Pulmonary Embolism

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Disclosures

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- **Lilly**

Epidemiology

Venous thrombo-embolism (VTE)

includes deep-vein thrombosis (DVT)
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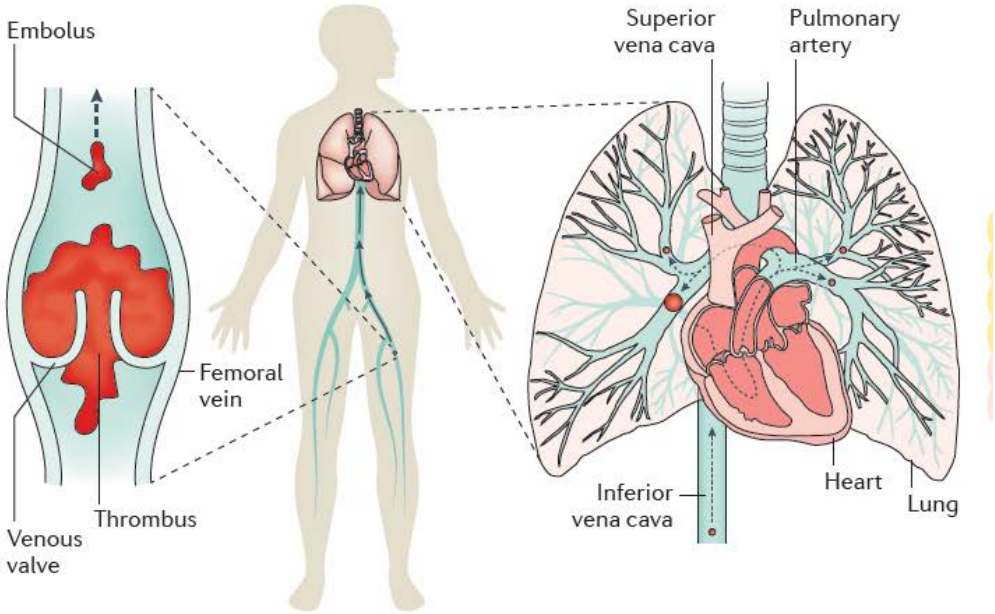

Epidemiology

Venous thrombo-embolism (VTE)

includes deep-vein thrombosis (DVT)
& pulmonary embolism (PE)

- is the third most common cause
  of vascular disease–related deaths
  after myocardial infarction and stroke

QUESTION: 1

The incidence of Pulmonary Embolism:

A. Is increasing
B. Is reducing
C. Is increasing, but mortality is reducing
D. Is reducing, but mortality is increasing

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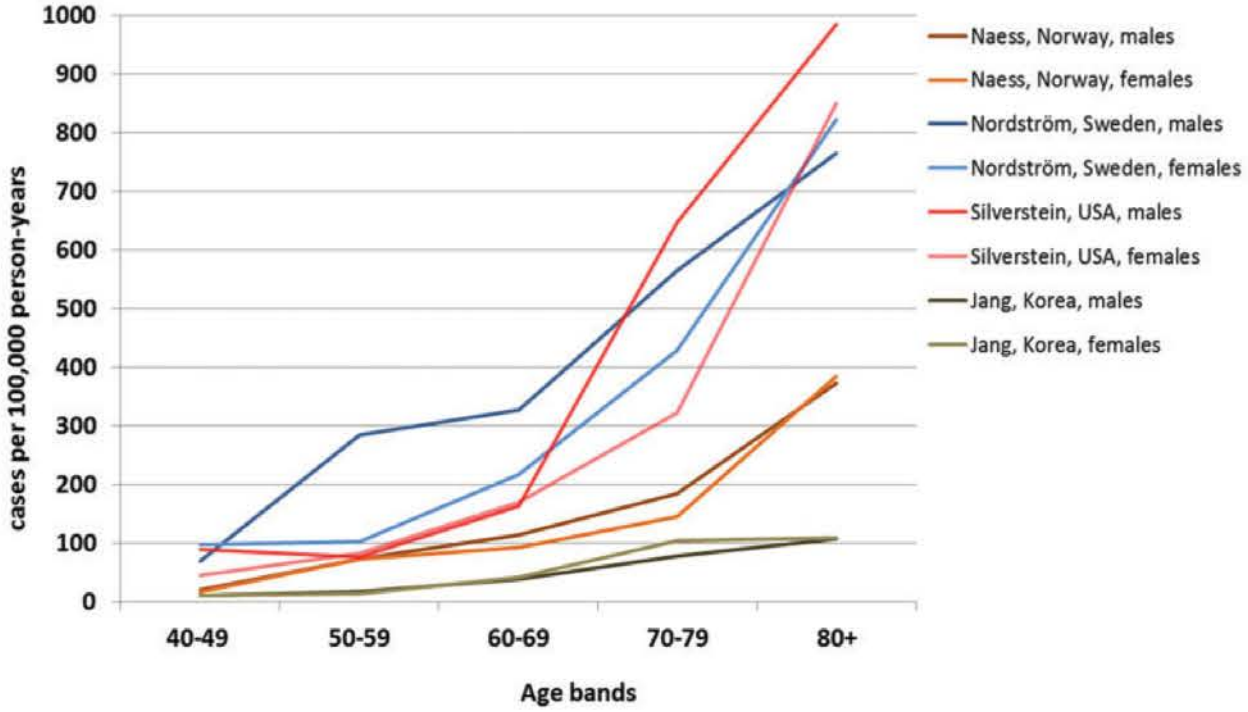
incidence

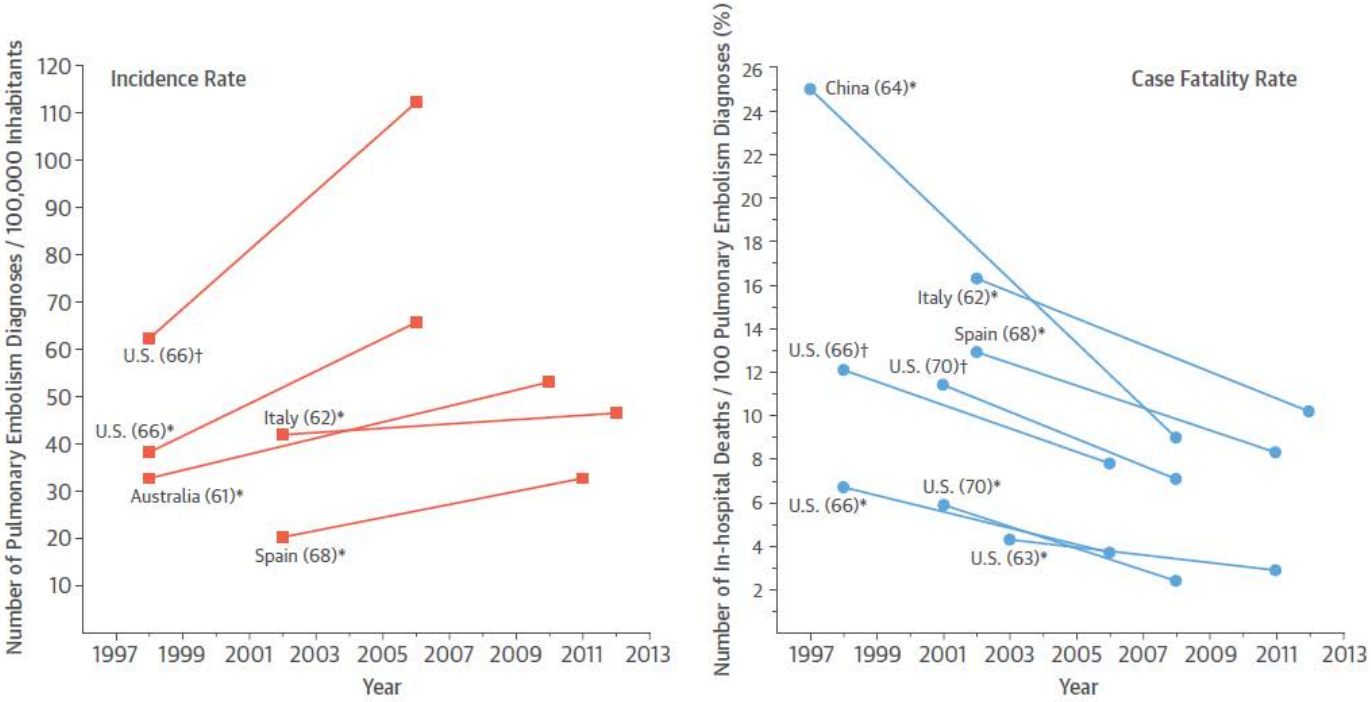
- 1 - 2 cases / 1000/ year in the general population
- is steadily increasing despite efforts to prevent the disease

Venous thromboembolism incidence according to age group



ESC consensus document on diagnosis and management of acute DVT
European Heart Journal (2017)

Global Trends in PE Incidence & Case Fatality Rates



Konstantinides et al. J Am Coll Cardiol 2016;67:976–90

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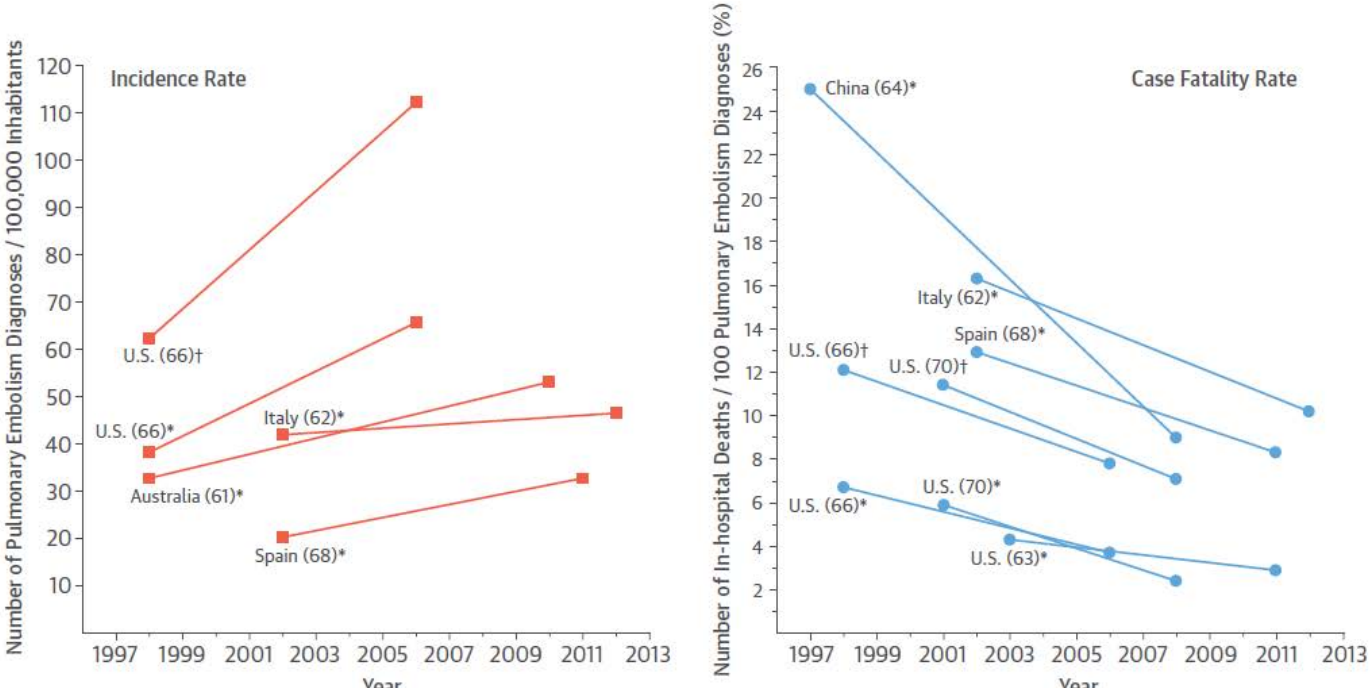


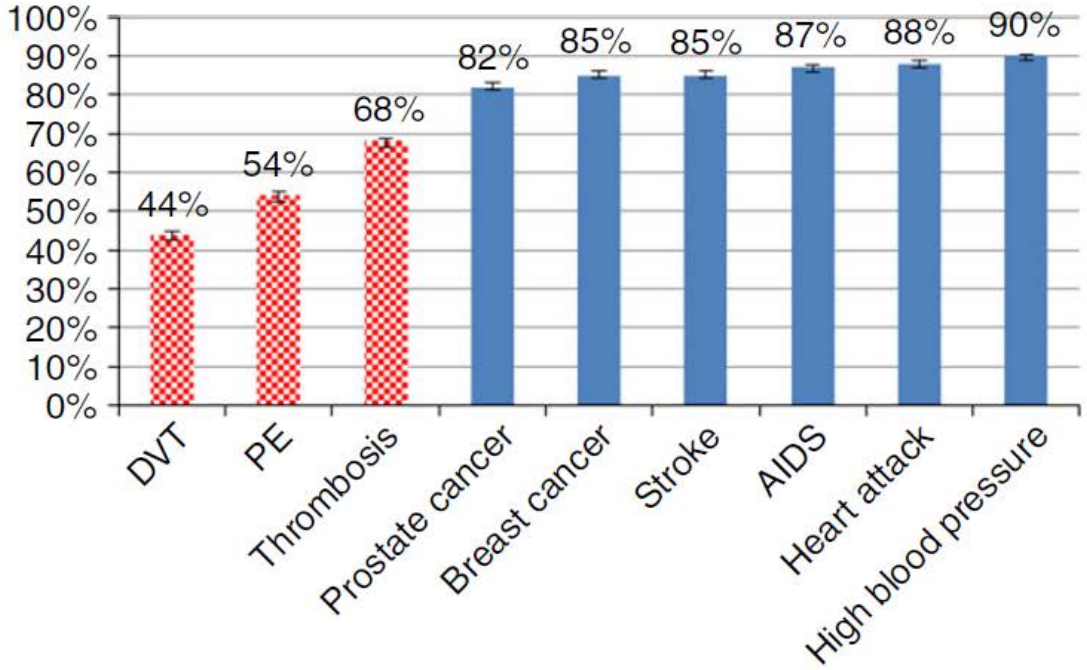
diagnosis and treatment of PE have both improved

Konstantinides et al. J Am Coll Cardiol 2016;67:976–90

RIETE Registry

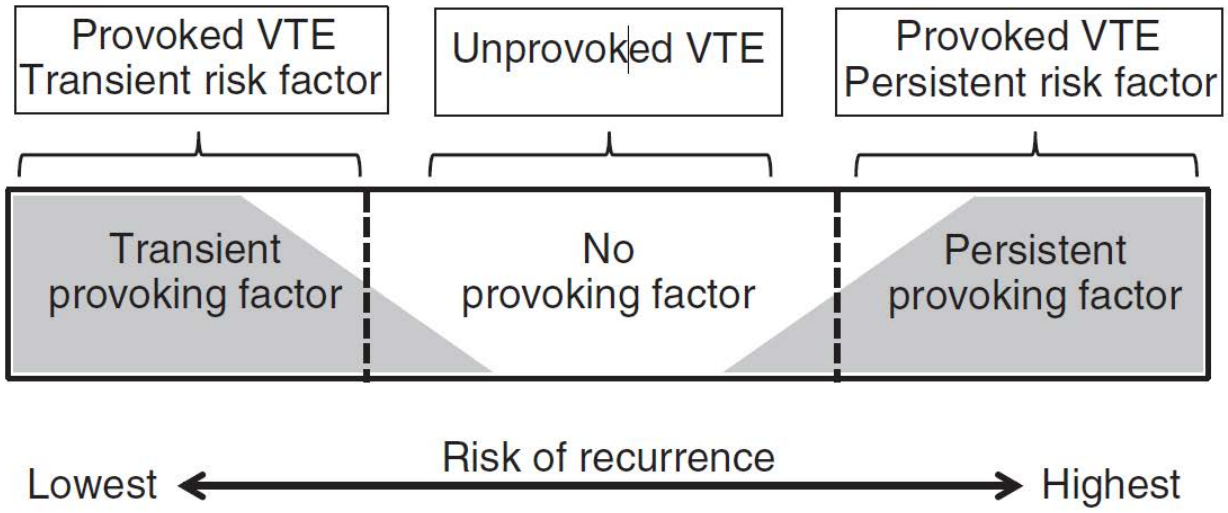
J Am Coll Cardiol 2016;67:162–70

Global public awareness of venous thromboembolism



J Thromb Haemost 2015; 13: 1365–71

Categorization of pts as having provoked or unprovoked VTE



J Thromb Haemost 2016; 14: 1480–3

Risk factors for venous thromboembolism

Clinical and environmental risk factors

Hypercoagulability

- Older age
- Active cancer
- Antiphospholipid syndrome
- Oestrogen therapy
- Pregnancy or puerperium
- Personal or family history of venous thromboembolism
- Obesity
- Autoimmune and chronic inflammatory diseases (eg, inflammatory bowel disease)
- Heparin-induced thrombocytopenia

Vascular damage

- Surgery
- Trauma or fracture
- Central venous catheter or pacemaker

Venous stasis or immobilisation

- Hospitalisation for acute medical illness
- Nursing-home residence
- Long-haul travel for more than 4 h
- Paresis or paralysis

Heritable risk factors

- Factor V Leiden — 3-7%
- Prothrombin 20210G→A mutation — 1-2%
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Non-0 blood group

Lancet 2016; 388: 3060–73

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15% surgery & immobilisation

20% cancer-related

Lancet 2016; 388: 3060–73

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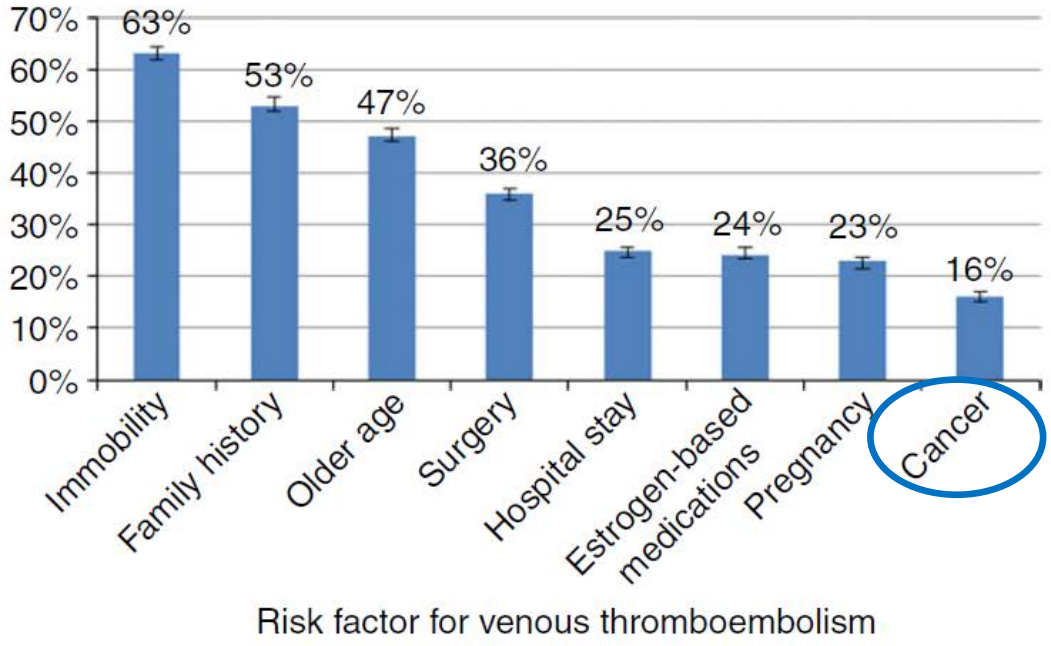

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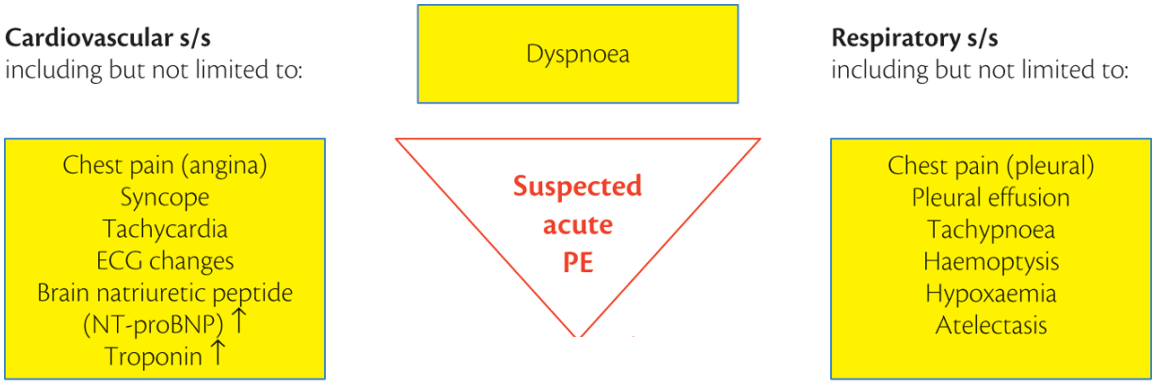
Three key steps are vital in the management of PE:

1. rapid, simple and accessible diagnosis

2. accurate triaging of PE (Risk Stratification) - appropriate treatment

3. optimal duration of treatment (assessment of recurrent VTE &/or anticoagulation associated bleeding)

Symptoms and signs and initial prognostic triage in suspected PE



The ESC Textbook of Intensive and Acute Cardiovascular Care (2018)

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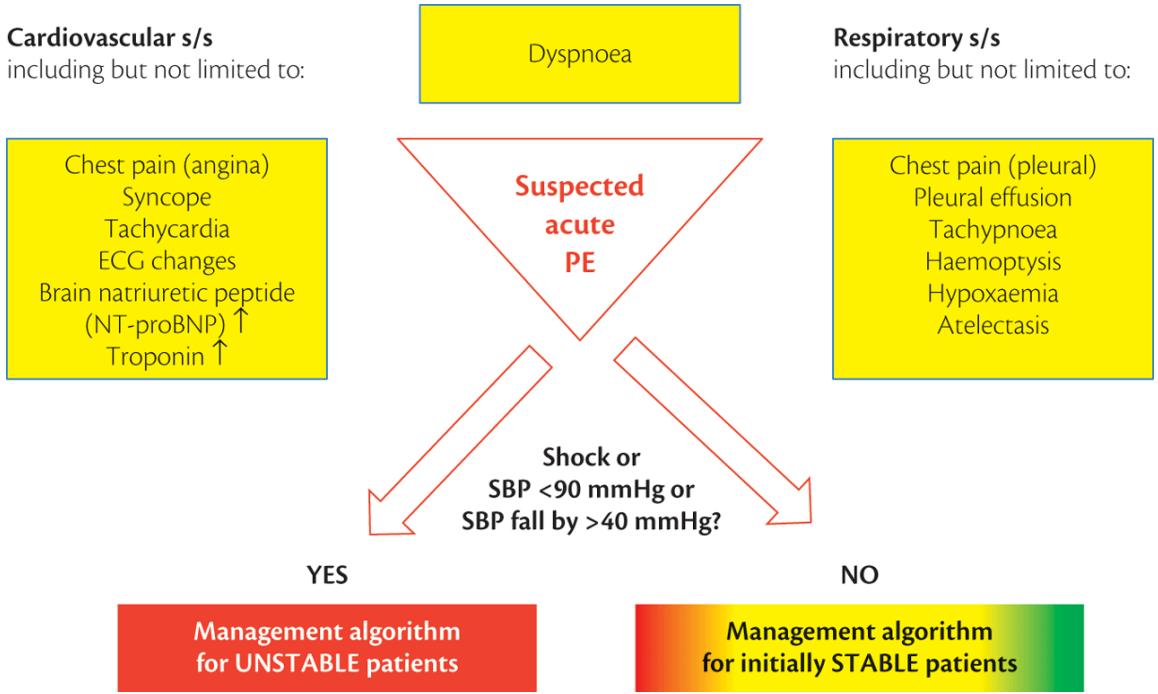

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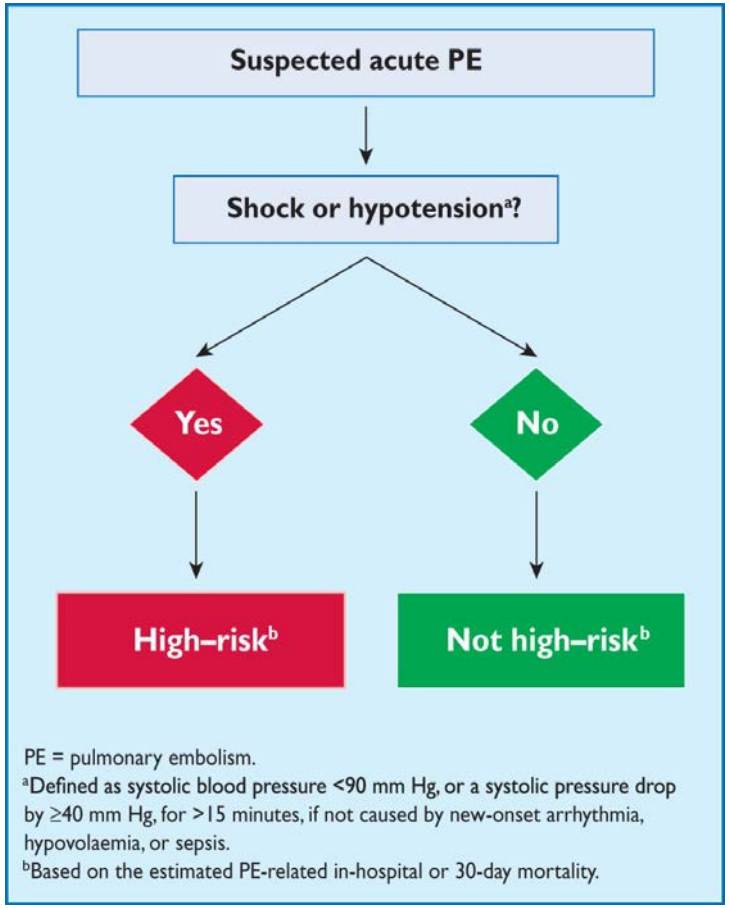

PE = pulmonary embolism.
[a]Defined as systolic blood pressure <90 mm Hg, or a systolic pressure drop by ≥40 mm Hg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.
[b]Based on the estimated PE-related in-hospital or 30-day mortality.

ESC GUIDELINES 2014

European Heart Journal

QUESTION: 2

We use the clinical probability assessment of PE to:

A. Safely exclude PE diagnosis
B. Avoid delays in cases of suspected severe PE
C. Minimize unnecessary testing for suspected PE
D. Guide treatment decisions for PE

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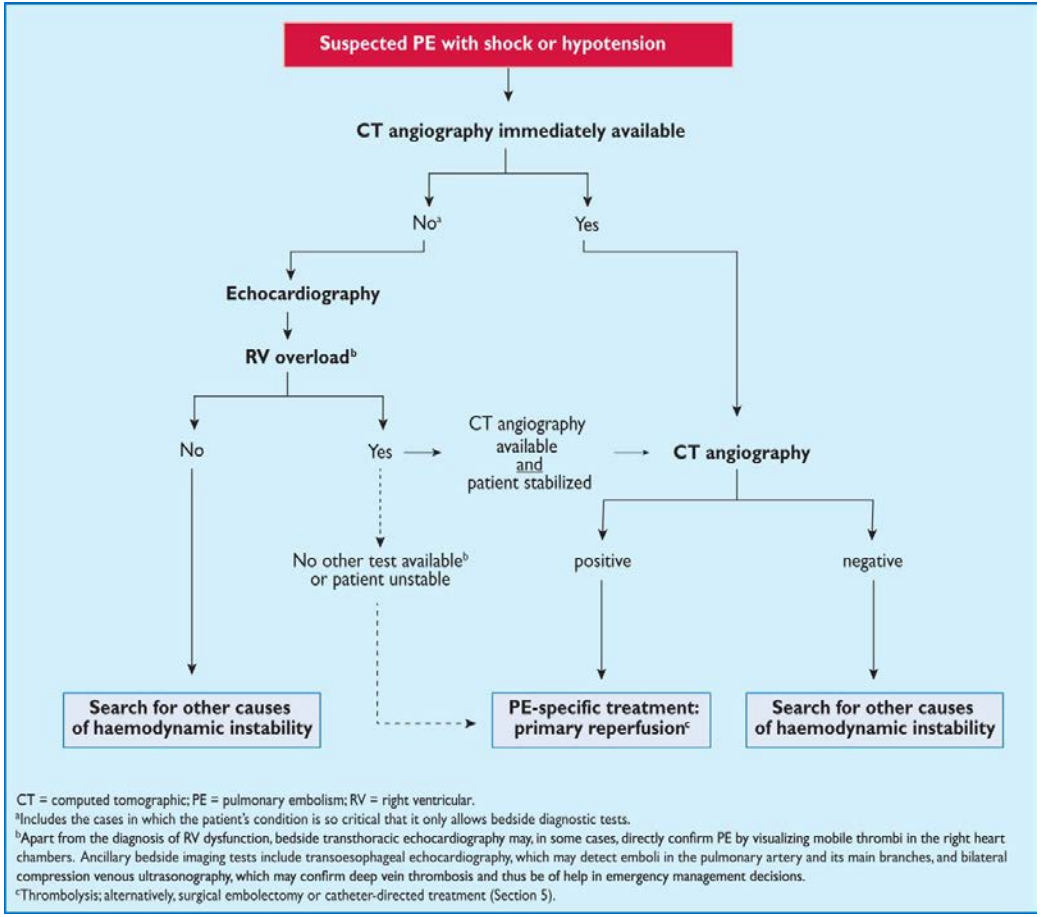

CT = computed tomographic; PE = pulmonary embolism; RV = right ventricular.

[a]Includes the cases in which the patient's condition is so critical that it only allows bedside diagnostic tests.

[b]Apart from the diagnosis of RV dysfunction, bedside transthoracic echocardiography may, in some cases, directly confirm PE by visualizing mobile thrombi in the right heart chambers. Ancillary bedside imaging tests include transoesophageal echocardiography, which may detect emboli in the pulmonary artery and its main branches, and bilateral compression venous ultrasonography, which may confirm deep vein thrombosis and thus be of help in emergency management decisions.

[c]Thrombolysis; alternatively, surgical embolectomy or catheter-directed treatment (Section 5).

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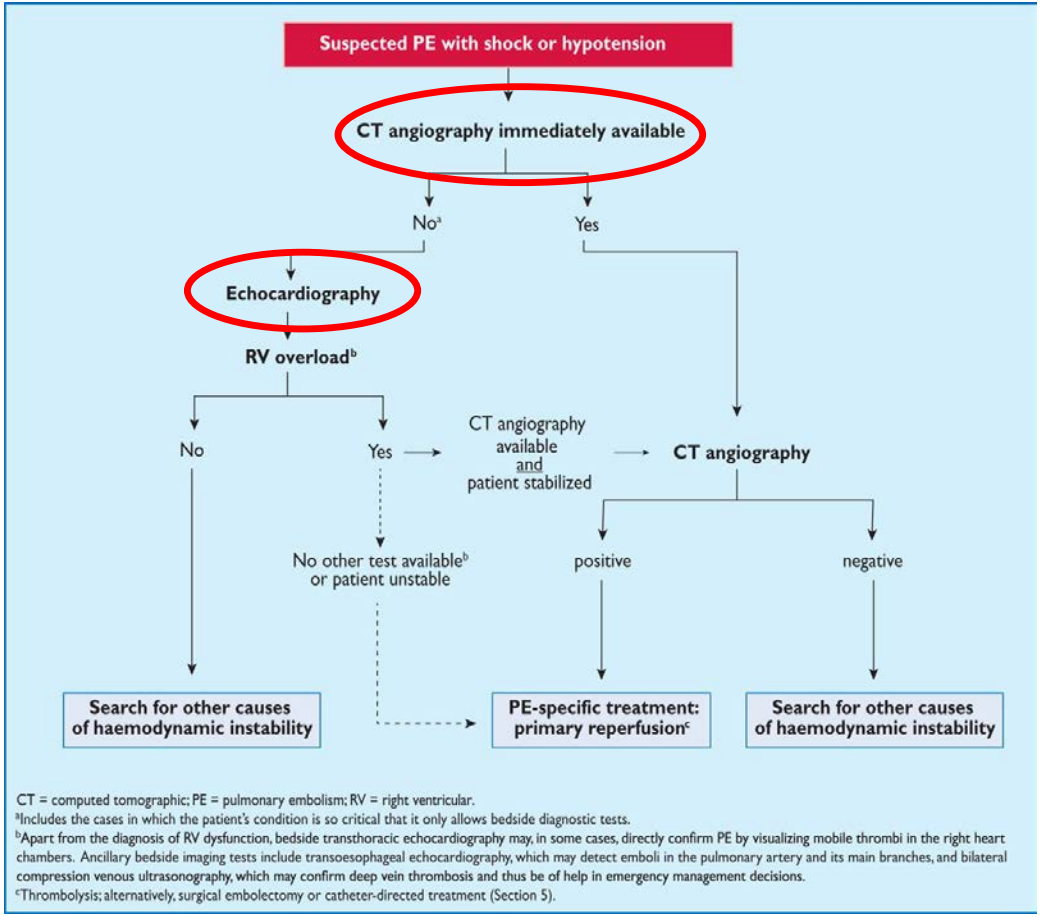

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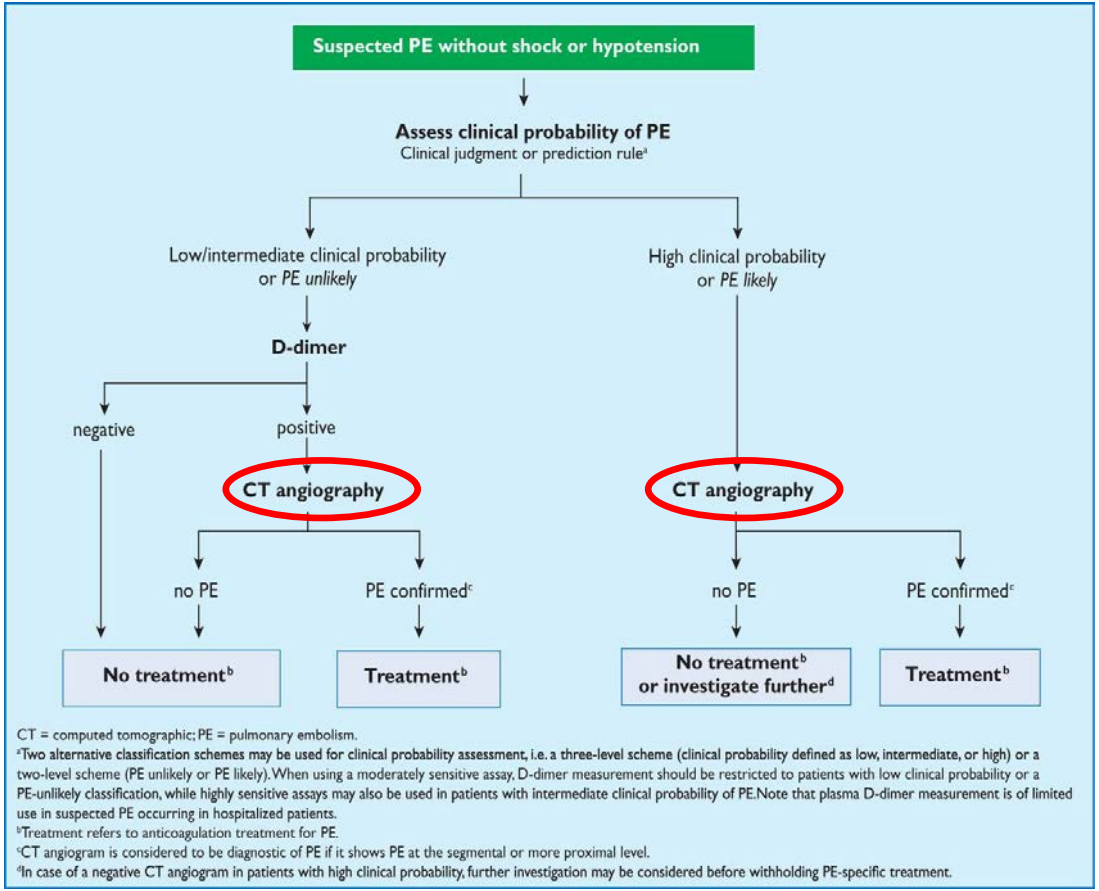

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[b]Treatment refers to anticoagulation treatment for PE.

[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.

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Complications associated with overtesting and overdiagnosis of PE

Complication	Associated Risk
Bleeding	• Major bleeding can occur in up to 12% of treated VTE patients[69,70] • Anticoagulation complications increased from 3.1 to 5.3 per 100,000 from 1998 to 2006 (P<.001)[69] • Bleeding risk may outweigh benefit in some populations, with a 5.3% major bleed rate in isolated subsegmental PE but only a 0.7% risk of recurrent VTE[71]
Cost	• Total charges for PE admission increased from $25,293 to $43,740 from 1998 to 2006[72] • Newer anticoagulants can cost $3000 annually and, although the warfarin drug itself is cheaper, the associated bridge and monitoring increase its cost[69,73,74]
Nephrotoxin exposure	• CTPA contrast nephropathy occurs in 14%–24% of patients, with higher rates in those with critical illness or renal comorbidities[75–77] • There are no protective effects from *N*-acetylcysteine, normal saline, or sodium bicarbonate[76]
Contrast dye allergy	• Although not studied specifically in CTPAs, it is recognized that mild contrast reactions occur in 15% of patients receiving iodinated contrast, moderate in 1%–2%, and severe in 0.2%[77]
Radiation	• Females have a significantly higher CTPA-related lifetime attributable risk of cancer death (vs males, 48.7 vs 42.1 per 100,000 for age group 20–29; P<.0001)[78] • Estimates suggest that 3 out of every 1000 20-year-old women who undergo CTPA will develop cancer[69,79]

Clin Chest Med 39 (2018) 473–482

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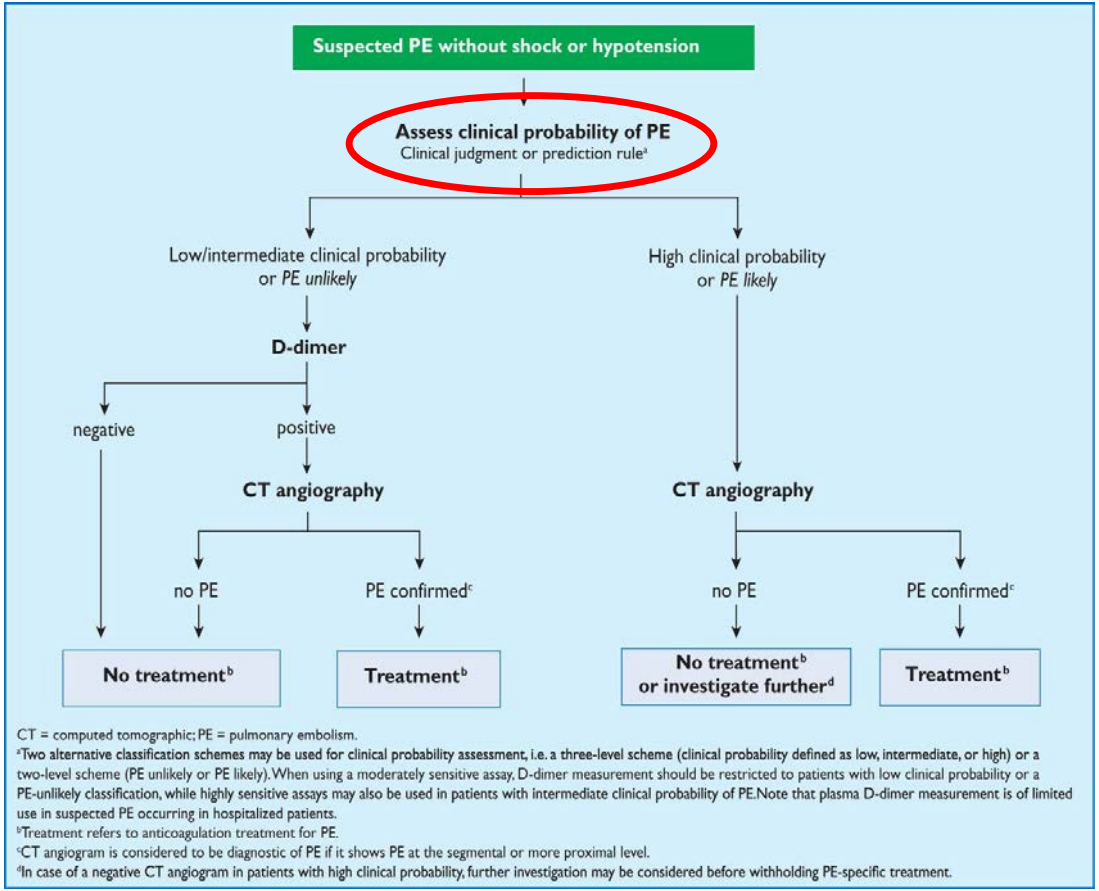
In recent studies <20% (in some studies only 5%) of pts investigated for a suspected PE actually have the disease

Clin Chest Med 39 (2018) 473–482



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Items	Clinical decision rule points	
Wells rule	**Original version[95]**	**Simplified version[107]**
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

Assessment of clinical probability

Revised Geneva score	**Original version[93]**	**Simplified version[108]**
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
PE likely	≥6	≥3

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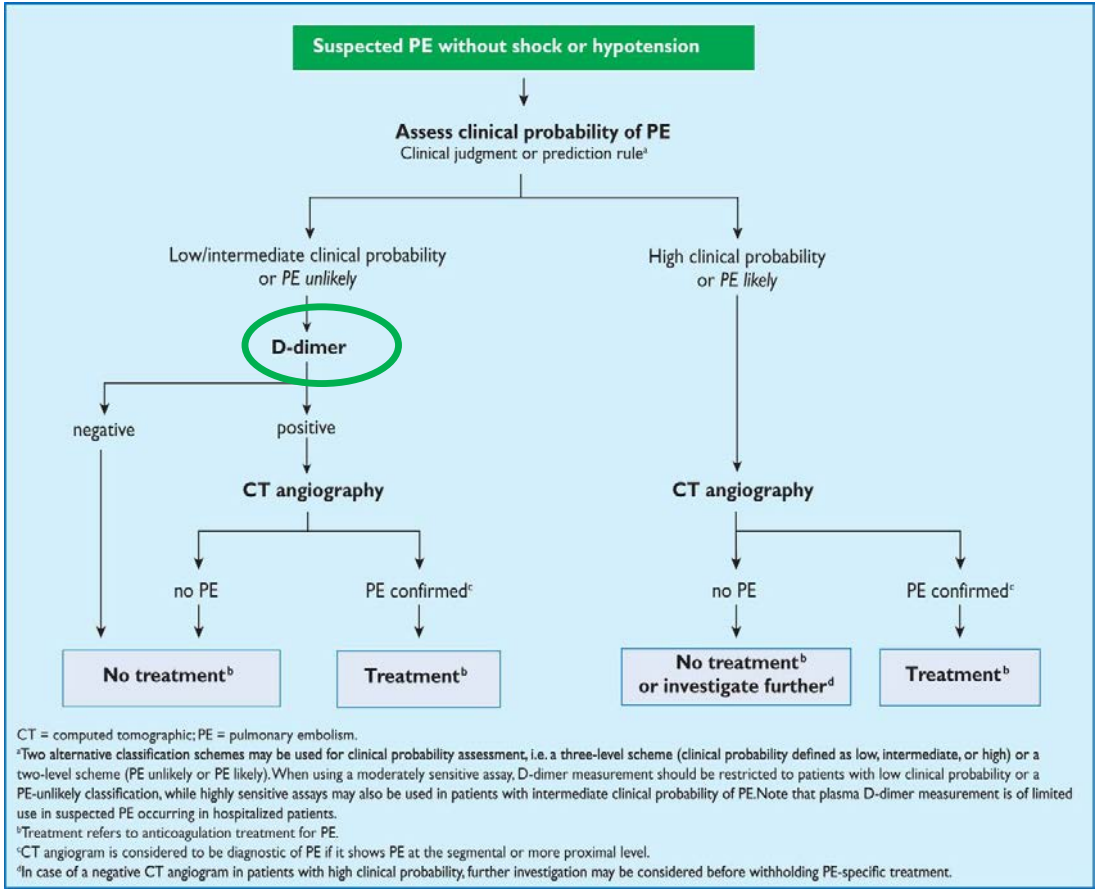

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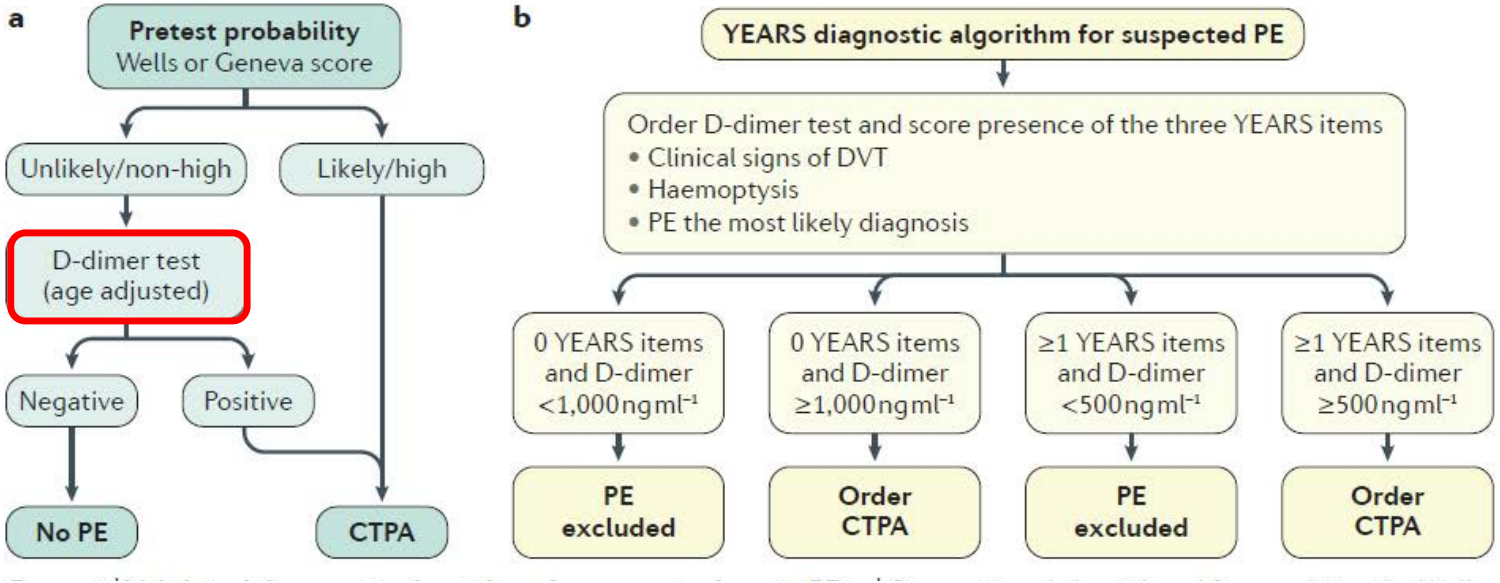
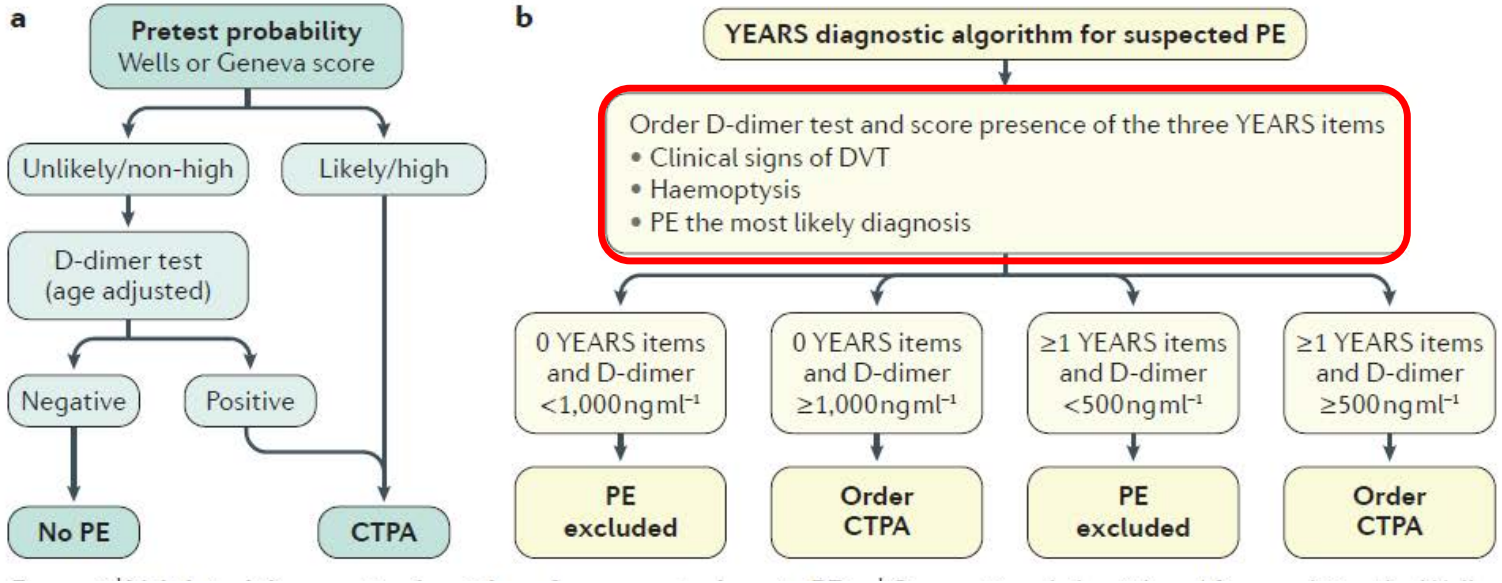


the **YEARS** study: Lancet, 390: 289-297, 2017



*Compared with the conventional algorithm, the YEARS algorithm spares the need for CTPA in an additional **14%** of patients with suspected PE*

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Pulmonary embolism rule-out criteria (PERC)

- age <50 years
- pulse rate <100/min
- SpO2 >94%
- no unilateral leg swelling
- no haemoptysis
- no surgery or trauma within 4 weeks
- no prior DVT or PE
- no oral hormone use

Patients meeting PERC criteria (PERC (–)) should not require any further testing including D-dimer

Emerg Med J 2013;30:701–706

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PERC rule should be used only in low-prevalence settings or for pts considered to have a low probability of PE

Emerg Med J 2013;30:701–706

Generally, the use of clinical decision rules and D-dimer testing

- **standardizes the diagnostic work-up for VTE**
- **reduces the use of invasive tests &**
- **is cost-effective**

- the diagnosis of PE is based on identifying clots in the pulmonary arteries

- the short-term prognosis of PE is mainly determined by RV function

Definitions used for stratification of pulmonary embolism

	Definition	Major Studies Using the Definition	Comment
Massive PE or ESC high	Persistent systolic hypotension (systolic blood pressure <90 mm Hg) or cardiogenic shock	Almost all studies	Initial appropriate management, including adequate use of intravenous fluids should be attempted before hypotension is attributed to acute PE
Submassive PE	Presence of RV dysfunction evidence by increased RV/LV ratio on CT or echocardiography	Tenecteplase or Placebo: Cardiopulmonary Outcomes at 3 Months (TOPCOAT) Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) AINEP Randomized Trial of Inhaled Nitric Oxide to Treat Acute Pulmonary Embolism (iNOPE)	Some studies have raised concerns about the prognostic utility of some of the echocardiographic factors, in isolation
Submassive PE	Defined by echocardiography or CT plus biomarkers	Pulmonary Embolism Thrombolysis Trial (PEITHO)	Mortality rate within the first 30 d after randomization of only 3.2% in the placebo group
Moderate PE	Defined by imaging findings	Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT)	Needs further validation on impact on prognosis
ESC intermediate-high	Absence of hypotension, positive PESI or sPESI but presence of RV dysfunction plus myocardial injury		Needs validation in a management study or RCT
ESC intermediate-low	Absence of hypotension, positive PESI or sPESI, but presence of RV dysfunction or myocardial injury or none		The difference in the risk of death in patients at intermediate to high and intermediate-low risk is not pronounced[46]

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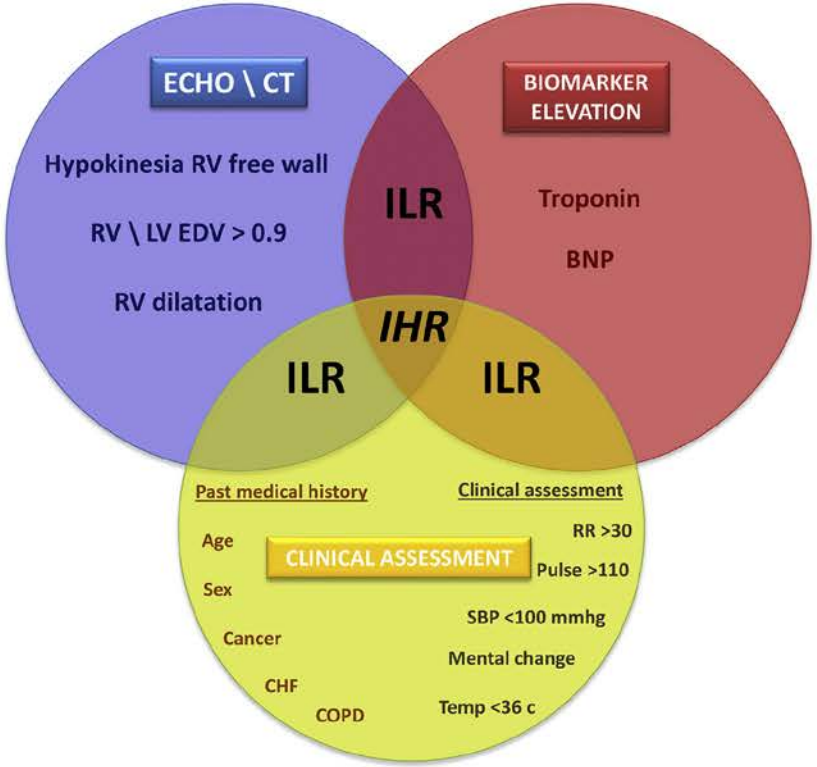
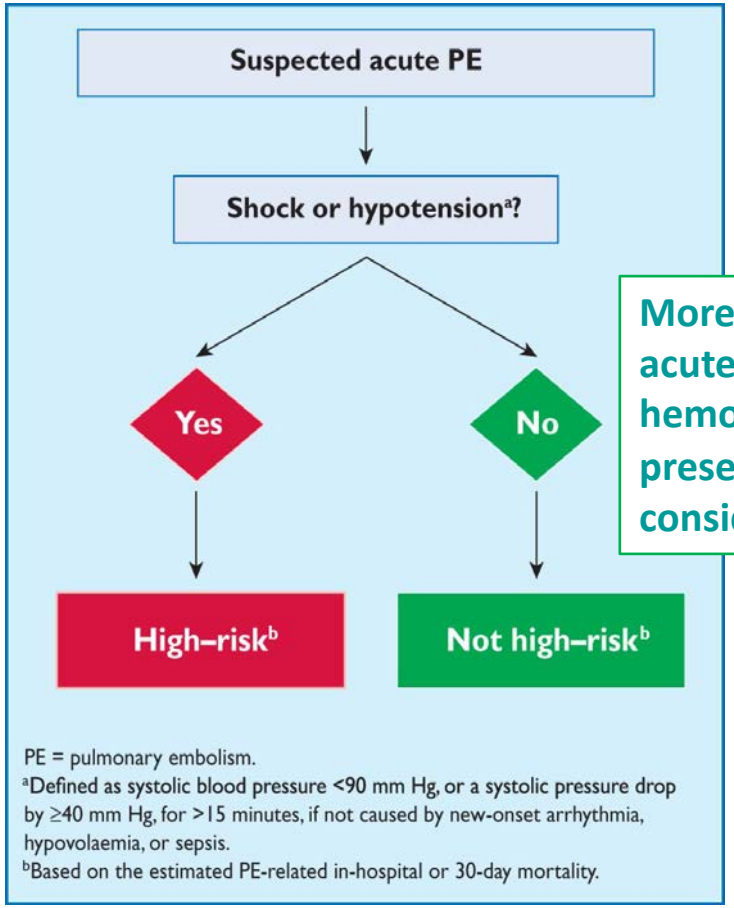
Clin Chest Med 39 (2018) 569–581

PE patient severity assessment



Progress in Cardiovascular Diseases 60 (2018) 613–621



More than **95%** of patients with acute PE are (or appear to be) hemodynamically stable at presentation & are thus **not** considered to be **at high risk**.

ESC GUIDELINES 2014

European Heart Journal

Original and simplified PESI (Pulmonary Embolism Severity Index)

Parameter	Original version[214]	Simplified version[218]
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 strata[a]	
	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%)

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The principal strength of the PESI lies in the reliable identification of pts at low risk for 30-day mortality (PESI classes I and II)

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1/3 of PE pts	**Class I:≤65 points** very low 30-day mortality risk (0–1.6%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)
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ESC GUIDELINES 2014

Classification of patients with acute PE based on early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

ESC GUIDELINES 2014

European Heart Journal

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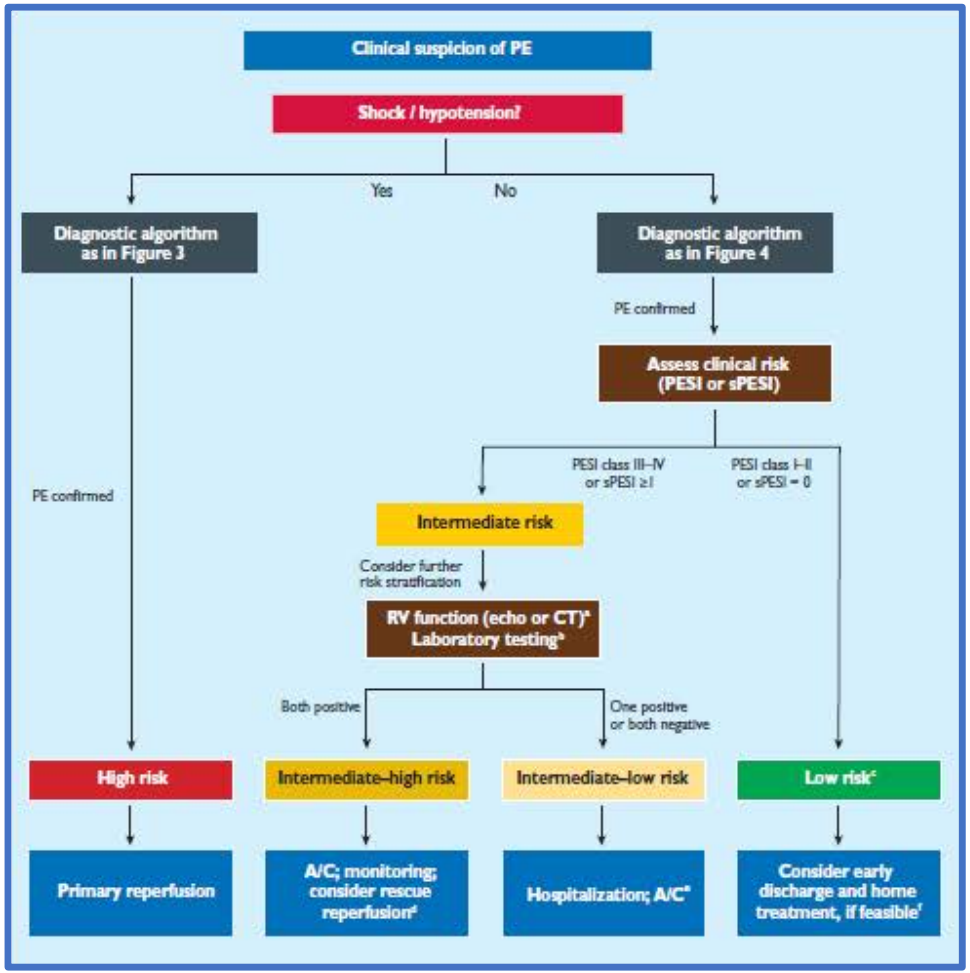
ESC GUIDELINES 2014

European Heart Journal

Risk-adjusted management strategies in acute PE



ESC GUIDELINES 2014

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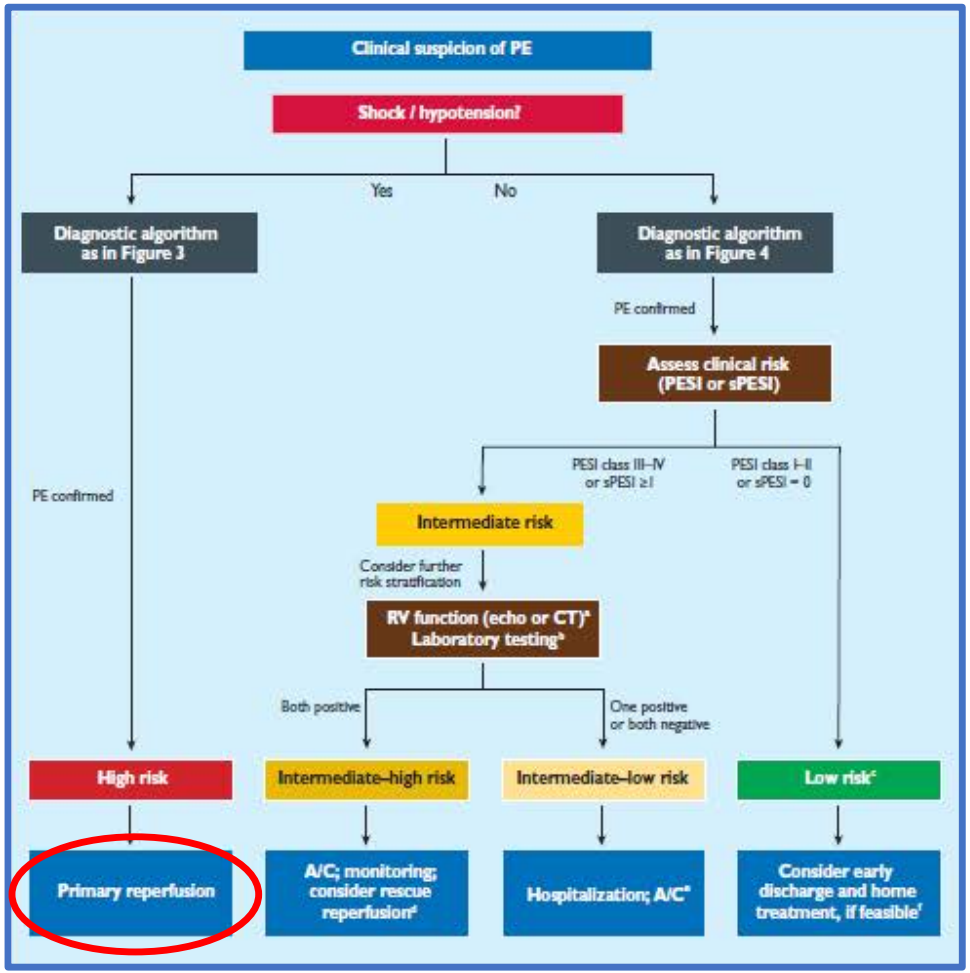


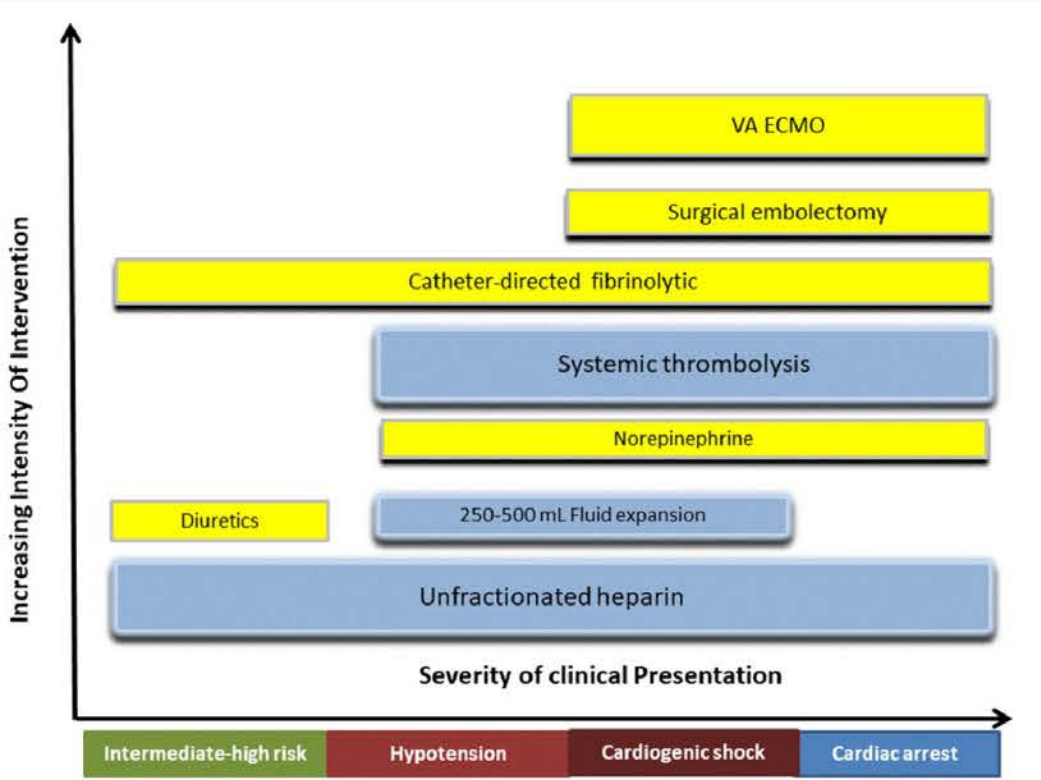
ESC GUIDELINES 2014

Contraindications of systemic thrombolysis

Absolute contraindications to thrombolysis
- History of prior intracranial hemorrhage
- Structural intracranial cerebrovascular disease (arteriovenous malformation)
- Intracranial malignancy
- Active bleeding or bleeding diathesis
- Recent surgery in spinal canal or brain
- Ischemic stroke within 3 mo
- Recent Closed head injury or facial trauma with radiographic evidence of brain injury

Relative contraindications
- Age >75 y
- Puncture of a noncompressible vessel
- Traumatic or prolonged cardiopulmonary resuscitation (>10 min)
- Internal bleeding (within 2–4 wk)
- History of chronic poorly controlled hypertension or severe uncontrolled hypertension on presentation
- History of ischemic stroke >3 mo

Med Clin N Am 103 (2019) 549–564

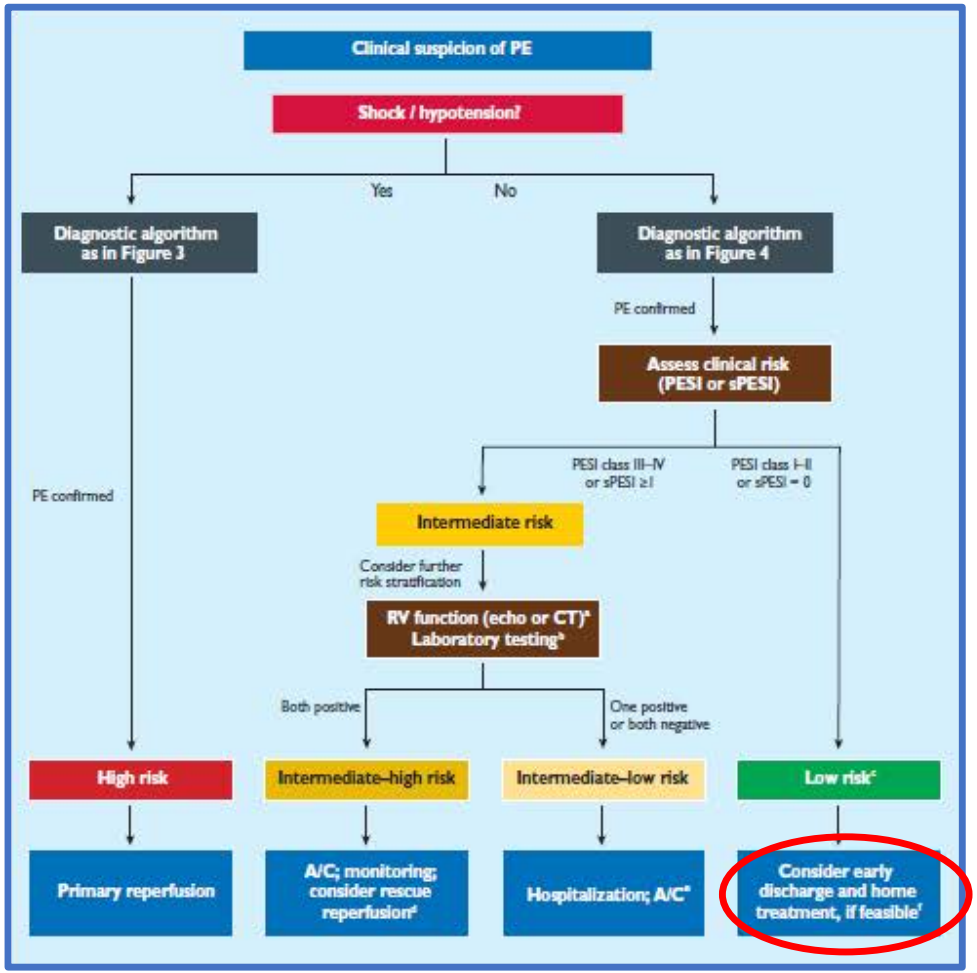


Aligning therapeutic options with the severity of pulmonary embolism

Yellow boxes represent therapies requiring confirmation in prospective clinical trials

Intensive Care Med (2019) 45:75–77

Risk-adjusted management strategies in acute PE



ESC GUIDELINES 2014

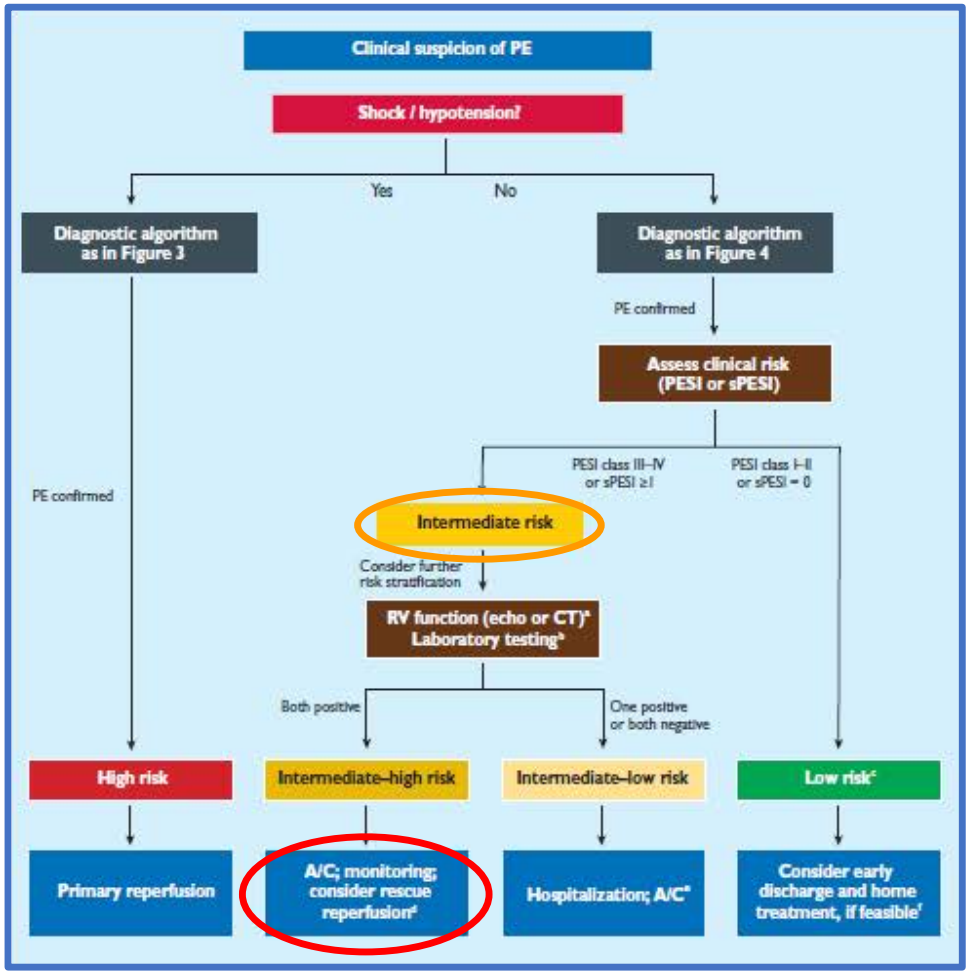
HESTIA clinical decision rule

If at least one of the following questions is answered with *yes*, the patient cannot be treated at home:

- Hemodynamically unstable?*
- Thrombolysis or embolectomy necessary?
- High risk for bleeding?†
- Oxygen supply to maintain oxygen saturation >90%?
- Pulmonary embolism diagnosed during anticoagulant treatment?
- Severe pain needing intravenous pain medication >24 h?
- Medical or social reason for treatment in the hospital >24 h?
- Creatinine clearance < 30 ml/min?‡
- Severe liver impairment?§
- Pregnant?
- Documented history of heparin-induced thrombocytopenia?

Am. J. Respir. Crit. Care Med. 194, 998–1006 (2016)

Risk-adjusted management strategies in acute PE



ESC GUIDELINES 2014

QUESTION: 3

A patient is diagnosed with intermediate-high risk PE. What is the most appropriate treatment?

A. Low-dose thrombolysis
B. Catheter directed thrombolysis
C. LMHW/HFH and ICU monitoring
D. DOACs and close monitoring

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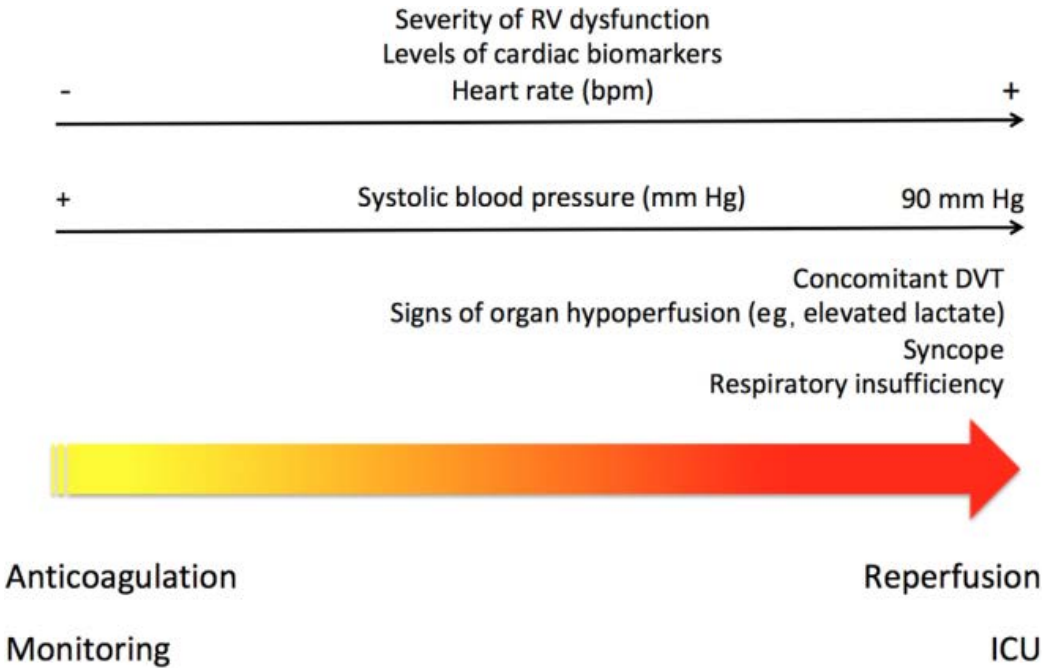
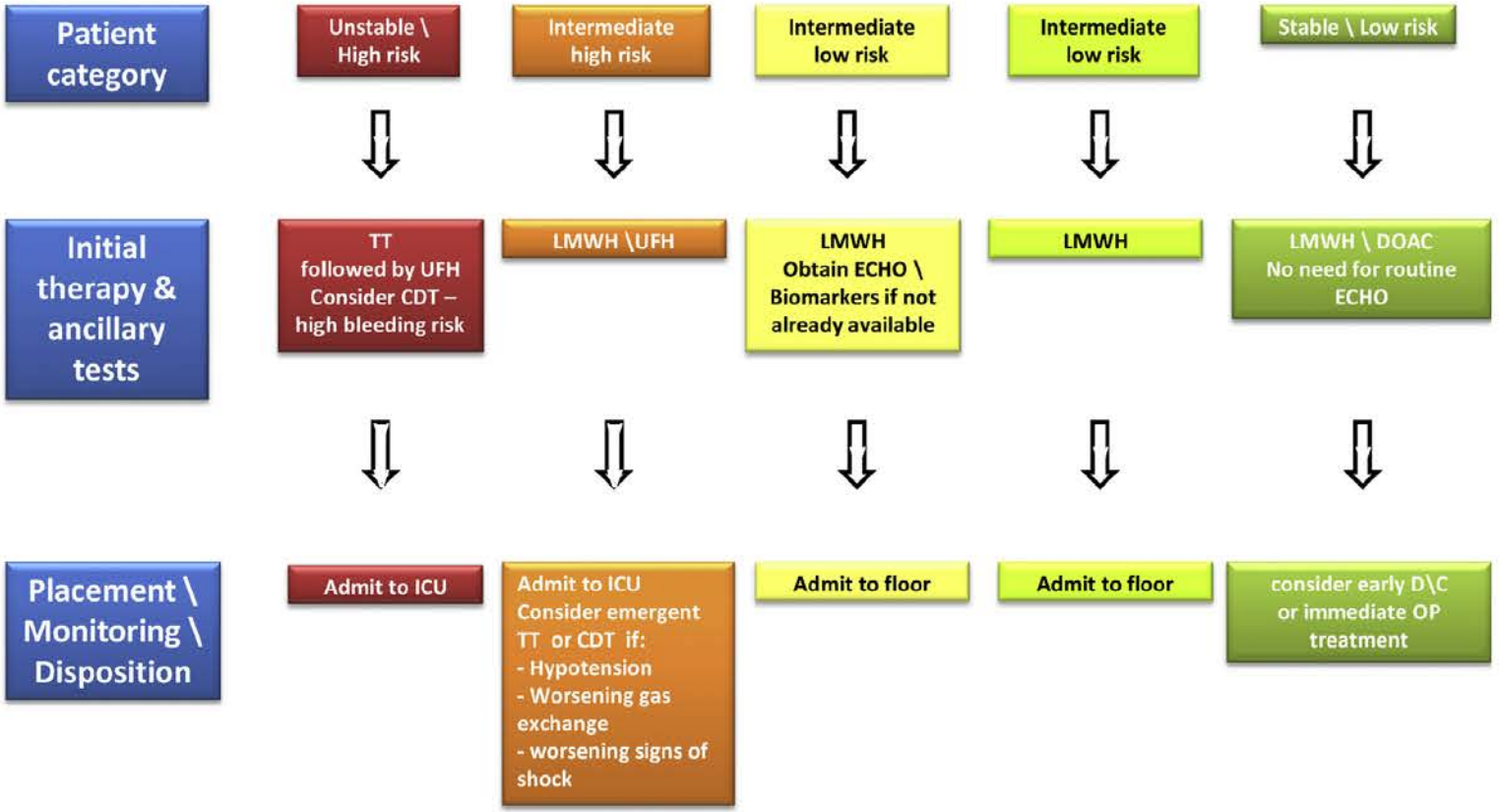
D. DOACs and close monitoring

A management approach to patients with intermediate-risk PE



Clin Chest Med 39 (2018) 569–581

PE patient treatment



Progress in Cardiovascular Diseases 60 (2018) 613–621

The mainstay of treatment for VTE is anticoagulation

Treatment consists of three phases:

- **an acute phase comprising the first 5–10 days after presentation of PE**
- **an intermediate phase between 10 days & 3 months after presentation**
- **an extended long-term phase beyond this period**

Anticoagulant therapies for deep vein thrombosis and pulmonary embolism

	Route of administration	Renal clearance	Half-life	Initial treatment dosing	Maintenance treatment dosing	Extended treatment dosing
Unfractionated heparin	Intravenous	~30%	~1·5 h	Maintain aPTT 1·5-times upper limit of normal	..	..
Low-molecular-weight heparin	Subcutaneous	~80%	3–4 h	Weight-based dosing	Weight-based dosing*	..
Fondaparinux	Subcutaneous	100%	17–21 h	Weight-based dosing	Weight-based dosing	..
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8–11 h; warfarin 36 h; phenprocoumon 160 h	Target at INR at 2·0–3·0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2·0–3·0	Maintain INR at 2·0–3·0
Dabigatran	Oral	~80%†	14–17 h	Requires at least 5 days heparin lead-in	150 mg twice a day	150 mg twice a day
Rivaroxaban	Oral	~33%‡	7–11 h	15 mg twice a day for 3 weeks	20 mg once a day	20 mg once a day
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Edoxaban	Oral	~35%‡	6–11 h	Requires at least 5 days heparin lead-in	60 mg once a day§	60 mg once a day§
Aspirin	Oral	~10%	15 min	..	..	80–100 mg once a day

aPTT=activated partial thromboplastin time. INR=international normalised ratio. *Treatment with low-molecular-weight heparin is recommended for patients with active cancer and pregnant women. †Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL per min. ‡Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL per min. §The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30–50 mL per min, a bodyweight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.

Lancet 2016; 388: 3060–73

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LMWH are preferred over UFH because of both superior efficacy and safety

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UFH should be used in pts undergoing thrombolysis (shorter half-life, ease of monitoring, and immediate reversal with protamine) in pts with severe renal impairment						
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8–11 h; warfarin 36 h; phenprocoumon 160 h	Target at INR at 2·0–3·0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2·0–3·0	Maintain INR at 2·0–3·0
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Vitamin K antagonists	Oral	..	phenprocoumon 160 h	least 5 days	..	..
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Vitamin K antagonists: narrow therapeutic index due to multiple drug–drug and drug–food interactions

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NOACs overcome many disadvantages of VKAs:
have little interaction with other medications and food
can be given in fixed doses without routine monitoring

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Dabigatran & Edoxaban: 5 day lead in with LMWH – switch without overlap

Rivaroxaban & Apixaban: single-drug approach without previous heparin
higher dose during the first 3 weeks (R) & 7 days (A)

aPTT=activated partial thromboplastin time. INR=international normalised ratio. *Treatment with low-molecular-weight heparin is recommended for patients with active cancer and pregnant women. †Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL per min. ‡Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL per min. §The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30–50 mL per min, a bodyweight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.

Lancet 2016; 388: 3060–73

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

- For VTE and no cancer,
  as long-term anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy, (all Grade 2B)
  &
  suggest VKA therapy over low-molecular-weight heparin (LMWH) therapy (Grade 2C).

- For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran, rivaroxaban, apixaban, or edoxaban (all Grade 2C).

CHEST 2016; 149(2):315-352

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

- For VTE and no cancer,
  as long-term anticoagular
  rivaroxaban, apixaban, or
  (VKA) therapy, (all Grade
  &
  suggest VKA therapy over low-molecular-weight heparin (LMWH) therapy (Grade 2C).

Excluded pts with
severe renal impairment
antiphospholipid syndrome
arterial thrombosis
a weight >120 kgr &
pregnant or breast feeding women

- For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran, rivaroxaban, apixaban, or edoxaban (all Grade 2C).

CHEST 2016; 149(2):315-352

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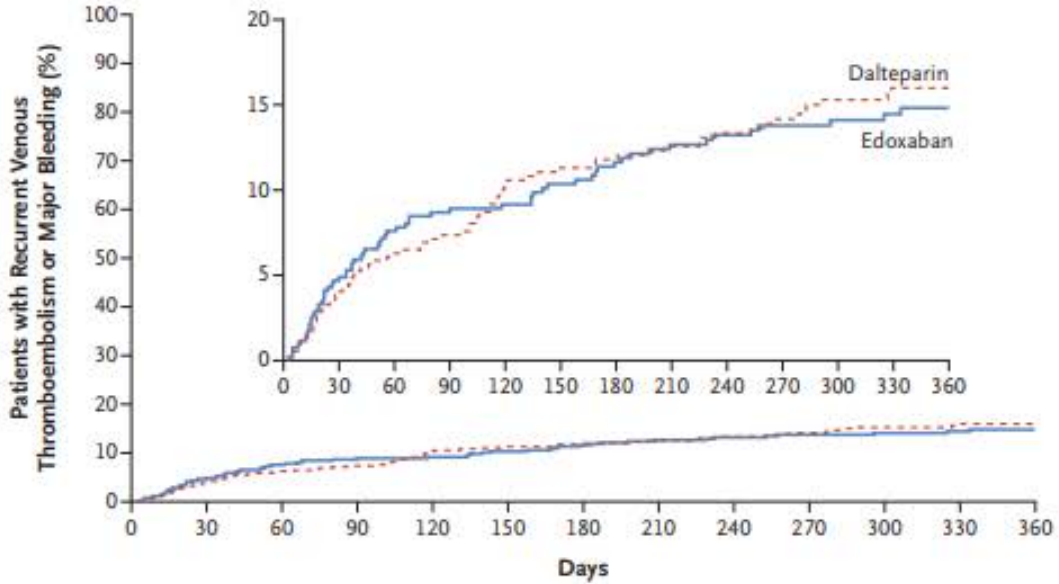
CHEST 2016; 149(2):315-352

Edoxaban for the Treatment of Cancer Associated Venous Thromboembolism



N Engl J Med, 2018; 378: 615–624

Duration of anticoagulant treatment

beyond the initial 3-month treatment

- **the risk of recurrent VTE**

versus

- **the risk of major bleeding**

should be assessed

Duration of anticoagulant treatment

beyond the initial 3-month treatment

- **the risk of recurrent VTE**

versus

- **the risk of major bleeding**

should be assessed

considerable risk :
pts with **unprovoked VTE**
11% **after 1 year**
40% **after 10 years**

Duration of anticoagulant treatment

beyond the initial 3-month treatment

- **the risk of recurrent VTE**

versus

- **the risk of major bleeding**

should be assessed

high risk :
elderly pts
pts with a history of **major bleeding**

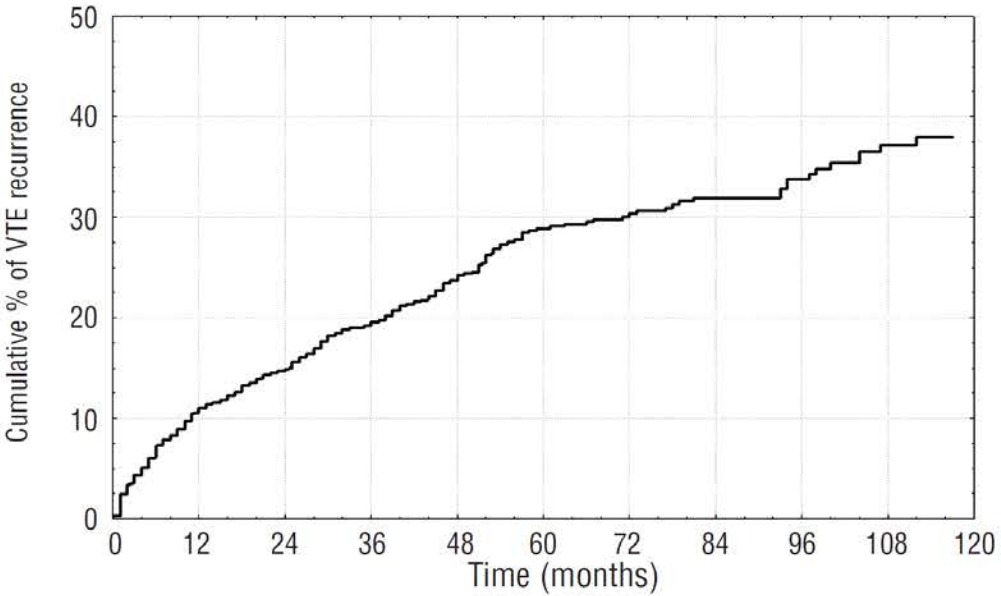
Currently, guidelines base duration of treatment mainly on whether the event was **provoked** or **unprovoked**

Recommendations for duration of anticoagulation after pulmonary embolism

Recommendations	Class[a]	Level[b]	Ref[c]
patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B	375
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B	360
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.[f]	IIa	B[e]	295, 370, 371
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	368, 369
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	

ESC GUIDELINES 2014

The risk of recurrent VTE after discontinuing anticoagulation in pts with acute proximal DVT or PE



Haematologica 2007; 92:199-205

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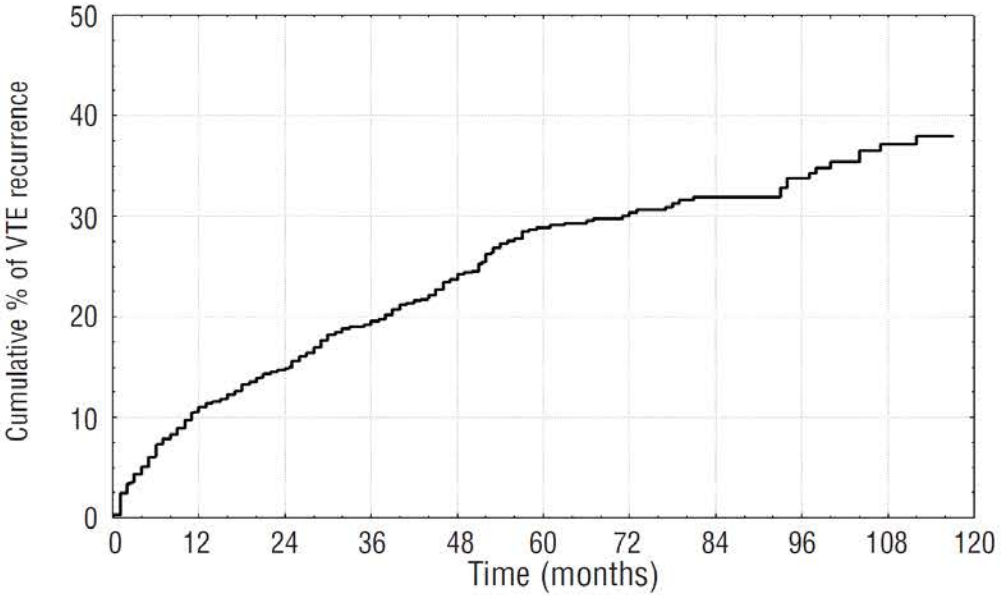

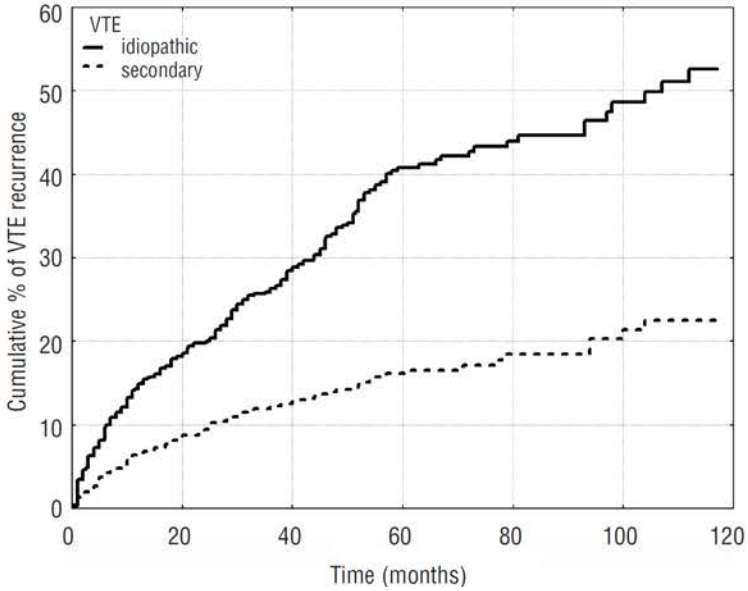

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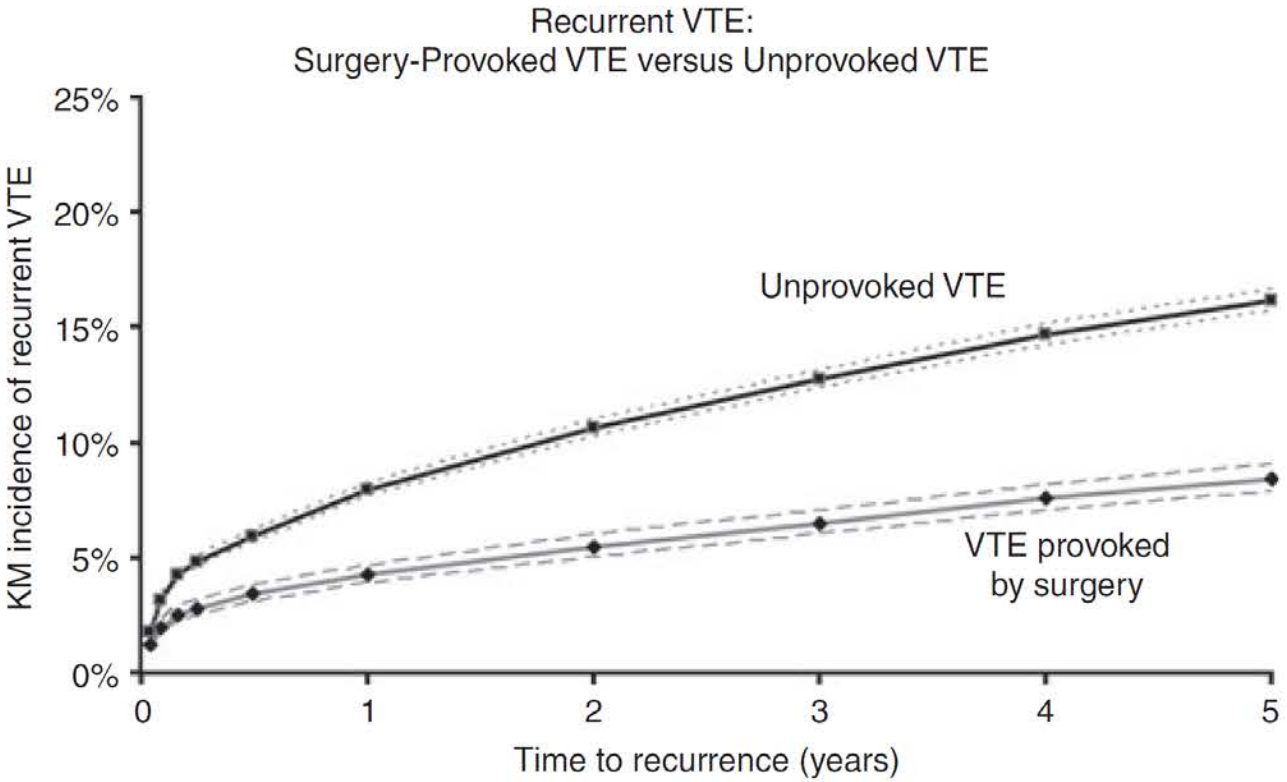

J Thromb Haemost 2010; 8: 987–97.

For pts with PE secondary to a **transient risk factor**, oral anticoagulation is recommended for **3 months**.

Extended oral anticoagulation is generally not recommended for patients with **provoked PE** provided that the transient risk factor no longer exists

Recommendations for duration of anticoagulation after pulmonary embolism

Recommendations	Class[a]	Level[b]	Ref[c]
with a second episode of unprovoked PE.			
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.[f]	IIa	B[e]	295, 370, 371
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	368, 369
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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	

ESC GUIDELINES 2014

Recommendations for duration of anticoagulation after pulmonary embolism

Recommendations	Class[a]	Level[b]	Ref[c]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is	I	B	358
with severe renal impairment) if extended anticoagulation treatment is necessary.[f]			
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	368, 369
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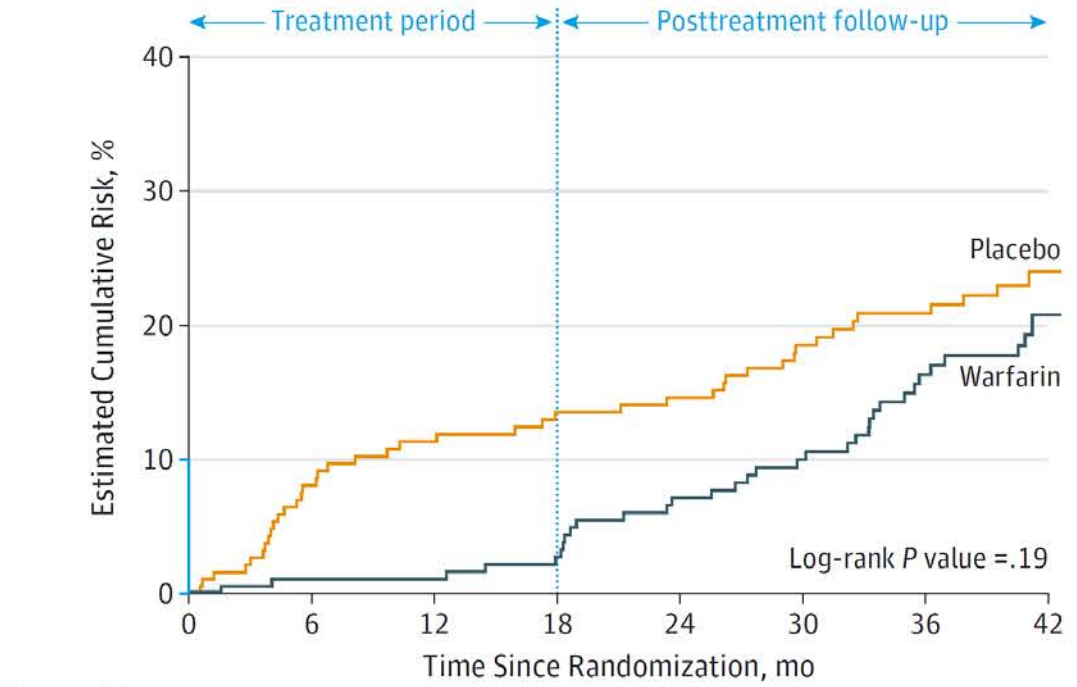
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

For pts with **unprovoked PE**, oral anticoagulation is recommended for **at least 3 months**.

Extended oral anticoagulation should be considered for pts with a **first episode of unprovoked PE** and **low bleeding risk**

Anticoagulation treatment of **indefinite duration** is recommended for patients with **a second episode of unprovoked PE**

ESC GUIDELINES 2014



No. at risk								
Placebo	187	170	162	158	155	140	117	104
Warfarin	184	182	180	174	168	150	120	110

JAMA. 2015;314(1):31-40

Recommendations for duration of anticoagulation after pulmonary embolism

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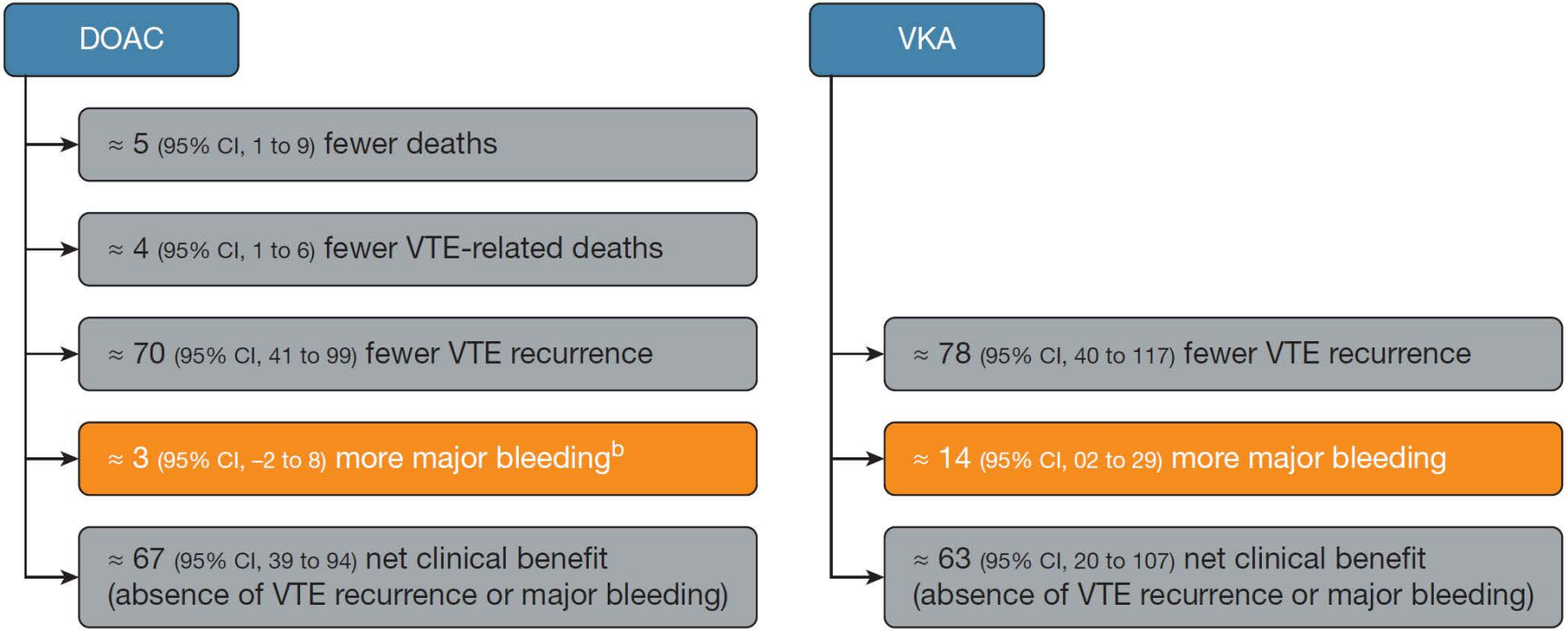
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

In pts who receive extended anticoagulation, the **risk–benefit ratio** of continuing should be **reassessed** at regular intervals

ESC GUIDELINES 2014

Extended Anticoagulation for VTE



CHEST 2019; 155(6):1199-1216

Risk of recurrence after a first episode of unprovoked VTE

Risk factors for DVT recurrence		
Proximal DVT location	Male sex	Persistence of residual vein thrombosis at ultrasound
Obesity	Non-zero blood group	High D-dimer values
Old age	Early PTS development	Role of inherited thrombophilia is controversial

Clinical prediction rules assessing risk of recurrent VTE after first episode of unprovoked VTE[71]

Score	**Vienna prediction model**	**DASH score**	**HERDOO-2**
Parameters	• D-dimer level at 3 weeks and 3, 9, 15, 24 months after stopping anticoagulation • Male sex • VTE location (Distal DVT, Proximal DVT, PE)	• Abnormal D-dimer 3–5 weeks after stopping anticoagulation • Male sex • Age<50 years • VTE not associated with oestrogen-progestatif therapy in women	• Abnormal D-dimer before stopping anticoagulation • Post thrombotic symptoms (hyperpigmentation, edema and redness) • Age ≥65 years • BMI ≥30
Validation study	Yes	Yes	Yes
Commentaries	Different nomograms are available to calculate risk of VTE recurrence at different time	Patients with low score (≤1) have an annual recurrence rate of 3.1%	It is applicable in women only. Women with low score (≤1) have an annual recurrence rate of 1.3%

ESC consensus document on diagnosis and management of acute DVT
European Heart Journal (2017)

- **Anticoagulants reduce the risk of recurrent VTE by 80% - 90%**
  at the cost of a 1% - 3% annual risk of major bleeding

- ***The continuation is justified when the annual risk of recurrence***
  is higher than 3% - 5%

In pts with cancer the 6 month risk of recurrence is 8% despite treatment
which strongly supports continuing anticoagulation
as long as the cancer is active

- After withdrawal of anticoagulant treatment
  the risk of recurrence - if anticoagulants are stopped after 6 or 12 months - is similar to that after 3 months

- Extended treatment for all patients with unprovoked VTE will expose a substantial proportion of pts to unnecessary risk of bleeding

- Anticoagulants are discontinued when
  the risk of anticoagulation-related bleeding
  outweighs
  the risk of recurrent VTE