovasc Ther. 2013;11:1503-1513. Abstract

23. James AH, Jamison MG, Brancazio LR, et al. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006;194:1311-1315. Abstract

24. ten Wolde M, Kraaijenhagen RA, Schiereck J, et al. Travel and the risk of symptomatic venous thromboembolism. Thromb Haemost. 2003;89:499-505. Abstract

25. Gavish I, Brenner B. Air travel and the risk of thromboembolism. Intern Emerg Med. 2011;6:113-116. Abstract

26. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107:I-9-I-16. Full text

27. Goldhaber SZ, Schoepf UJ. Pulmonary embolism after coronary artery bypass grafting. Circulation. 2004;109:2712-2715. Full text Abstract

28. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008;168:2377-2381. Full text Abstract

29. Doyle BJ, Rihal CS, Gastineau DA, et al. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol. 2009;53:2019-2027. Full text Abstract

30. Farley TM, Meirik O, Chang CL, et al. Effects of different progestogens in low estrogen oral contraceptives on venous thromboembolic disease. Lancet. 1995;346:1582-1588.

31. Reid R, Leyland N, Wolfman W, et al. SOGC clinical practice guidelines: oral contraceptives and the risk of venous thromboembolism: an update. No. 252, December 2010. Int J Gynaecol Obstet. 2011;112:252-256. Abstract

32. Martínez F, Ramírez I, Pérez-Campos E, et al. Venous and pulmonary thromboembolism and combined hormonal contraceptives. Systematic review and meta-analysis. Eur J Contracept Reprod Health Care. 2012;17:7-29. Abstract

33. Watson HG, Baglin TP. Guidelines on travel-related venous thrombosis. Br J Haematol. 2011;152:31-34. Abstract

34. Kuzu MA, Ozaslan C, Koksoy C, et al. Vascular involvement in Behcet's disease: 8-year audit. World J Surg. 1994;18:948-953. Abstract

35. Murin S, Marelich GP, Arroliga AC, et al. Hereditary thrombophilia and venous thromboembolism. Am J Respir Crit Care Med. 1998;158:1369-1373. Full text Abstract

36. De Stefano V, Chiusolo P, Paciaroni K, et al. Epidemiology of factor V Leiden: clinical implications. Semin Thromb Hemost. 1998;24:367-379. Abstract

37. Rosendaal FR, Koster T, Vandenbroucke JP, et al. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood. 1995;85:1504-1508. Full text Abstract

38. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, et al. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. Blood. 2012;120:933-946. Full text Abstract

39. Martinelli I, Battaglioli T, Razzari C, et al. Type and location of venous thromboembolism in patients with factor V Leiden or prothrombin G20210A and in those with no thrombophilia. J Thromb Haemost. 2007;5:98-101. Abstract

40. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med. 2002;346:752-763. Abstract

41. Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med. 2007;146:278-288. Abstract

42. White RH, Gettner S, Newman JM, et al. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med. 2000;343:1758-1764. Full text Abstract

43. Kaboli P, Henderson MC, White RH. DVT prophylaxis and anticoagulation in the surgical patient. Med Clin North Am. 2003;87:77-110. Abstract

44. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793-800. Full text Abstract

45. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-879. Full text Abstract

46. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ. 2006;332:325-329. Full text Abstract

47. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med. 2010;153:8-18. Abstract

48. Muntz J. Duration of deep vein thrombosis prophylaxis in the surgical patient and its relation to quality issues. Am J Surg. 2010;200:413-421. Abstract

49. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e1S-e23S. Abstract

50. Bump GM, Dandu M, Kaufman SR, et al. How complete is the evidence for thromboembolism prophylaxis in general medicine patients? A meta-analysis of randomized controlled trials. J Hosp Med. 2009;4:289-297. Abstract

51. Philbrick JT, Shumate R, Siadaty MS, et al. Air travel and venous thromboembolism: a systematic review. J Gen Intern Med. 2007;22:107-114. Full text Abstract

52. Agarwal VP, Phung OJ, Tongbram V, et al. Statin use and the prevention of venous thromboembolism: a meta-analysis. Int J Clin Pract. 2010;64:1375-1383. Abstract

53. Debourdeau P, Kassab CD, Le GG, et al. 2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer: report from the working group. Ann Oncol. 2009;20:1459-1471. Full text Abstract

54. Kidane B, Madani AM, Vogt K, et al. The use of prophylactic inferior vena cava filters in trauma patients: a systematic review. Injury. 2012;43:542-547. Abstract

55. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e691S-e736S. Full text Abstract

56. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol. 2011;57:700-706. Full text Abstract

57. Miniati M, Prediletto R, Formichi B, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med. 1999;159:864-871. Full text Abstract

58. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med. 1998;129:997-1005. Abstract

59. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest. 1997;112:974-979. Full text Abstract

60. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-420. Abstract

61. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144:165-171. Abstract

62. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med. 2011;154:709-718. Full text Abstract

63. Raja AS, Greenberg JO, Qaseem A, et al. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015;163:701-711. Full text Abstract

64. Righini M, Perrier A, De Moerloose P, et al. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost. 2008;6:1059-1071. Full text Abstract

65. Dunn KL, Wolf JP, Dorfman DM, et al. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. J Am Coll Cardiol. 2002;40:1475-1478. Abstract

66. Carrier M, Righini M, Djurabi RK, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism: a systematic review of management outcome studies. Thromb Haemost. 2009;101:886-892. Full text Abstract

67. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352:1760-1768. Full text Abstract

68. Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200-1208. Full text Abstract

69. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost. 2010;8:1716-1722. Full text Abstract

70. Arnold RW, Janitz E, Poulton TB, et al. Pulmonary CT angiography to evaluate for pulmonary embolism in children visiting adult-centered community hospitals. AJR Am J Roentgenol. 2011;196:W823-W830. Full text Abstract

71. Clemens S. Newer modalities for detection of pulmonary emboli. Am J Med. 2007;120(10 Suppl 2):S2-S12. Abstract

72. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. J Thromb Haemost. 2013;11:412-422. Abstract

73. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172:1041-1046. Full text Abstract

74. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378:41-48. Abstract

75. Cavallazzi R, Nair A, Vasu T, et al. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008;34:2147-2156. Abstract

76. Wicki J, Perneger TV, Junod AF, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med. 2001;161:92-97. Full text Abstract

77. Sukhija R, Aronow WS, Ahn C, et al. Electrocardiographic abnormalities in patients with right ventricular dilation due to acute pulmonary embolism. Cardiology. 2006;105:57-60. Abstract

78. Stein PD, Goldhaber SZ, Henry JW, et al. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. Chest. 1996;109:78-81. Abstract

79. Worsley DF, Alavi A, Aronchick JM, et al. Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study. Radiology. 1993;189:133-136. Abstract

REFERENCES

80. van Belle A, Buller HR, Huisman MV, et al; Writing Group for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006;295:172-179. Full text Abstract

81. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354:2317-2327. Full text Abstract

82. Chen MM, Coakley FV, Kaimal A, et al. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008;112:333-340. Abstract

83. Bajc M, Bitzen U, Olsson B, et al. Lung ventilation/perfusion SPECT in the artificially embolized pig. J Nucl Med. 2002;43:640-647. Full text Abstract

84. Reinartz P, Wildberger JE, Schaefer W, et al. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med. 2004;45:1501-1508. Full text Abstract

85. Reinartz P, Kaiser HJ, Wildberger JE, et al. SPECT imaging in the diagnosis of pulmonary embolism: automated detection of match and mismatch defects by means of image-processing techniques. J Nucl Med. 2006;47:968-973. Full text Abstract

86. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000;101:2817-2822. Full text Abstract

87. Vieillard-Baron A, Page B, Augarde R, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. Intensive Care Med. 2001;27:1481-1486. Abstract

88. Gibson NS, Sohne M, Buller HR. Prognostic value of echocardiography and spiral computed tomography in patients with pulmonary embolism. Curr Opin Pulm Med. 2005;11:380-384. Abstract

89. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomized trial assessing right-ventricular function and pulmonary perfusion. Lancet. 1993;341:507-511. Abstract

90. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143-1150. Full text Abstract

91. Kruger S, Graf J, Merx MW, et al. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J. 2004;147:60-65. Abstract

92. Sohne M, ten Wolde M, Buller HR. Biomarkers in pulmonary embolism. Curr Opin Cardiol. 2004;19:558-562. Abstract

93. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation. 2003;107:2545-2547. Full text Abstract

94. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation. 2002;106:1263-1268. Full text Abstract

95. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. Circulation. 2004;109:2160-2167. Full text Abstract

96. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;85:462-468. Abstract

97. Stein PD. Fever in acute pulmonary embolism. Chest. 2000;117:39-42. Abstract

98. Rutschmann OT, Cornuz J, Poletti PA, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? Thorax. 2007;62:121-125. Abstract

99. Tillie-Leblond I, Marquette CH, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med. 2006;144:390-396. Abstract

100. Tow DE, Wagner HN. Urokinase pulmonary embolism trial: Phase I results. JAMA. 1970;214:2163-2172.

101. Kearon C, Akl EA, Ornelas J, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315-352. Full text Abstract

102. Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review. Ann Emerg Med. 2012;60:651-662.e4. Abstract

103. Soar J, Nolan JP, Böttiger BW, et al; Adult advanced life support section collaborators. European Resuscitation Council Guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation. 2015;95:100-147.

104. Colquhoun MC, Handley AJ, Evans TR, eds. ABC of resuscitation. 5th ed. Wiley-Blackwell; 2003.

105. Mercat A, Diehl JL, Meyer G, et al. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. Crit Care Med. 1999;27:540-544. Abstract

106. Manier G, Castaing Y. Influence of cardiac output on oxygen exchange in acute pulmonary embolism. Am Rev Respir Dis. 1992;145:130-136. Abstract

107. Aissaoui N, Martins E, Mouly S, et al. A meta-analysis of bed rest versus early ambulation in the management of pulmonary embolism, deep vein thrombosis, or both. Int J Cardiol. 2009;137:37-41. Abstract

108. Galanis T, Keiffer G, Merli G. The new oral anticoagulants for the treatment of venous thromboembolism: a new paradigm shift in antithrombotic therapy. Curr Ther Res Clin Exp. 2014;76:76-83. Full text Abstract

109. Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160:181-188. Full text Abstract

110. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33:654-656. Full text Abstract

111. Urokinase-streptokinase pulmonary embolism trial: Phase II results. JAMA. 1974;229:1606-1613. Abstract

112. Uflacker R. Interventional therapy for pulmonary embolism. J Vasc Interv Radiol. 2001;12:147-164. Abstract

113. De Gregorio MA, Gimeno MJ, Mainar A, et al. Mechanical and enzymatic thrombolysis for massive pulmonary embolism. J Vasc Interv Radiol. 2002;13:163-169. Abstract

114. Kuo WT, Gould MK, Louie JD, at al. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol. 2009;20:1431-1440. Abstract

115. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010;125:e82-e86. Abstract

116. Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol. 1998;82:966-970. Abstract

117. Konstantinides SV, Torbicki A, Agnelli G, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033-3069. Full text Abstract

118. Van de Werf F, Ardissino D, Betriu A, et al; task force on the management of acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2003;24:28-66. Full text Abstract

119. Engelberger RP, Kucher N. Catheter-based reperfusion treatment of pulmonary embolism. Circulation. 2011;124:2139-2144. Full text Abstract

120. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: Results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg. 2005;129:1018-1023. Abstract

121. Digonnet A, Moya-Plana A, Aubert S, et al. Acute pulmonary embolism: a current surgical approach. Interact Cardiovasc Thorac Surg. 2007;6:27-29. Full text Abstract

122. Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. Cochrane Database Syst Rev. 2010;(2):CD006212. Full text Abstract

123. American College of Radiology; Society of Interventional Radiology. ACR-SIR practice parameter for the performance of inferior vena cava (IVC) filter placement for the prevention of pulmonary embolism. 2014. http://www.acr.org/ (last accessed 30 June 2016). Full text

124. Stein PD, Matta F, Keyes DC, et al. Impact of vena cava filters on in-hospital case fatality rate from pulmonary embolism. Am J Med. 2012;125:478-484. Full text Abstract

125. Muriel A, Jiménez D, Aujesky D, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol. 2014;63:1675-1683. Abstract

126. Rajasekhar A, Streiff MB. Vena cava filters for management of venous thromboembolism: a clinical review. Blood Rev. 2013;27:225-241. Abstract

127. PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation. 2005;112:416-422. Full text Abstract

128. Decousus H, Leizorovicz A, Parent F, et al; Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med. 1998;338:409-416. Full text Abstract

129. Hao Q, Dong BR, Yue J, et al. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2015;(9):CD004437. Full text Abstract

130. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014;311:2414-2421. Full text Abstract

131. Angel de Gregorio M, Laborda A, de Blas I, et al. Endovascular treatment of a haemodynamically unstable massive pulmonary embolism using fibrinolysis and fragmentation: experience with 111 patients in a single centre - why don't we follow ACCP recommendations? Arch Bronconeumol. 2011;47:17-24. Full text Abstract

132. Baglin T, Bauer K, Douketis J, et al; SSC of the ISTH. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. J Thromb Haemost. 2012;10:698-702. Full text Abstract

133. Baglin T, Gray E, Greaves M, et al; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010;149:209-220. Full text Abstract

134. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e419S-e494S. Full text Abstract

135. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-2424. Abstract

136. Becattini C, Lignani A, Masotti L, et al. D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis. 2012;33:48-57. Abstract

137. Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep vein thrombosis or pulmonary embolism. Thromb Haemost. 2002;88:407-414. Abstract

138. Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA. 1998;279:458-462. Abstract

139. Becattini C, Agnelli G, Pesavento R, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006;130:172-175. Full text Abstract

140. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257-2264. Full text Abstract

141. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342-2352. Full text Abstract

142. Pitlick JM, Crannage A, Murphy J. Use of low-molecular-weight heparin for the treatment of venous thromboembolism in patients with cancer: A review of the literature. J Pharm Technol. 2009;25:244-249.

143. Garcia-Alamino JM, Ward AM, Alonso-Coello CP, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev. 2010;(4):CD003839. Full text Abstract

144. Becattini C, Agnelli G, Schenone A, et al; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959-1967. Full text Abstract

Images

Wells' score	Original	Simplified
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1

Figure 1: The difference between the scores in the original modified Wells' score and the simplified version

Created by the BMJ Evidence Centre team

Geneva score	Original	Simplified
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Previous PE or DVT	3	1
Heart rate 75-94 bpm ≥95 bpm	3 5	1 2
Unilateral limb pain	3	1
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active cancer	2	1
Age >65 years	1	1
Clinical probability*		
PE unlikely	≤5	≤2
PE likely	>5	>2

* The revised Geneva score was formerly available as 3-category scheme (i.e., 0-3 = low probability of PE; 4-10 = intermediate probability of PE; and ≥11 = high probability of PE), but was recently made into the 2-category scheme shown above.

Figure 2: The difference between the scores in the original revised Geneva score and the simplified version

Created by the BMJ Evidence Centre team

Clinical probability score	D-dimer level	Action
PE unlikely	Normal	Diagnosis ruled out; no further testing required
	Abnormal	Imaging required
PE likely	Normal	Imaging required
	Abnormal	Imaging required

Figure 3: Summary of clinical action required based on clinical probability score and D-dimer level result

Created by the BMJ Evidence Centre team

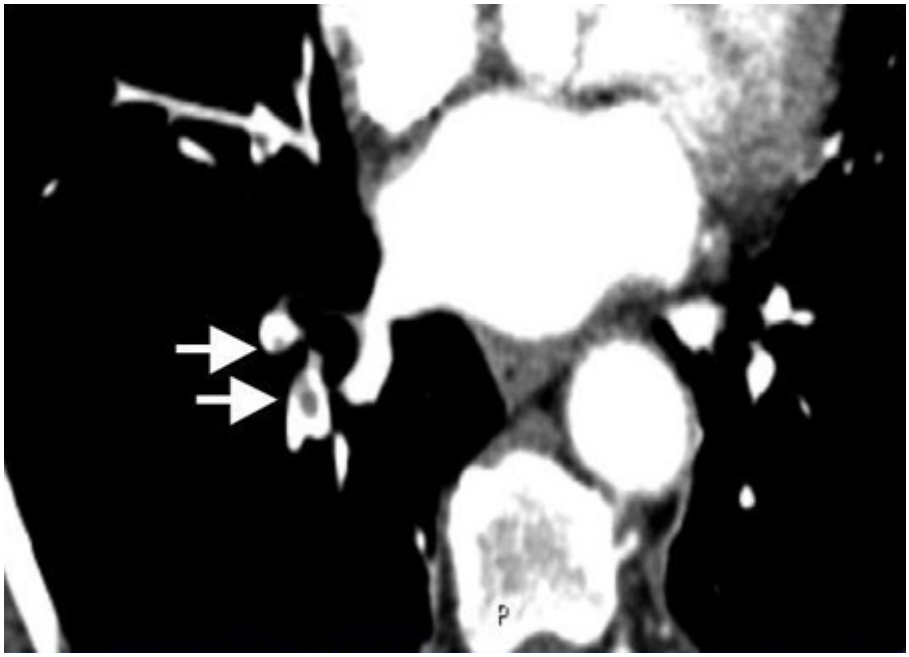

Figure 4: Contrasted CTPA scan showing subsegmental right pulmonary artery emboli (see arrows)

From the collection of Seth W. Clemens; used with permission

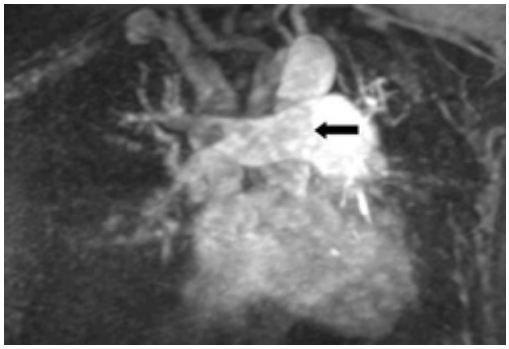

Figure 5: Gd-MRA showing a right main pulmonary artery pulmonary embolism (see arrow)

From the collection of Seth W. Clemens; used with permission

Disclaimer

This content is meant for medical professionals situated outside of the United States and Canada. The BMJ Publishing Group Ltd ("BMJ Group") tries to ensure that the information provided is accurate and up-to-date, but we do not warrant that it is nor do our licensors who supply certain content linked to or otherwise accessible from our content. The BMJ Group does not advocate or endorse the use of any drug or therapy contained within nor does it diagnose patients. Medical professionals should use their own professional judgement in using this information and caring for their patients and the information herein should not be considered a substitute for that.

This information is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition such standards and practices in medicine change as new data become available, and you should consult a variety of sources. We strongly recommend that users independently verify specified diagnosis, treatments and follow up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the agent to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region. This information is provided on an "as is" basis and to the fullest extent permitted by law the BMJ Group and its licensors assume no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information.

View our full Website Terms and Conditions.

Contributors:

// Authors:

Geno Merli, MD

Professor of Medicine and Surgery
Section of Vascular Medicine, Department of Surgery, Co-Director, Jefferson Vascular Center, Sidney Kimmel Medical College at Thomas Jefferson University, Thomas Jefferson University Hospitals, Philadelphia, PA
DISCLOSURES: GM has received grants or research support from BMS, J&J, Sanofi-Aventis, Portola, and Janssen; he has served as a Scientific Consultant for BMS, J&J, and Sanofi-Aventis.

Luis H. Eraso, MD, MPH

Assistant Professor of Medicine and Surgery
Section of Vascular Medicine, Department of Surgery, Sidney Kimmel Medical College at Thomas Jefferson University, Thomas Jefferson University Hospitals, Philadelphia, PA
DISCLOSURES: LHE declares that he has no competing interests.

Taki Galanis, MD

Assistant Professor of Medicine and Surgery
Section of Vascular Medicine, Department of Surgery, Sidney Kimmel Medical College at Thomas Jefferson University, Thomas Jefferson University Hospitals, Philadelphia, PA
DISCLOSURES: TG declares that he has no competing interests.

Geoffrey Ouma, DO

Assistant Professor of Medicine and Surgery
Section of Vascular Medicine, Department of Surgery, Sidney Kimmel Medical College at Thomas Jefferson University, Thomas Jefferson University Hospitals, Philadelphia, PA
DISCLOSURES: GO declares that he has no competing interests.

// Acknowledgements:

Dr Geno Merli, Dr Luis H. Eraso, Dr Taki Galanis, and Dr Geoffrey Ouma would like to gratefully acknowledge Dr Miguel Angel de Gregorio, Dr Alicia Laborda, and Dr Seth W. Clemens, previous contributors to this monograph. MAG, AL, and SWC declare that they have no competing interests.

// Peer Reviewers:

Keith Wille, MD, MSPH

Associate Professor of Medicine
University of Alabama at Birmingham, Birmingham, AL
DISCLOSURES: KW declares that he has no competing interests.

John R. Charpie, MD, PhD

Associate Professor of Pediatrics
Medical Director, Pediatric Cardiothoracic Intensive Care Unit, University of Michigan Congenital Heart Center, C.S. Mott Children's Hospital, Ann Arbor, MI
DISCLOSURES: JRC declares that he has no competing interests.

Contributors:

Sanjeev Wasson, MD

Advanced Clinical Fellow
Cleveland Clinic Foundation, Cleveland, OH
DISCLOSURES: SW declares that he has no competing interests.

David Jimenez, MD, PhD

Respiratory Physician and Associate Professor
Ramón y Cajal Hospital and Alcalá de Henares University, Respiratory Department and Medicine Department, Madrid, Spain
DISCLOSURES: DJ has received consulting fees from Boehringer Ingelheim, Bayer, Leo-Pharm, and Rovi, and lecture fees from Sanofi Aventis.