ESC guidelines of acute pulmonary embolism

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Epidemiology

- Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most frequent cardiovascular disease with an ***overall annual incidence of 100–200 per 100,000 inhabitants.***
- Overall, PE is a major cause of mortality, morbidity, and hospitalization in Europe.
- As estimated on the basis of an epidemiological model, over ***317 000 deaths*** were related to ***VTE*** in six countries of the European Union (with a total population of 454.4 million) in 2004.
- Of these cases, ***34%*** presented with ***sudden fatal PE*** and 59% were deaths resulting from PE that remained undiagnosed during life; ***only7%***of the patients who died early were ***correctly diagnosed with PE before death.***

Predisposing factors

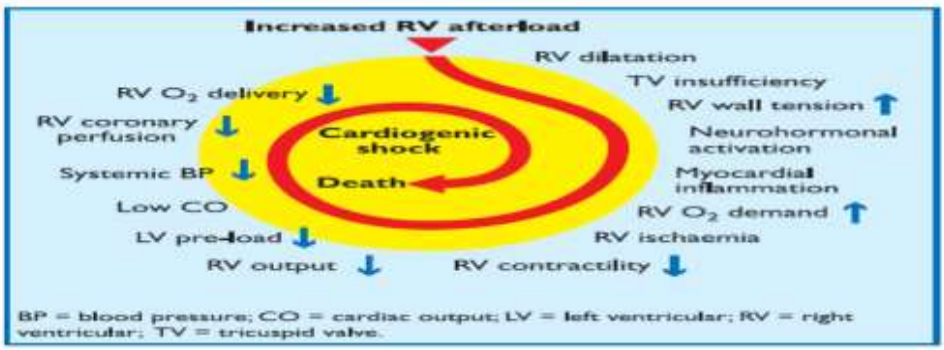
- VTE is considered to be a consequence of the interaction between patient-related—usually permanent—risk factors and setting-related—usually temporary—risk factors.
- VTE is considered to be ***'provoked'*** in the presence of a temporary or reversible risk factor (such as surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy) within the last 6 weeks to 3 months before diagnosis.
- It is ***'unprovoked'*** in the absence of these factors.
- PE may also occur in the absence of any known risk factor

Natural history

- The risk of ***VTE is highest during the first two post-operative weeks*** but remains elevated for two to three months.
- ***Antithrombotic prophylaxis significantly reduces the risk of perioperative VTE***.
- Registries and hospital discharge datasets of unselected patients with PE or VTE yielded 30-day all-cause mortality rates between 9% and 11%, and three-month mortality ranging between 8.6% and 17%.

- ***The rate of recurrence is highest during the first two weeks and declines thereafter.*** During the early period, active cancer and failure to rapidly achieve therapeutic levels of anticoagulation appear to independently predict an increased risk of recurrence.
- Recurrence is more frequent after multiple VTE episodes as opposed to a single event, and after unprovoked VTE as opposed to the presence of temporary risk factors, particularly surgery.
- It is also more frequent in women who continue hormone intake after a VTE episode, and in patients who have suffered PE or proximal vein thrombosis compared to distal (calf) vein thrombosis.

Pathophysiology



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ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

Diagnosis

Table 3 Clinical characteristics of patients with suspected PE in the emergency department (adapted from Pollack *et al.* (2011)).[82]

Feature	PE confirmed (n = 1880)	PE not confirmed (n = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

Assessment of clinical probability

Wells rule	Original version[9]	Simplified version[10]
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

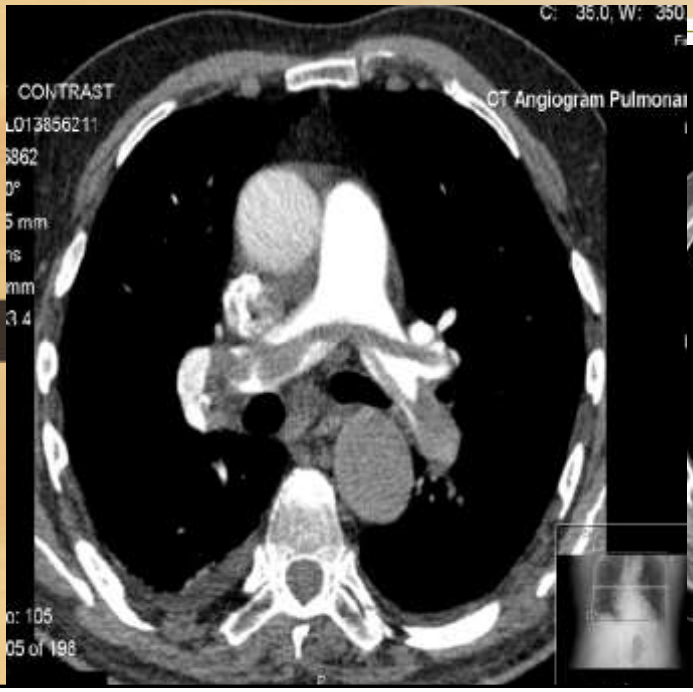
Revised Geneva score	Original version[9]	Simplified version[10]
Previous PE or DVT	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2

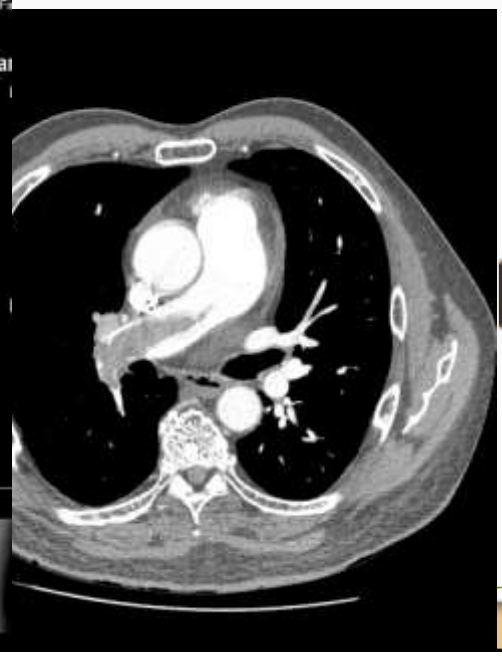
D-dimer testing

- In the emergency department, a negative ELISA D-dimer, in combination with clinical probability, ***can exclude the disease without further testing in approximately 30% of patients with suspected PE.***

Computed tomographic pulmonary angiography

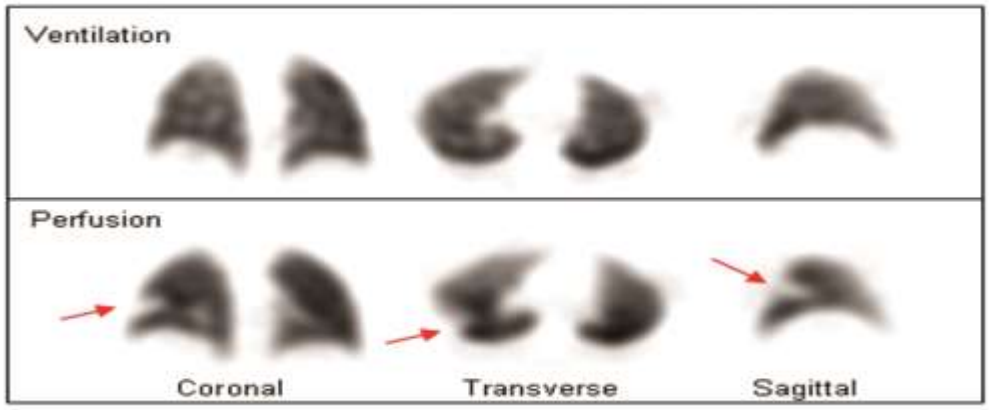
- Multi-detector computed tomographic (MDCT) angiography with high spatial and temporal resolution ***has become the method of choice*** for imaging the pulmonary vasculature in patients with suspected PE.
- It allows ***adequate visualization of the pulmonary arteries down to at least the segmental level***





Lung scintigraphy

- Ventilation–perfusion scintigraphy (V/Q scan) is an ***established diagnostic test for suspected PE. It is safe and few allergic reactions have been described.***
- Being a radiation- and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in outpatients with low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnancy, in patients with history of contrast medium-induced anaphylaxis and strong allergic history, in severe renal failure, and in patients with myeloma and paraproteinaemia.



Pulmonary angiography

- Pulmonary angiography ***has for decades remained the 'gold standard'*** for the diagnosis or exclusion of PE, but is ***rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy.***
- Pulmonary angiography is more often used to guide percutaneous catheter-directed treatment of acute PE.

Echocardiography

- Echocardiographic findings—based either on a ***disturbed RV ejection pattern or on depressed contractility of the RV free wall compared with the RV apex ('McConnell sign')—were reported to retain a high positive predictive value for PE***, even in the presence of pre-existing cardiorespiratory disease.
- Additional echocardiographic signs of pressure overload may be required to avoid a false diagnosis of acute PE in patients with RV free wall hypokinesia or akinesia due to RV infarction, which may mimic the McConnell sign.
- Measurement of the tricuspid annulus plane systolic excursion (TAPSE)may also be useful.

Laboratory tests and biomarkers

1) Markers of right ventricular dysfunction:

- In normotensive patients with PE, the positive predictive value of elevated BNP or NT-proBNP concentrations for early mortality is low.
- NT-proBNP plasma concentrations of ***600 pg/mL*** were identified ***as the optimal cut-off value for the identification of elevated risk .***
- On the other hand, low levels of BNP or NT-proBNP can identify patients with a favourable short-term clinical outcome based on their high negative predictive value.

2) Markers of myocardial injury

- Elevated ***plasma troponin*** concentrations on admission have been reported in connection with PE and were associated with ***worse prognosis***.

3) Other (non-cardiac) laboratory biomarkers:

- Elevated serum creatinine levels and a decreased (calculated) glomerular filtration rate are related to 30-day all-cause mortality in acute PE.

Clinical classification of pulmonary embolism severity

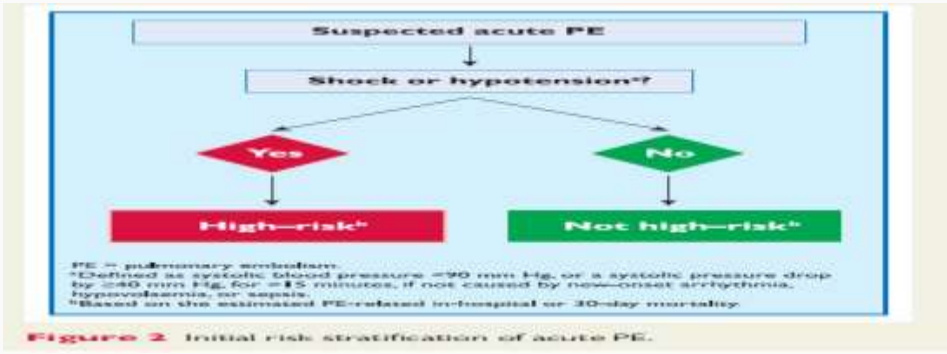
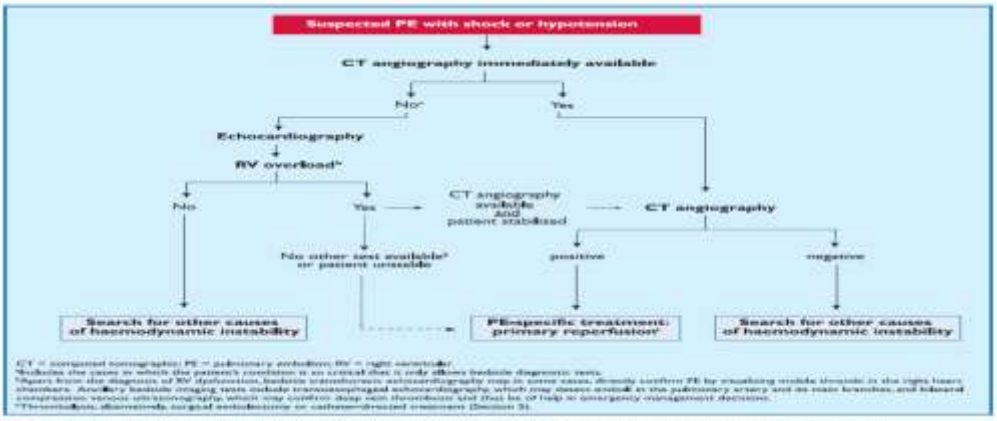
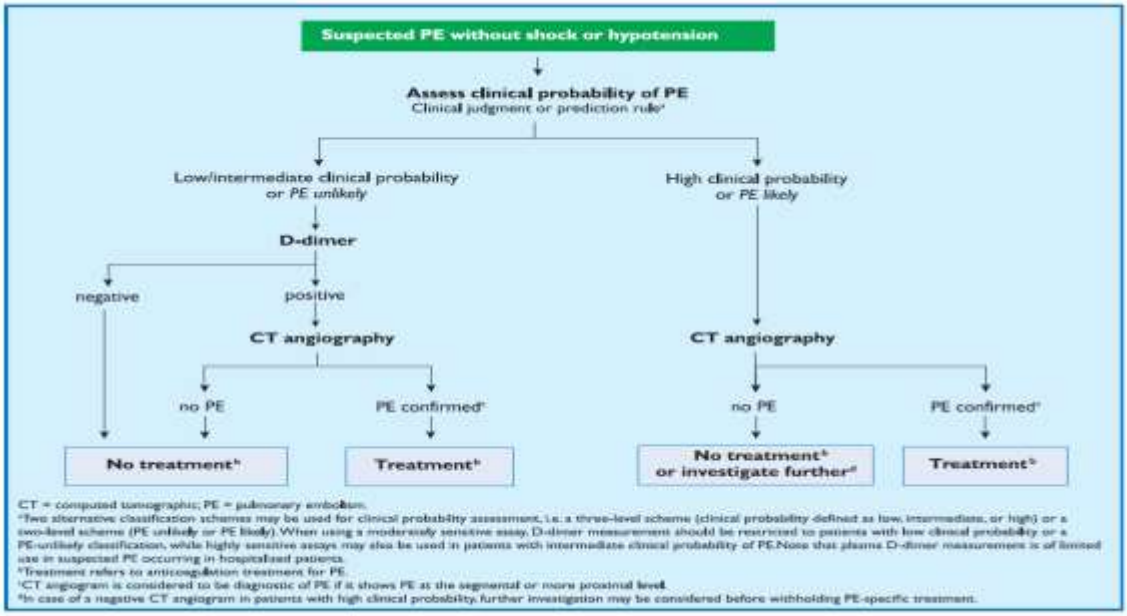


Figure 2 Initial risk stratification of acute PE.

Diagnostic strategies



gure 3 Proposed diagnostic algorithm for patients with suspected high-risk PE, i.e. presenting with shock or hypotension.



CT = computed tomographic; PE = pulmonary embolism.
[a]Two alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients.
[b]Treatment refers to anticoagulation treatment for PE.
[c]CT angiogram is considered to be diagnostic of PE if it shows PE at the segmental or more proximal level.
[d]In case of a negative CT angiogram in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment.

Figure 4 Proposed diagnostic algorithm for patients with suspected not high-risk pulmonary embolism.

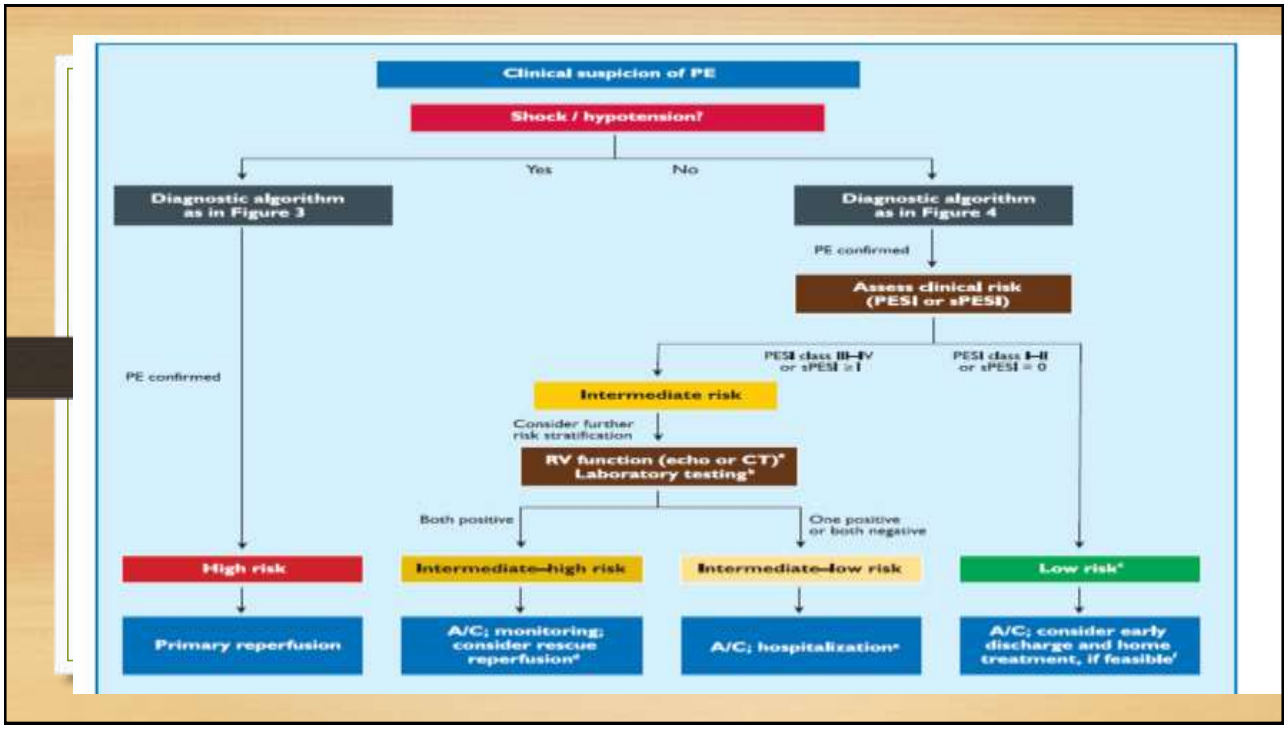
Risk stratification

Table 7 Original and simplified PESI

Parameter	Original version[7,8]	Simplified version[7,8]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk stratification*	
	Class I: ≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

b.p.m. = beats per minute; PESI = Pulmonary embolism severity index.
*Based on the sum of points.

Treatment



Treatment in the acute phase

- ***Haemodynamic and respiratory support:***
- Modest (500 mL) fluid challenge may help to increase cardiac index in patients with PE, low cardiac index, and normal BP.
- Use of vasopressors is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment.
- Norepinephrine appears to improve RV function via a direct positive inotropic effect, while also improving RV coronary perfusion by peripheral vascular alpha-receptor stimulation and the increase in systemic BP.
- Its use should probably be limited to hypotensive patients.

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]
PE with shock or hypotension (high-risk)		
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE.	I	C
Thrombolytic therapy is recommended.	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[e]	IIa	C
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of 'rescue' reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.[g]	IIb	B

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[f]			
Anticoagulation: combination of parenteral treatment with VKA			
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354
Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B	297
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]	293, 294
As an alternative to VKA treatment, administration of edoxaban[e] is recommended following acute-phase parenteral anticoagulation.	I	B	298
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A	293, 295–298

Thrombolytic treatment

- 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 RV function.***

- Administration over 2 hours are preferable to prolonged infusions of first-generation thrombolytic agents over 12–24 hours.
- Reteplase and desmoteplase have been tested against recombinant tissue plasminogen activator (rtPA) in acute PE, with similar results in terms of haemodynamic parameters

Surgical embolectomy

- The ***first successful surgical pulmonary embolectomy was performed in 1924***, several decades before the introduction of medical treatment for PE.
- Multidisciplinary teams enjoying the early and active involvement of cardiac surgeons have recently reintroduced the concept of surgical embolectomy for high-risk PE, and also for selected patients with intermediate-high-risk PE, particularly if thrombolysis is contraindicated or has failed.
- Surgical embolectomy has also been successfully performed in patients with right heart thrombi straddling the interatrial septum through a patent foramen ovale.

Figure-2: Embolectomy revealed multiple large emboli in the pulmonary vasculature of patient.

Percutaneous catheter-directed treatment

- The objective of interventional treatment is the removal of obstructing thrombi from the main pulmonary arteries to facilitate RV recovery and improve symptoms and survival.
- For patients with absolute contraindications to thrombolysis, interventional options include
- (i) thrombus fragmentation with pigtail or balloon catheter.
- (ii) rheolytic thrombectomy with hydrodynamic catheter devices
- (iii) suction thrombectomy with aspiration catheters and
- (iv) rotational thrombectomy

Venous filters

- Venous filters are usually placed in the infrarenal portion of the inferior vena cava (IVC).
- If a thrombus is identified in the renal veins, suprarenal placement may be indicated.
- Venous filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs, and in patients with objectively confirmed recurrent PE despite adequate anticoagulation treatment.
- There are no data to support the routine use of venous filters in patients with free-floating thrombi in the proximal veins.

Recommendations for venous filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

Anticoagulation

- Within this period, acute-phase treatment consists of administering parenteral anticoagulation ***[unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux] over the first 5–10 days***.
- Parenteral heparin ***should overlap with the initiation of a vitamin K antagonist (VKA);*** alternatively, it can be followed by administration of one of the new oral anticoagulants: dabigatran or edoxaban.
- If ***rivaroxaban or apixaban is given instead, oral treatment with one of these agents should be started directly or after a 1–2 day administration of UFH, LMWH or fondaparinux***.
- In this latter case, acute-phase treatment consists of an increased dose of the oral anticoagulant over the first 3 weeks (for rivaroxaban), or over the first 7 days (for apixaban).

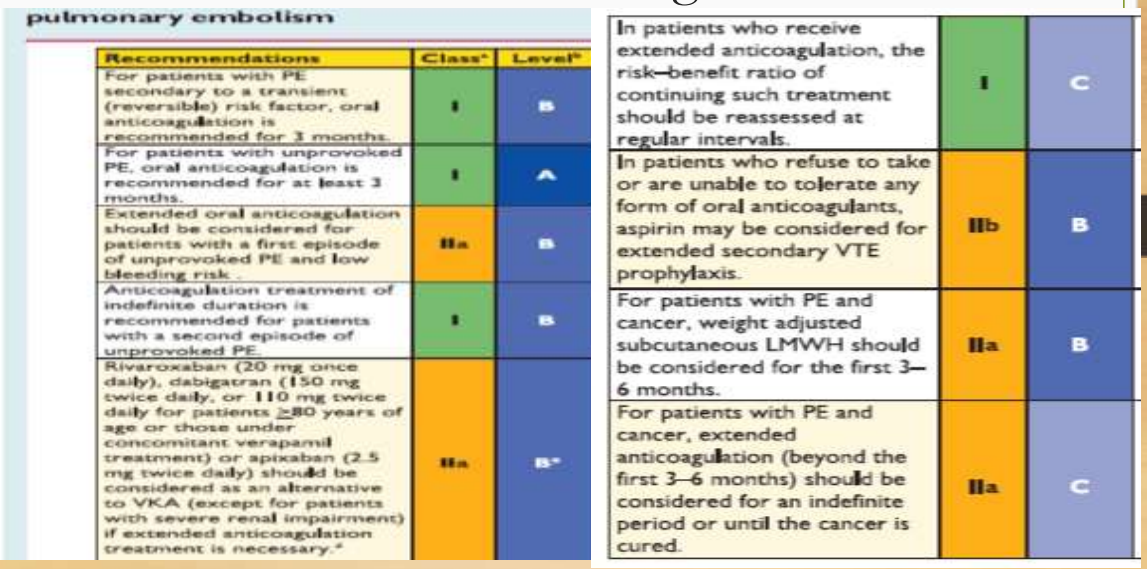
Table 10 Low molecular weight heparin and pentasaccharide (fondaparinux) approved for the treatment of pulmonary embolism

	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg[a]	Every 12 hours Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b] or 200 IU/kg[b]	Every 12 hours[b] Once daily[b]
Nadroparin[c]	86 IU/kg or 171 IU/kg	Every 12 hours Once daily
Fondaparinux	5 mg (body weight <50 kg); 7.5 mg (body weight 50–100 kg); 10 mg (body weight >100 kg)	Once daily

Early discharge and home treatment

Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.	IIa	B

Duration of anticoagulation



pulmonary embolism

Recommendations	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[c]	IIa	B[c]
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B
For patients with PE and cancer, weight adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

Specific problems

- Pregnancy:
- Pregnancy does not alter the clinical features of PE but, as pregnant women often complain of breathlessness, this symptom should be interpreted with caution.

Table 14 Estimated radiation absorbed in procedures used for diagnosing PE (adapted from Bajc *et al.* (2009)[430] and Chunilal *et al.* (2009)).[431]

Test	Estimated foetal radiation exposure (mSv)	Estimated maternal radiation exposure to breast tissue (mSv)
Chest X-ray	<0.01	0.01
Perfusion lung scan with technetium-99m labelled albumin Low dose: 40 MBq High dose: 200 MBq	 0.11–0.20 0.20–0.60	 0.28–0.50 1.20
Ventilation lung scan	0.10–0.30	<0.01
Computed tomographic angiography	0.24–0.66	10–70

Recommendations for pulmonary embolism in pregnancy

Recommendations	Class*	Level†	
Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.	I	C	
D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.	IIb	C	4
Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.	IIb	C	
Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray.	IIb	C	
CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available.	IIa	C	
A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.	I	B	4

Pulmonary embolism and cancer

Recommendations for pulmonary embolism in cancer

Recommendations	Class*	Level*	Ref*
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C	447–449, 463
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B	98, 443
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B	278, 376, 377
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

Thank you