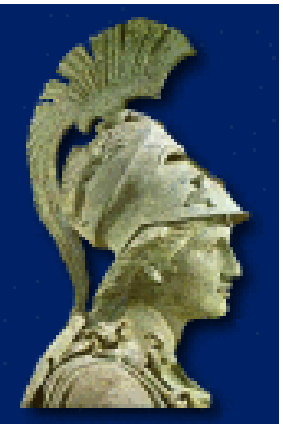
Πνευμονική εμβολή



Ηρακλής Τσαγκάρης

Αναπληρωτής Καθηγητής Εντατικής Θεραπείας

Αττικό Νοσοκομείο

Δήλωση συμφερόντων

Συμμετοχή σε συνέδρια, κλινικές μελέτες ή συμβουλευτικά των εταιρειών Actelion, Bayer, ELPEN, Galenica, Glaxo GSK, Lilly, MSD, Pfizer

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ESC GUIDELINES

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

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

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PULMONARY EMBOLISM

Pulmonary embolus (PE) refers to obstruction of the pulmonary artery or one of its branches by material (eg, thrombus, tumor, air, or fat), originated elsewhere in the body.

- ✓ Acute pulmonary embolism (PE) is a form of venous thromboembolism (VTE) that is common and sometimes fatal.

(> 50% of pts with proximal DVT have concurrent PE at presentation)[1]

- ✓ 70% of pts with PE have DVT.[2]

- ✓ Most emboli arise from lower extremity proximal veins (iliac, femoral, and popliteal), but may also originate in right heart, inferior vena cava, the pelvic, the renal and upper extremity veins.

1.Moser KM, et al. Frequent asymptomatic PE in pts with deep venous thrombosis. JAMA 1994;271: 223–225.

2.Kearon C. Natural history of venous thromboembolism. Circulation 2003;107(23 Suppl. 1):I22–I30.

Classification (1)

- Acute : Patients with acute PE typically develop symptoms and signs immediately after obstruction of pulmonary vessels.
- Subacute : Some patients with PE may also present subacutely within days or weeks following the initial event.
- Chronic : Patients with chronic PE slowly develop symptoms of pulmonary hypertension over many years (ie, chronic thromboembolic pulmonary hypertension; CTEPH).

Classification (2)

- Hemodynamically unstable PE (shock) : that which results in hypotension. Often (but not always) caused by large (massive) PE. NOT all patients with massive PE develop hypotension.
- Hemodynamically stable PE : PE that does not meet the definition of hemodynamically unstable PE.

Spectrum of severity : from small asymptomatic PE to mild or borderline hypotension that stabilizes in response to fluid therapy, or "intermediate" PE (presents with right ventricle dysfunction).

Classification (3)

- Saddle PE : lodges at the bifurcation of the main pulmonary artery, often extending into the right and left main pulmonary arteries.

  (3-6% of PE patients, 22% are hemodynamically unstable)

- Lobar PE

- Segmental PE

- Subsegmental PE

Thrombi in the peripheral segmental or subsegmental branches are more likely to cause pulmonary infarction and pleuritis

Classification (4)

- Symptomatic PE : presence of symptoms that usually leads to the radiologic confirmation of PE
- Asymptomatic PE : incidental finding of PE on imaging in a patient without symptoms (eg, contrast-enhanced computed tomography)

Pulmonary Embolism

- Epidemiology
- Risk factors
- Diagnosis
- Therapy

Pulmonary embolism (PE)

- ✓ PE is a well-recognised and significant cause of morbidity and mortality, estimated to be associated with more than 300 000 deaths per year in Europe alone (Cohen, Thromb Hemost, 2007).
- ✓ Many fatal cases (7%) are not diagnosed *pre mortem* because of the nonspecific clinical symptoms with which patients often present.
- ✓ A recent german analysis calculated the cost of the first year of PE treatment to be in excess of €20 000 (Kröger, Vasc Med, 2012).

PE ‘epidemy’

- ✓ There is growing evidence suggesting over-diagnosis of PE

Randomized comparison : although CT detected PE more frequently than V/Q scanning, three-month outcomes were similar, regardless of the diagnostic method used.

- ✓ United States : 80% rise in the apparent incidence of PE after the introduction of CT, without a significant impact on mortality.

Pulmonary Embolism

- Epidemiology
- Risk factors
- Diagnosis
- Therapy

Risk Factors

Table 3 Predisposing factors for venous thromboembolism

Predisposing factor	Patient-related	Setting-related
Strong predisposing factors (odds ratio >10)		
Fracture (hip or leg)		✓
Hip or knee replacement		✓
Major general surgery		✓
Major trauma		✓
Spinal cord injury		✓
Moderate predisposing factors (odds ratio 2–9)		
Arthroscopic knee surgery		✓
Central venous lines		✓
Chemotherapy		✓
Chronic heart or respiratory failure	✓	
Hormone replacement therapy	✓	
Malignancy	✓	
Oral contraceptive therapy	✓	
Paralytic stroke	✓	
Pregnancy/postpartum		✓
Previous VTE	✓	
Thrombophilia	✓	
Weak predisposing factors (odds ratio <2)		
Bed rest >3 days		✓
Immobility due to sitting (e.g. prolonged car or air travel)		✓
Increasing age	✓	
Laparoscopic surgery (e.g. cholecystectomy)		✓
Obesity	✓	
Pregnancy/antepartum	✓	
Varicose veins	✓	

Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J 2008; 29:2276–2315*

There could be no risk factors (20% ICOPER).

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

VTE as a risk factor

- Three quarters of VTEs are recurrences, mainly after stopping treatment.
- About 25% of patients with VTE have no apparent provoking risk factor ("unprovoked" or "idiopathic" venous thromboembolism), 50% have a temporary provoking risk factor such as recent surgery or estrogen therapy, and 25% have cancer.
- Half of VTE episodes are associated with hospitalization, and about half of these are in surgical patients and half occur after hospital discharge.

Lapner, BMJ 2013;346:f757

Recently identified predisposing factors for venous thromboembolism

- ✓ In fertile women, oral contraception is the most frequent predisposing factor for VTE.
- ✓ When occurring during pregnancy, VTE is a major cause of maternal mortality.

(The risk is highest in the third trimester of pregnancy and over the 6 weeks of the postpartum period, being up to 60 times higher 3 months after delivery)

- ✓ IVF further increases the risk of pregnancy-associated VTE.

Cross-sectional study from a Swedish registry : the overall risk of PE was particularly increased during the first trimester of pregnancy [hazard ratio (HR) 6.97]

- ✓ In post-menopausal women who receive hormone replacement therapy, the risk of VTE varies widely depending on the formulation used.

Pulmonary Embolism

- Epidemiology
- Risk factors
- Diagnosis
- Therapy

Clinical presentation : NOT helpful

	VTE	Other diseases
✓ Tachypnea :	70%	70 %
✓ Tachycardia :	25%	25 %
✓ Temperature :	7%	17% (> 38,5)
✓ Cyanosis :	10%	10 %

1. Wells P.S: Ann. Int. Med. 1998;129
2. Stein P.D. Chest 1997; 112

Clinical Signs

THERE ARE NO SYMPTOMS WITH > 80% SENSITIVITY

	VTE	Other diseases
Dyspnea	80%	60%
Pleuritic Pain	50%	40%
Cough	25%	25%
Hemoptysis	10%	10%
Shock	22%	10%

It is critical that a high level of suspicion be maintained

such that clinically relevant cases are not missed

Clinical probability assessment (I)

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
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

% PE patients

10%
30%
65%

Clinical probability assessment (II)

Revised Geneva score	Original version[93]	Simplified version[108]
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	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

% PE patients

10%
30%
65%

Clinical Probability for DVT

Active cancer	+1
Paralysis, paresis, recent casting of leg	+1
Bedridden (>3 days) or major (>12 weeks)	+1
Entire leg swollen	+1
Calf swelling (>3cm) compared to other leg	+1
Pitting edema greater in symptomatic leg	+1
Collateral non varicose superficial veins	+1
Localized tenderness along deep venous system	+1
Previously documented DVT	+1
Alternative Dx as or more likely than DVT	-2

Score: DVT unlikely <2 DVT likely ≥2

Wells PS, et al Lancet 1997; 350:1795-98; N Engl J Med 2003;349: 1227-35

Diagnostic criterion	Clinical probability of PE		
	Low	Intermediate	High
Exclusion of PE			
D-dimer			
Negative result, highly sensitive assay	+	+	–
Negative result, moderately sensitive assay	+	±	–
Chest CT angiography			
Normal multidetector CT alone	+	+	±
V/Q scan			
Normal perfusion lung scan	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–
Confirmation of PE			
Chest CT angiogram showing at least segmental PE	+	+	+
High probability V/Q scan	+	+	+
CUS showing proximal DVT	+	+	+

Diagnostic criterion	Clinical probability of PE	
	PE unlikely	PE likely
Exclusion of PE		
D-dimer		
Negative result, highly sensitive assay	+	–
Negative result, moderately sensitive assay	+	–
Chest CT angiography		
Normal multidetector CT alone	+	±
V/Q scan		
Normal perfusion lung scan	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	–
Confirmation of PE		
Chest CT angiogram showing at least segmental PE	+	+
High probability V/Q scan	+	+
CUS showing proximal DVT	+	+

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
D-dimer					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–
Chest CT angiography					
Normal multidetector CT alone	+	+	±	+	±
V/Q scan					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–	+	–
Confirmation of PE					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

D dimers testing

- ✓ The specificity of D-dimer in suspected PE decreases steadily with age, to almost 10% in patients > 80 years
- ✓ Age-adjusted cut-off values : age x 10 mg/L above 50 years
- ✓ They increase specificity from 34–46% while retaining a sensitivity above 97%.

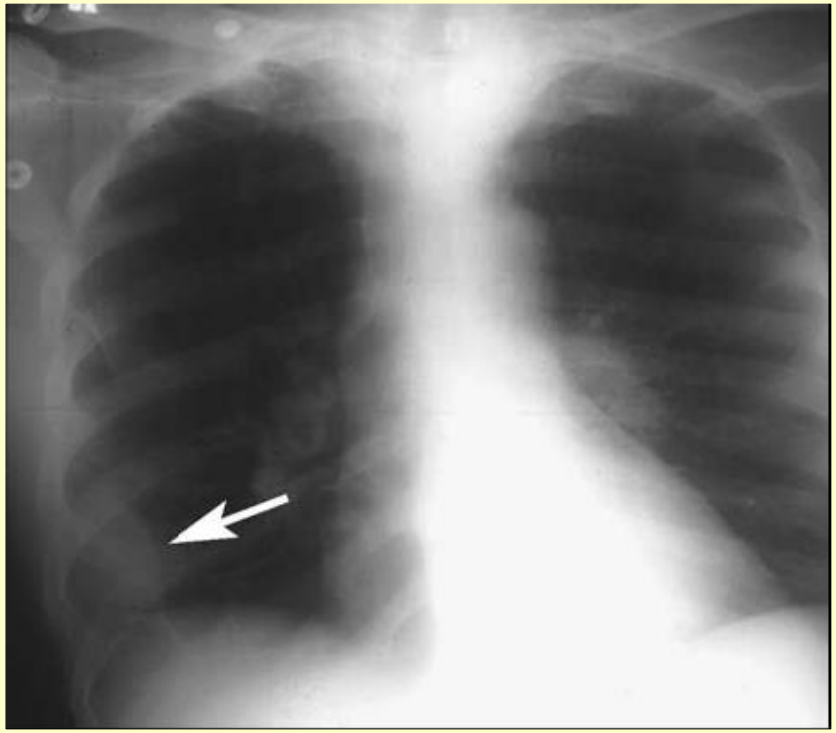
Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
D-dimer					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–

Diagnostic Imaging

- ✓ Chest X-ray
- ✓ Ventilation-perfusion scintigraphy (V/Q scan)
- ✓ Multiple detector computed tomography (MDCT)
- ✓ Conventional angiography
- ✓ MRI
- ✓ Compression venous ultrasonography

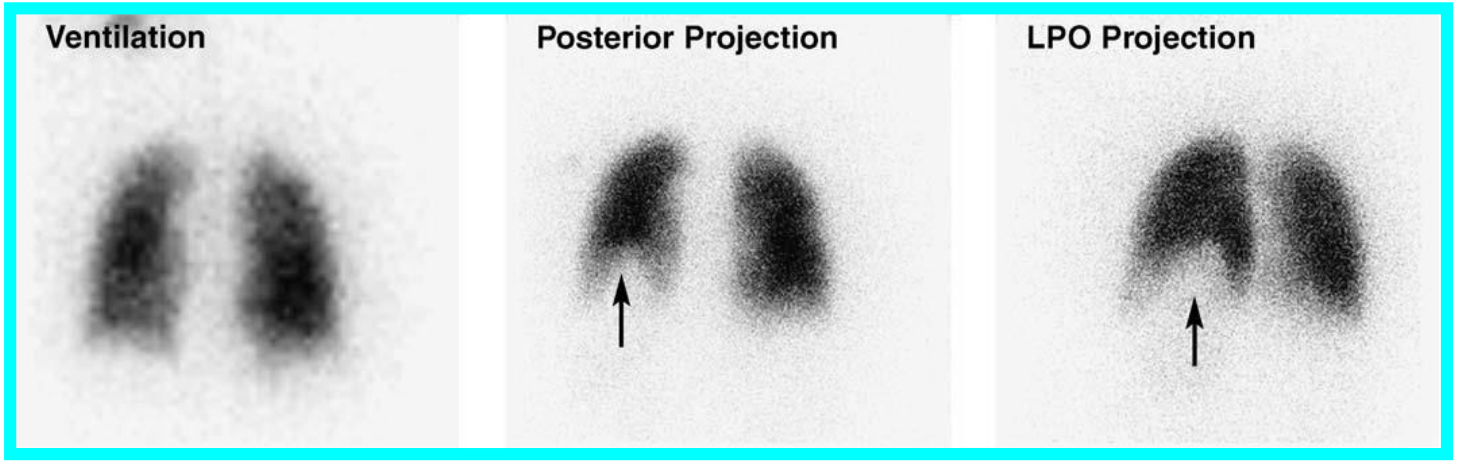
Chest X-ray

- ✓ Positive, in the majority of cases. (88% in PIOPED study).
- ✓ Nonspecific findings (cardiomegaly, pleural effusion, elevated hemidiaphragm, pulmonary artery dilatation, parenchymal infiltrates, etc.).
- ✓ Specific findings, rare (Hampton's hump, Westermark's sign).



Ventilation-Perfusion Scan V/Q Scan

- ✓ **Ventilation / perfusion mismatch**
- ✓ **Normal V/Q Scan excludes PE (NPV> 95%)**
- ✓ **High probability V/Q Scan → Relatively high PPV (85-90%)**
- ✓ **High prevalence of non – diagnostic tests (40-70%).**



V/Q scan

- ✓ A normal perfusion scan is very safe for excluding PE.
- ✓ Although less well validated, the combination of a nondiagnostic V/Q scan in a patient with a low clinical probability of PE is an acceptable criterion for excluding PE.

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
V/Q scan					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–	+	–

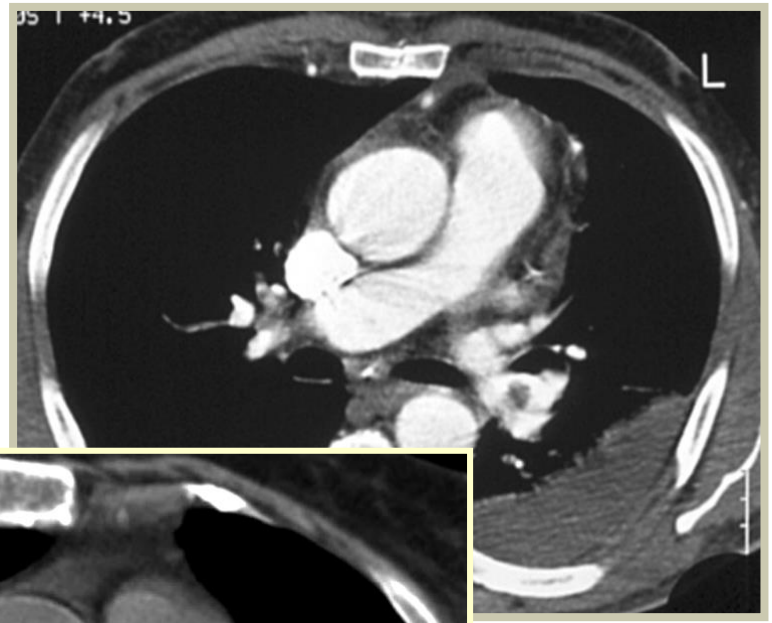
CT : the new gold standard

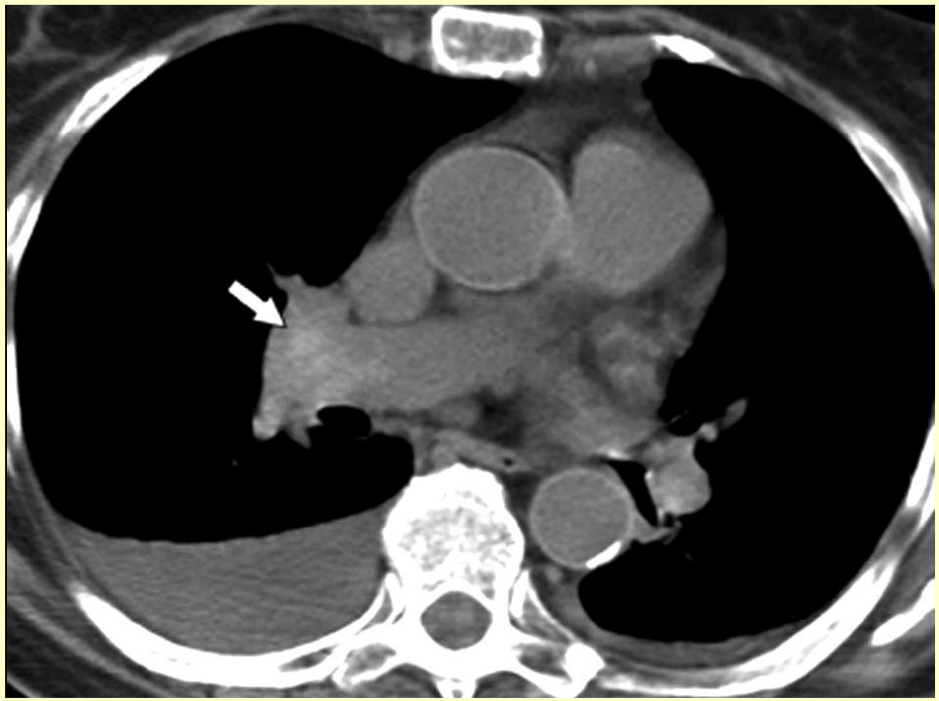
- ✓ A negative MDCT is an adequate criterion for excluding PE in patients with a non high clinical probability of PE.

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
Chest CT angiography					
Normal multidetector CT alone	+	+	±	+	±

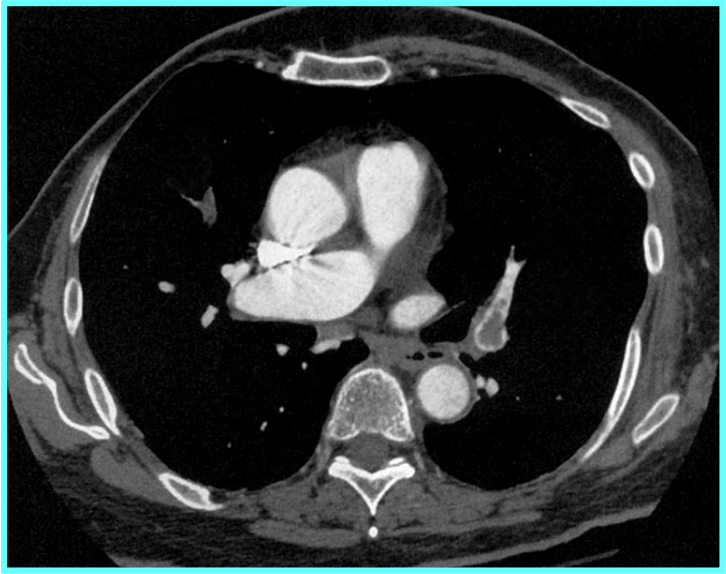
- ✓ Whether patients with a negative CT and a high clinical probability should be further investigated is controversial.

RIM SIGN

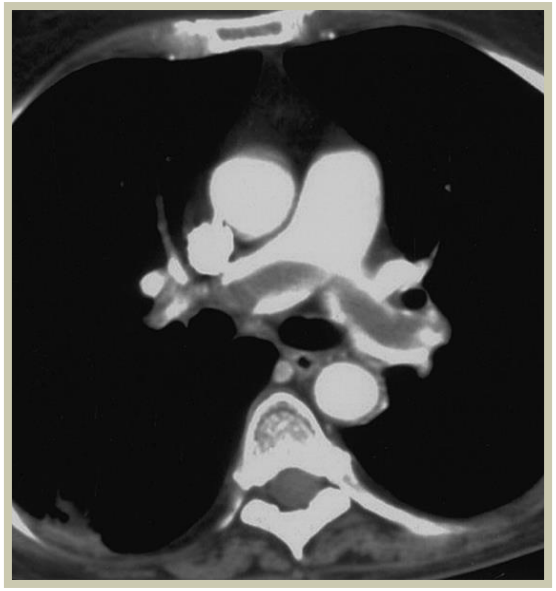


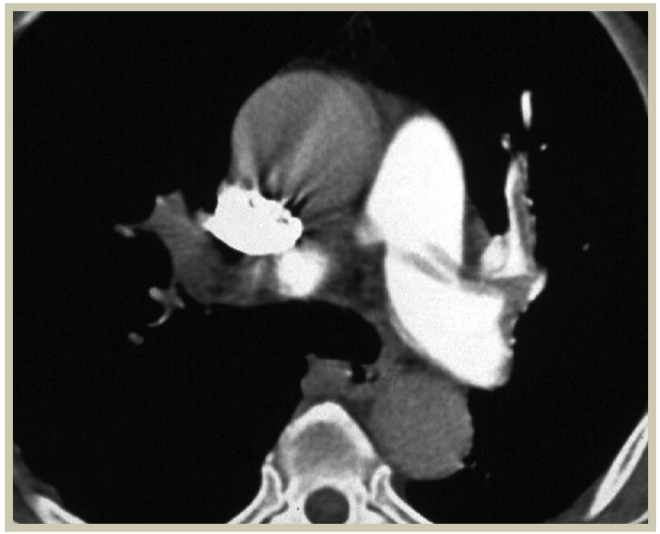


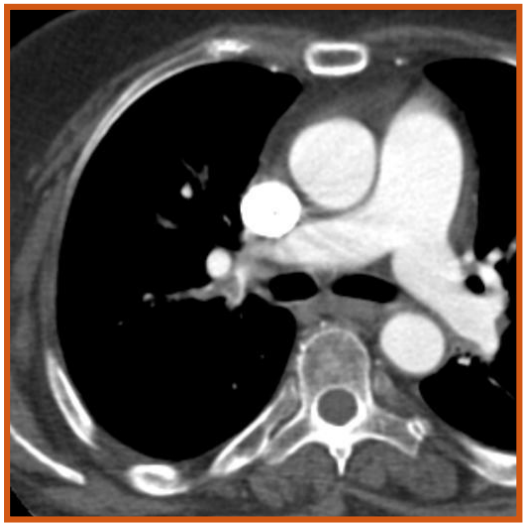
RAILROAD TRACK SIGN

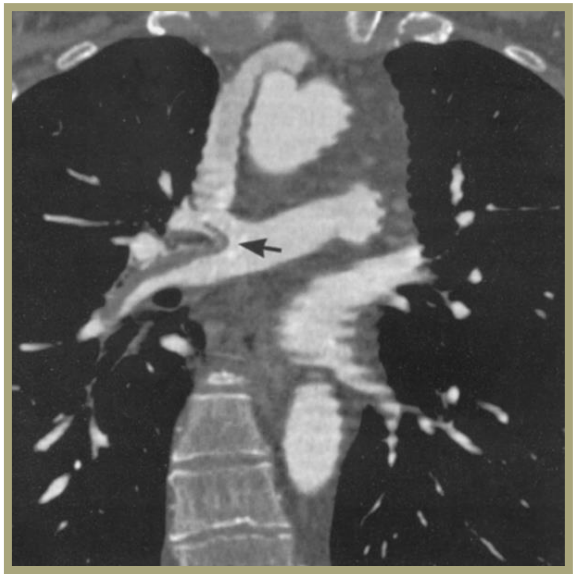


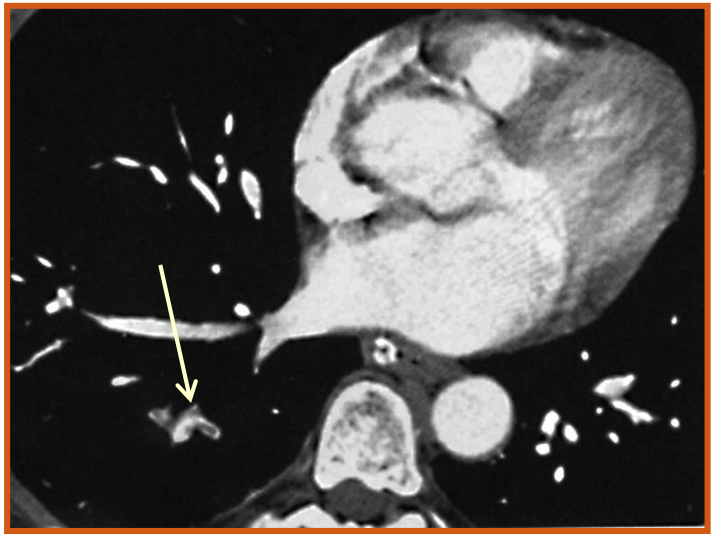
RIDING OR SADDLE EMBOLUS

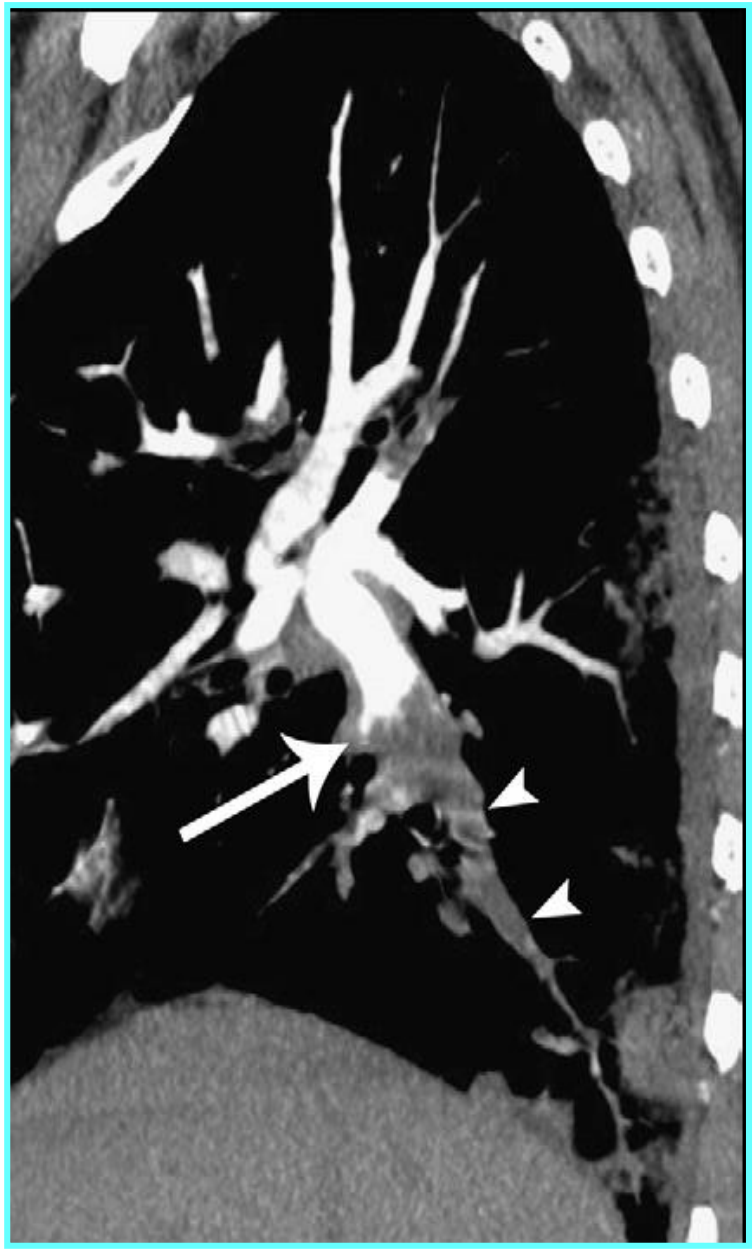




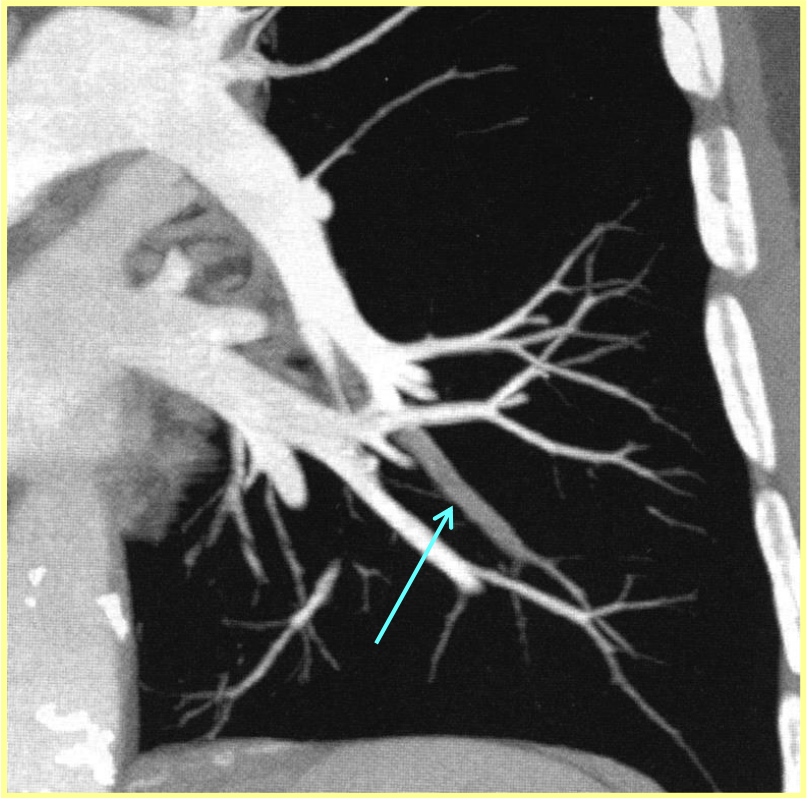




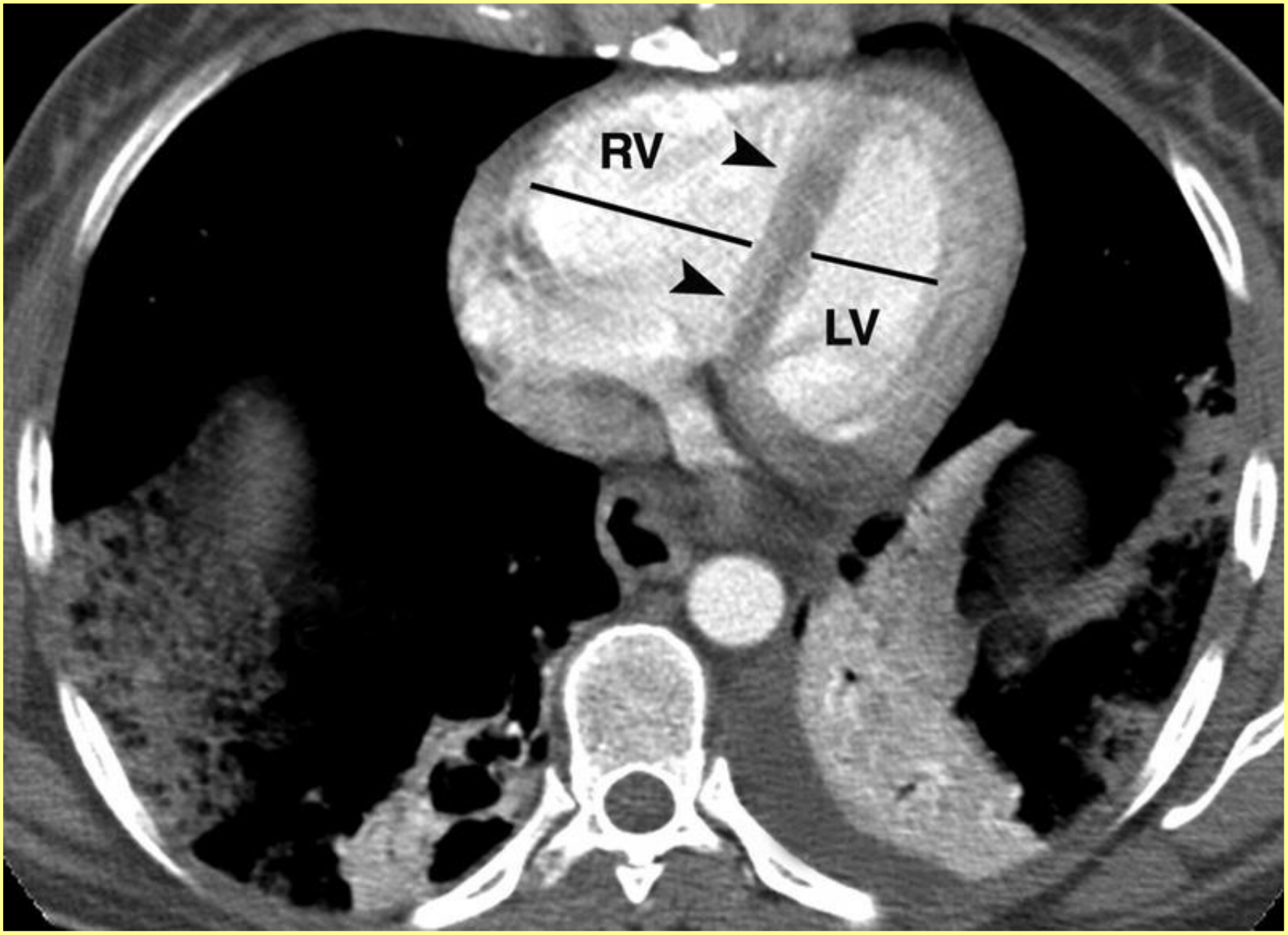


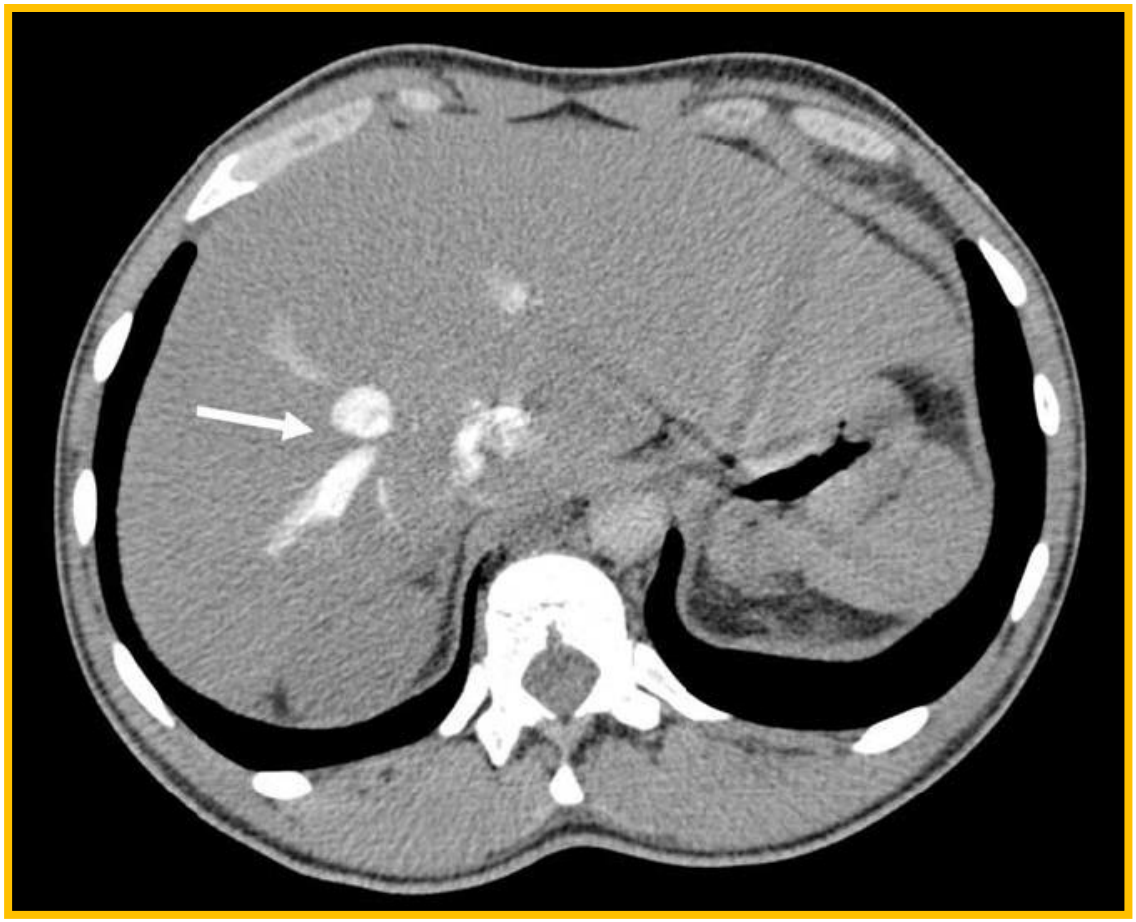


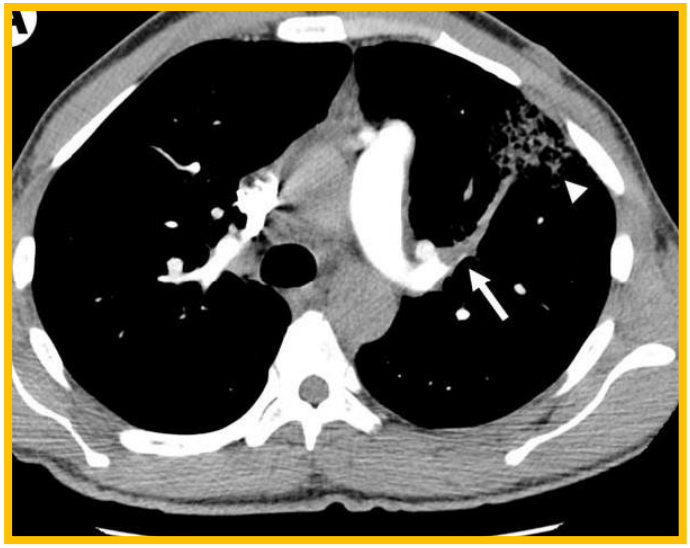
VESSEL “CUT-OFF” SIGN

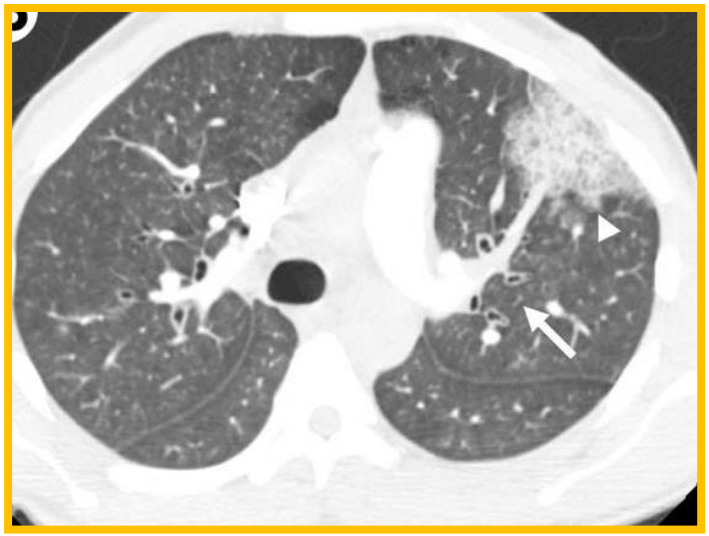


RV Dysfunction







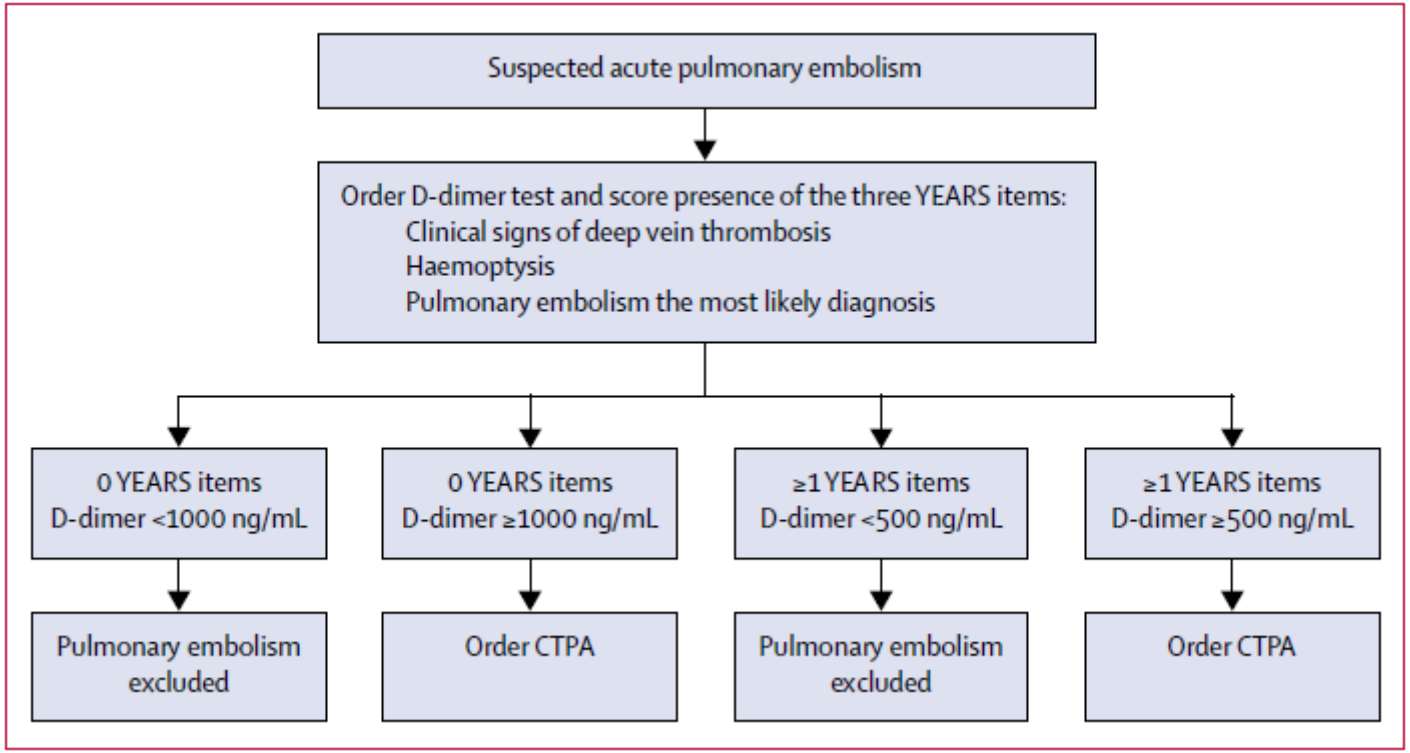


Acute PE
Infractions

- ✓ Peripheral , triangular, broad pleural-based lession
- ✓ No radiocontrast uptake
- ✓ No airbronchogram
- ✓ Vascular sign

Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

Tom van der Hulle, Whitney Y Cheung, Stephanie Kooij, Ludo F M Beenen, Thomas van Bemmel, Josien van Es, Laura M Faber, Germa M Hazelaar, Christian Heringhaus, Herman Hofstee, Marcel M C Hovens, Karin A H Kaasjager, Rick C J van Klink, Marieke J H A Kruip, Rinske F Loeffen, Albert T A Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Liselotte M van der Pol, Suzanne Schol-Gelok, Marije ten Wolde, Frederikus A Klok, Menno V Huisman



Published online May 23, 2017

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Confirmation of PE					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

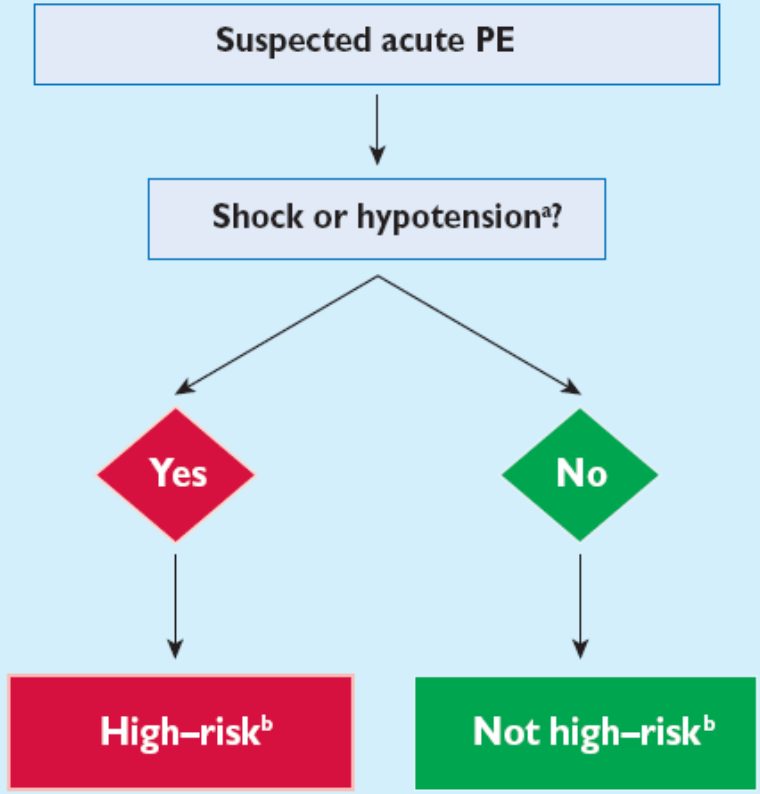
Pulmonary Embolism

- Epidemiology
- Risk factors
- Diagnosis
- Therapy

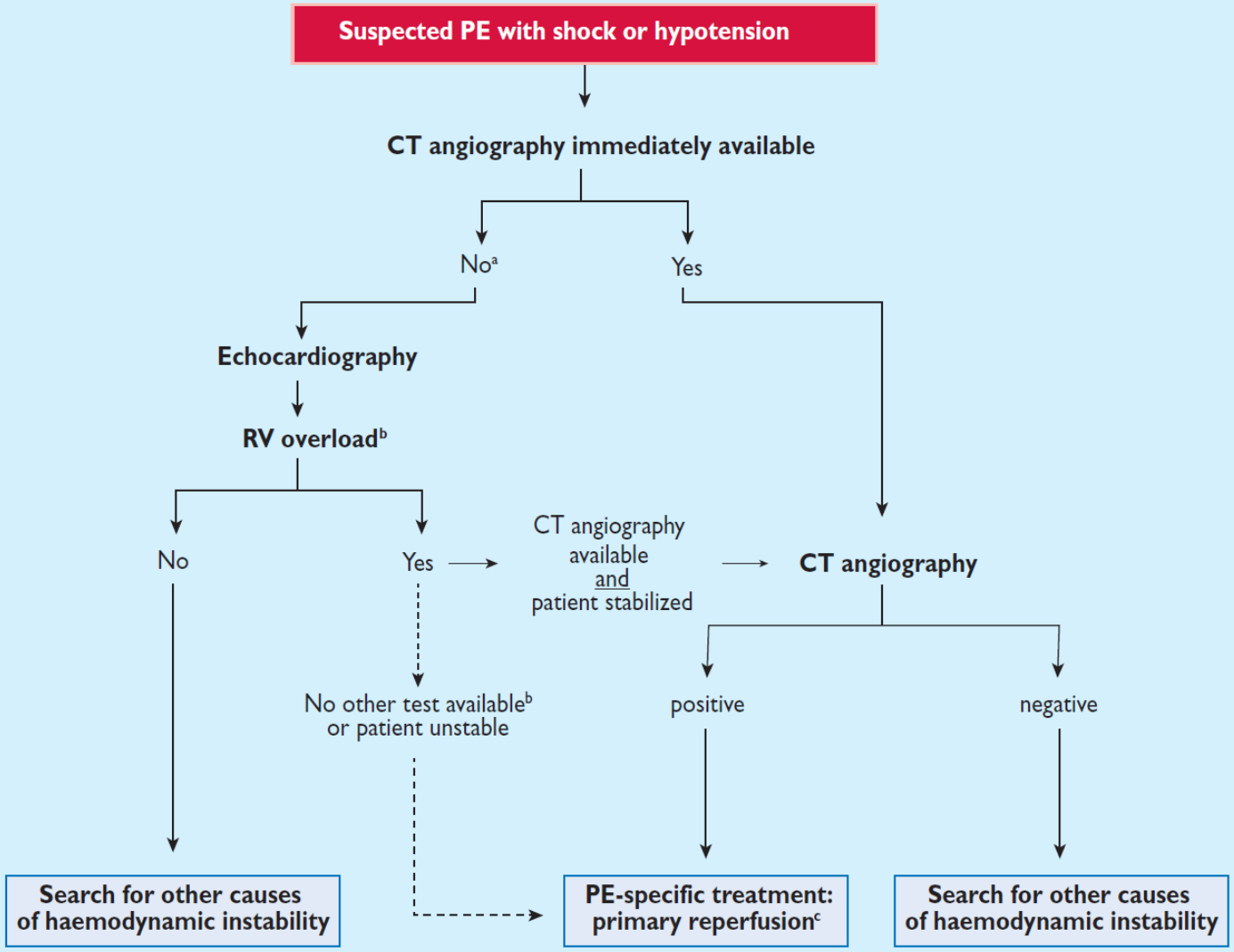
Major outcomes associated with PE

- Recurrent thromboembolism
- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Death (PE left untreated, is associated with an overall mortality of up to 30 percent)

Risk stratification of acute PE



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.

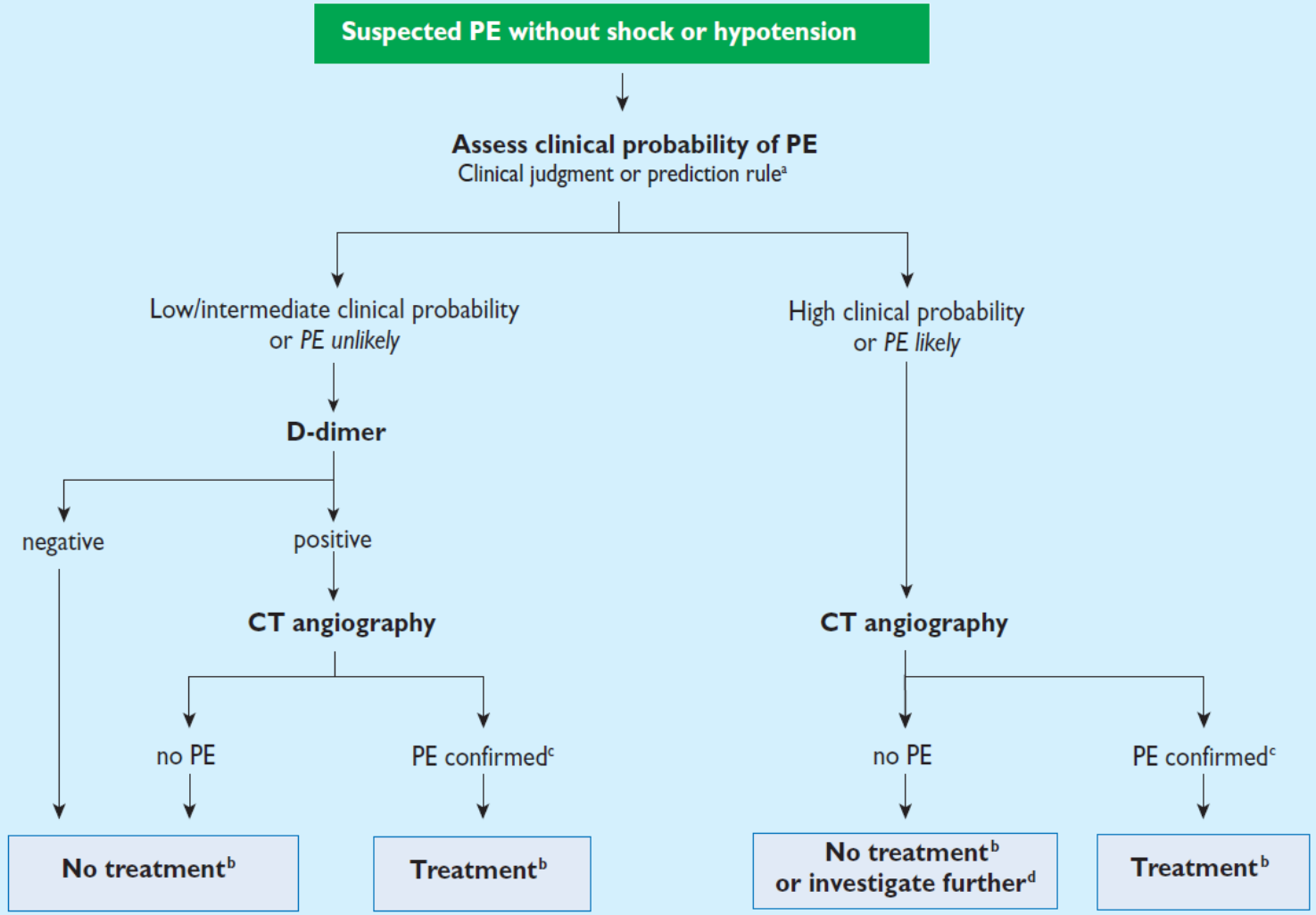


CT = computed tomographic; PE = pulmonary embolism; RV = right ventricle.

[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).



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.

Classification of patients with acute PE based on early mortality risk

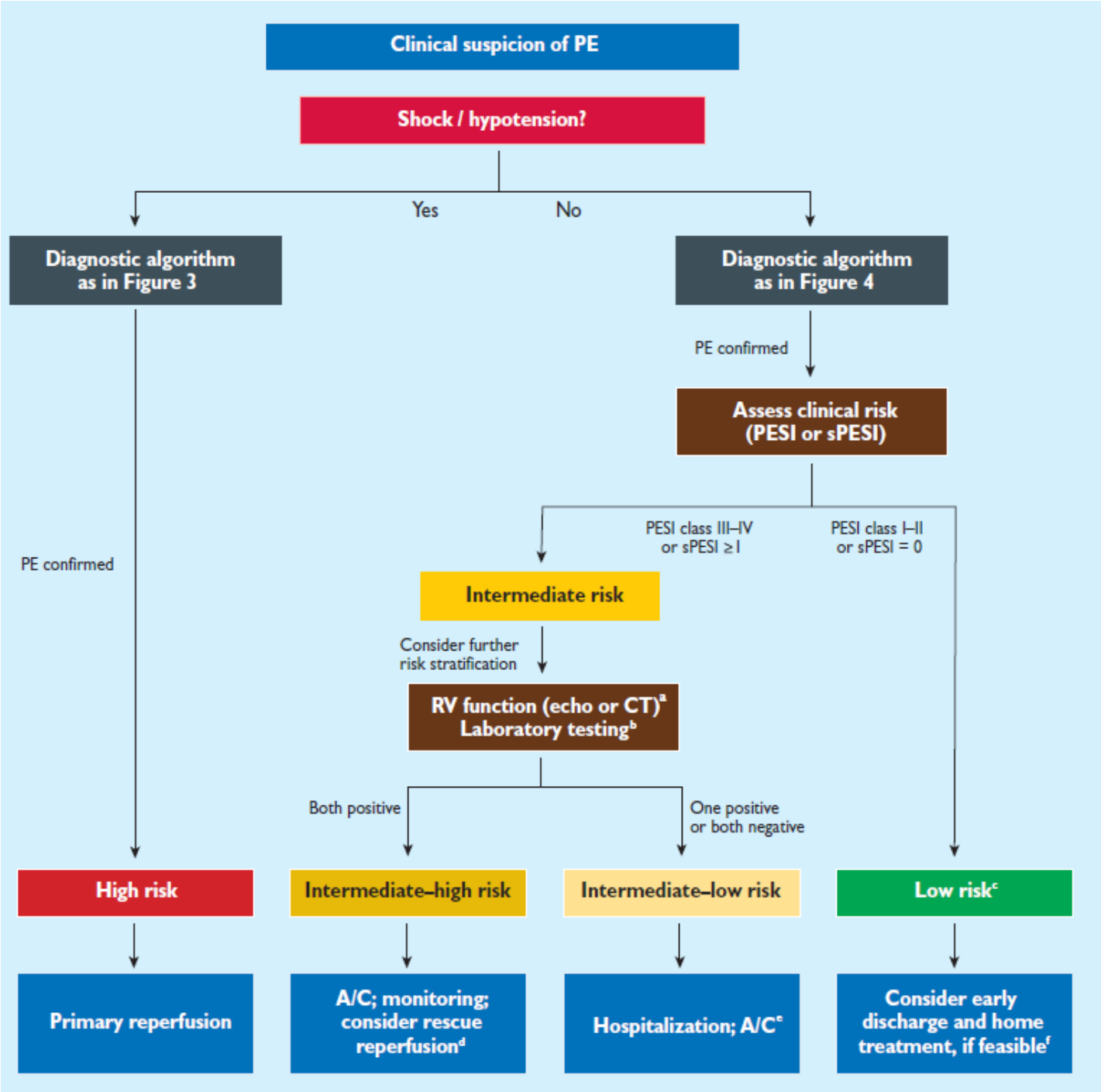
Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI >I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none)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

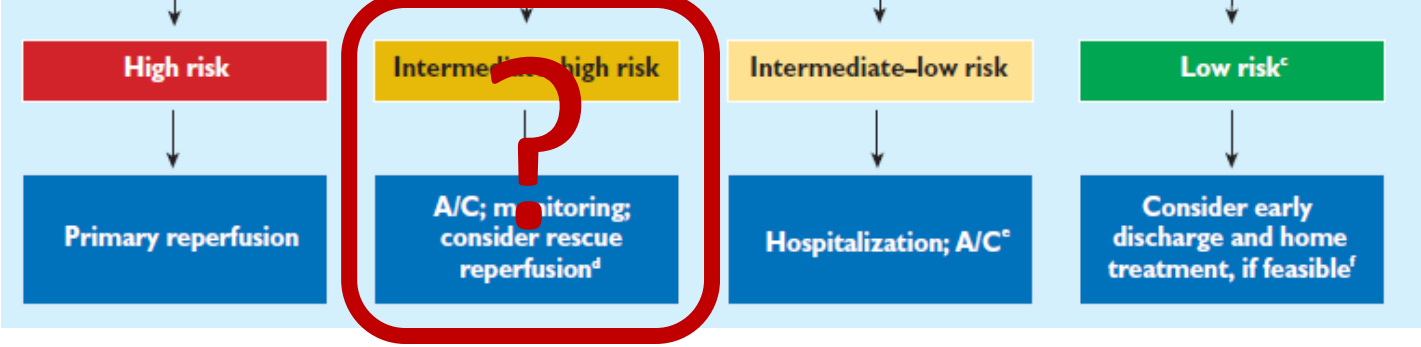
PESI (Pulmonary embolism severity index)

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%)

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 >I[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]	


Clinical suspicion of PE
Shock / hypotension?
Yes
No
Diagnostic algorithm as in Figure 3
Diagnostic algorithm as in Figure 4
PE confirmed
Assess clinical risk (PESI or sPESI)
PE confirmed
PESI class III–IV or sPESI ≥ I
PESI class I–II or sPESI = 0
Intermediate risk
Consider further risk stratification
RV function (echo or CT)[a]
Laboratory testing[b]
Both positive
One positive or both negative
High risk
Intermediate–high risk
Intermediate–low risk
Low risk[c]
Primary reperfusion
A/C; monitoring; consider rescue reperfusion[d]
Hospitalization; A/C[e]
Consider early discharge and home treatment, if feasible[f]

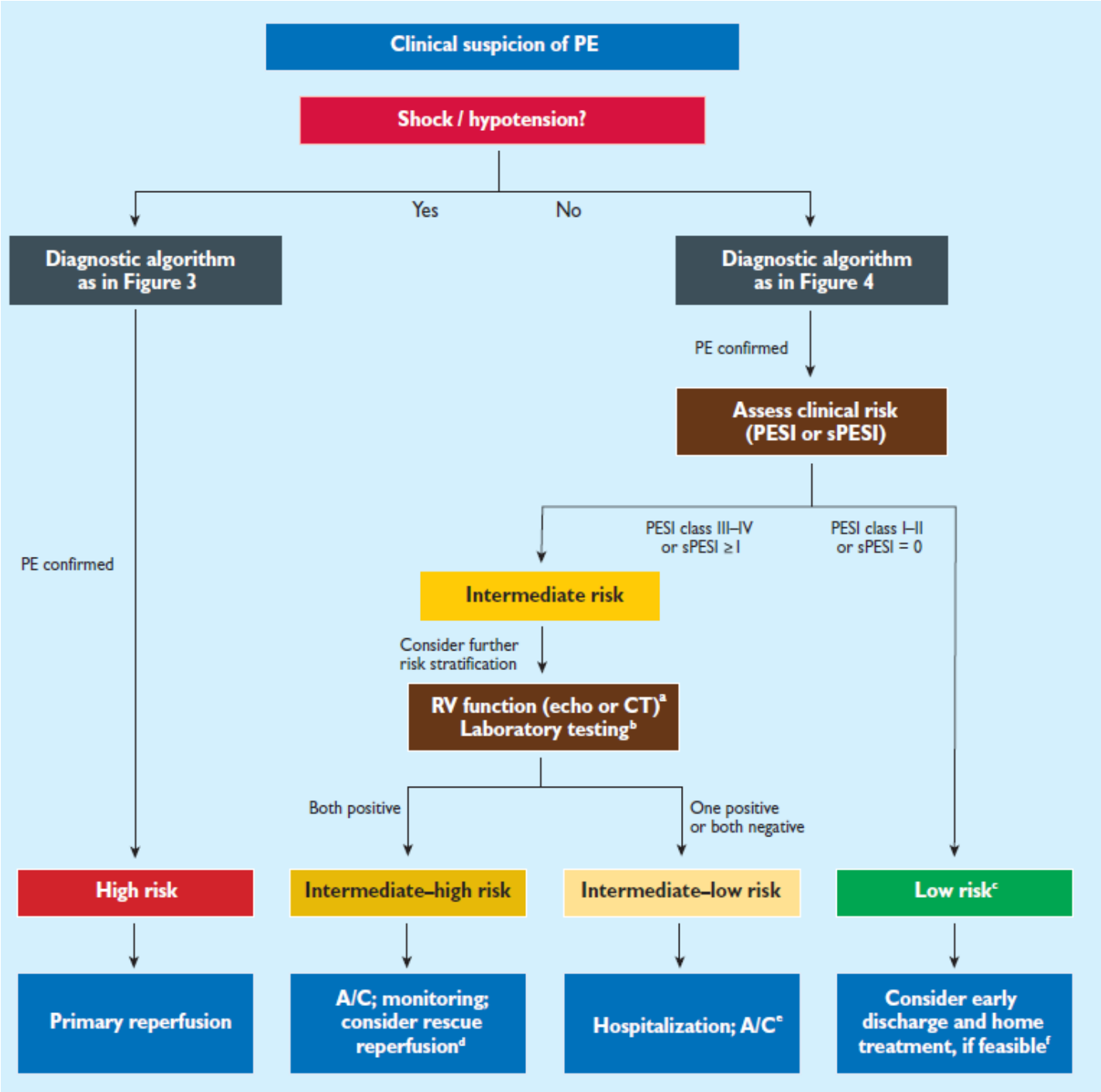


- Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT“ Trial). Am J Cardiol 2013; 111: 273–277.
- Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129: 479–486.
- Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370: 1402–1411.

CONCLUSIONS

In patients with intermediate-risk pulmonary embolism, fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke. (Funded by the Programme Hospitalier de Recherche Clinique in France and others; PEITHO EudraCT number, 2006-005328-18; ClinicalTrials.gov number, NCT00639743.)

N ENGL J MED 370;15 NEJM.ORG APRIL 10, 2014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Intermediate risk
Consider further risk stratification
RV function (echo or CT)[a]
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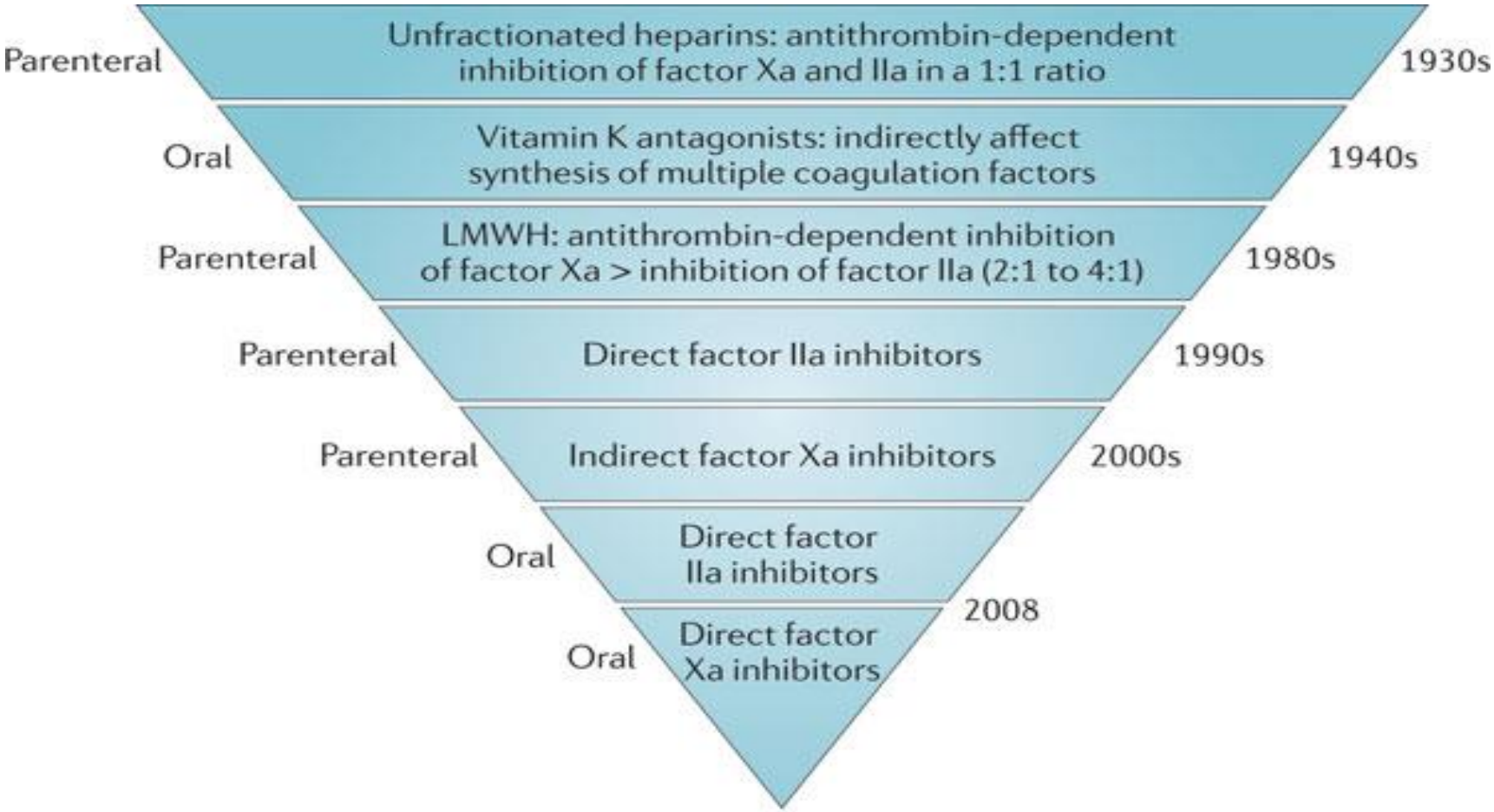
Low risk[c]
Primary reperfusion
A/C; monitoring; consider rescue reperfusion[d]
Hospitalization; A/C[e]
Consider early discharge and home treatment, if feasible[f]

The evolution of anticoagulants



Nature Reviews | Drug Discovery

Disadvantages of vitamin K antagonists

- ✓ Slow onset of action - Delayed return to baseline - Need for concomitant administration of fast-acting anticoagulants.
- ✓ Need for frequent monitoring.
- ✓ Interaction with drugs – diet.
- ✓ Affected by genetic factors (CYP2C9 and VKORC1 polymorphisms)

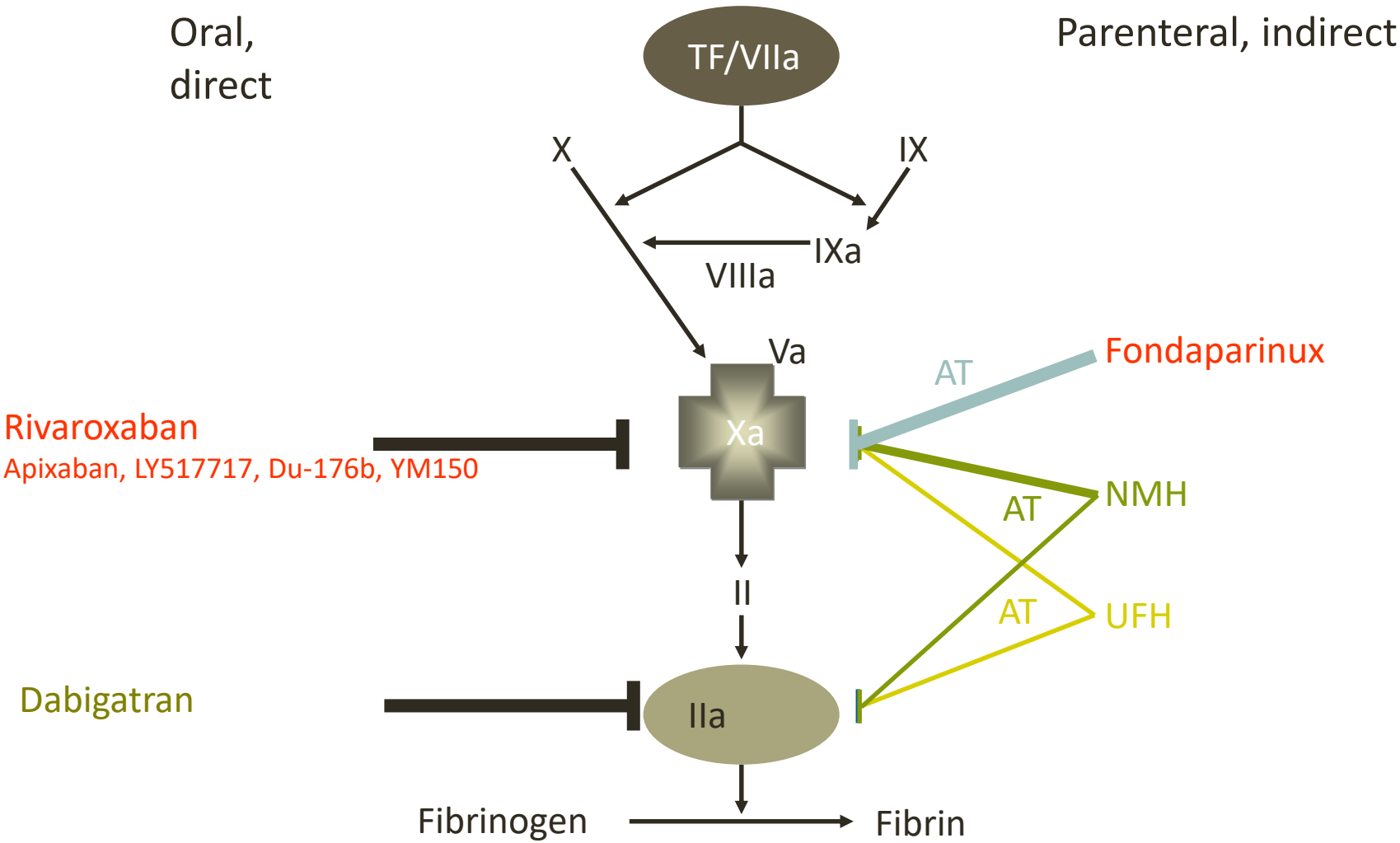
⇩

- ✓ Development of new drugs (dabigatran- rivaroxaban- …)

Risk factors for major bleeding during anticoagulant therapy

- ✓ old age, particularly above 75 years
- ✓ previous gastrointestinal bleeding, particularly if not associated with a reversible cause,
- ✓ previous non-cardioembolic stroke,
- ✓ chronic renal or hepatic disease,
- ✓ concomitant antiplatelet therapy (to be avoided if possible),
- ✓ other serious acute or chronic illness
- ✓ poor anticoagulant control,
- ✓ suboptimal monitoring of anticoagulant therapy.

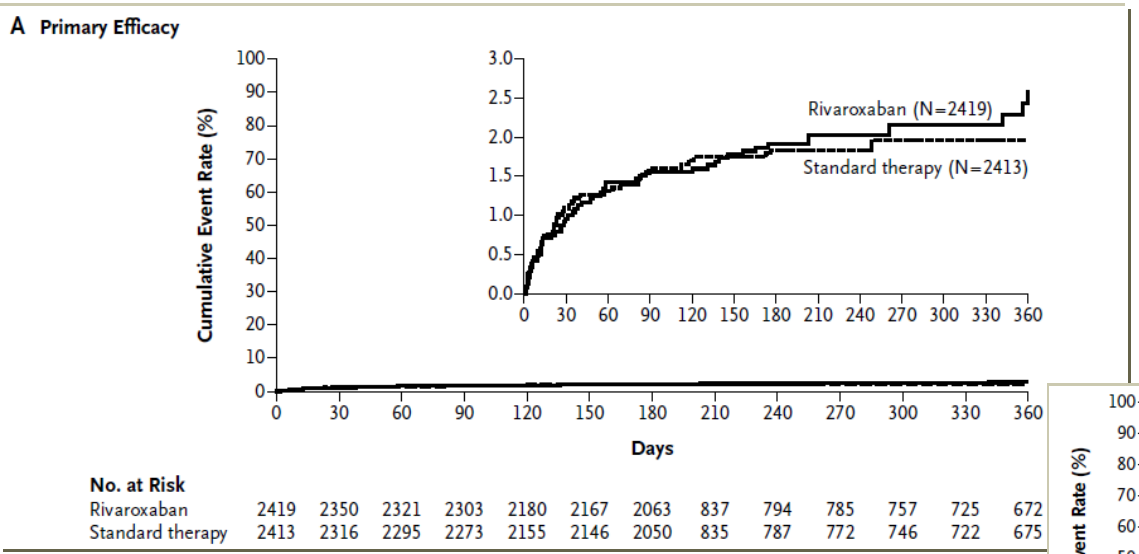
New Anticoagulants

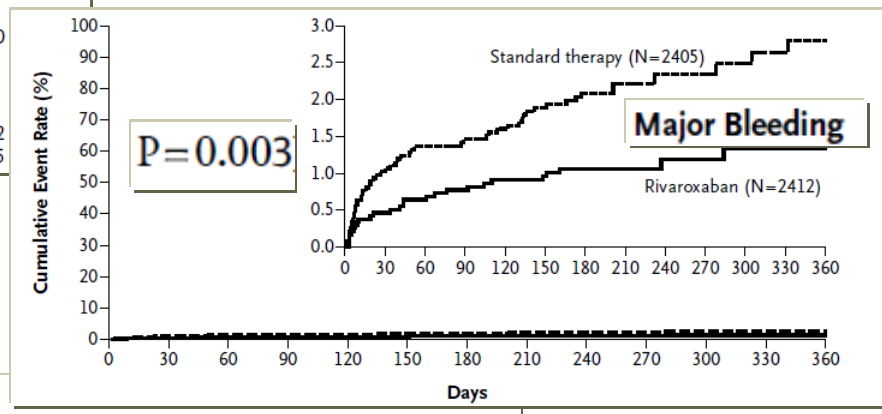


Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

N Engl J Med 2012;366:1287-97.





CONCLUSIONS

A fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit–risk profile. (Funded by Bayer HealthCare and Janssen Pharmaceuticals; EINSTEIN-PE ClinicalTrials.gov number, NCT00439777.)

European Heart Journal Advance Access published August 29, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

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

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svitil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

Recommendations for acute phase treatment

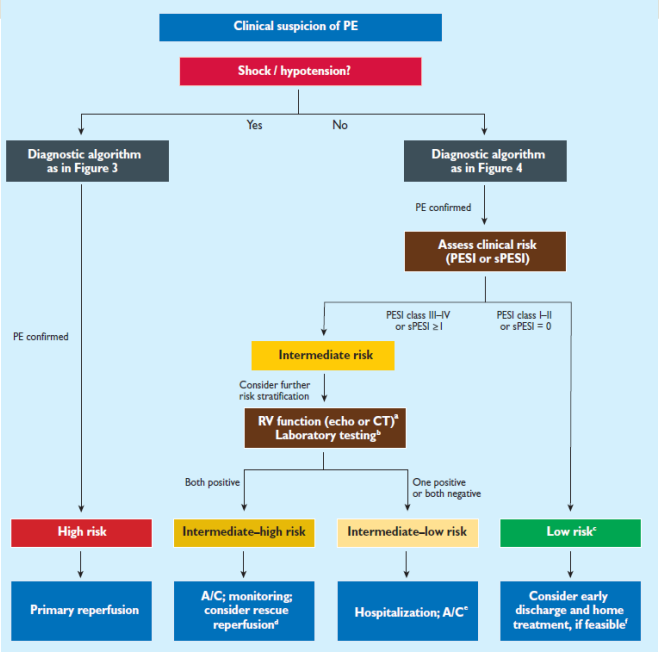
Recommendations	Class	Level
PE without shock or hypotension (intermediate-or low-risk)		
Anticoagulation: combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0)	I	B

Recommendations for acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate-or low-risk)		
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
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
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 acutephase parenteral anticoagulation.	I	B
As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in	III	A

Recommendations for acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate-or low-risk)		
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



Recommendations for acute phase treatment

PE with shock or hypotension (high-risk)

Recommendations	Class	Level
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	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	IIa	C

The current place of thrombolysis

- In high-risk PE with hemodynamic instability, the use of systemic thrombolysis reduces mortality by half * (n=4 studies, 224 pts).
- Thrombolytic drugs triple the risk of major hemorrhage and intracranial hemorrhage (ICH), with a global incidence of major bleeding of 9.9% and of ICH of ~ 2%.
- Given the poor prognosis of PE with shock, thrombolysis is both recommended by the ACCP (IIB) and the ESC (IB) guidelines

** Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2015;36(10):605-14*

Thrombolysis failure

- Less than 5% of high risk PE present persistent shock despite vasopressors and thrombolysis or shock and contraindications to thrombolysis.
- In those particular situations, reperfusion methods by surgical thrombectomy (ESC 1C, ACCP 2C) or thrombolysis directed by catheter (ESC IIaC, ACCP 2C) can be considered, depending on local expertise

Recommendations for duration of anticoagulation after pulmonary embolism

Recomendations	Class	Level
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.	IIa	B
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

NOACs vs. Warfarin

Advantages of NOACs

- ✓ No INR monitoring.
- ✓ No bridging.
- ✓ Better patient compliance to treatment.
- ✓ Fewer medications.
- ✓ Fewer interactions with food and other diseases.
- ✓ Better management during the perioperative period.
- ✓ Probably better safety and efficacy for patients not adequately controlled with warfarin

NOACs are favoured over VKA in the 2016 ACCP recommendations (2B)

NOACs vs. Warfarin

Disadvantages of NOACs

- ✓ **Higher cost.**
- ✓ No clear advantage for patients adequately controlled with warfarin.
- ✓ Worst patient compliance when BID dosing is required.
- ✓ In cases where a dose is missed, the risk of adverse events is increased (short half life).
- ✓ No specific antidote-NOT ANY MORE
- ✓ Increased frequency of G/E complications and interruption of treatment.
- ✓ The lack of monitoring may involve worst patient compliance
- ✓ Renal monitoring and dose adjustments ae required.
- ✓ OPEN ISSUES: Obesity, Interactions

Antidotes to NOACs

- **Source:**
  FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa: Praxbind approved for specific emergency situations http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm. Published October 16, 2015.
- Idarucizumab (Praxbind), a humanized monoclonal antibody fragment that binds to dabigatran (Pradaxa; both Boehringer Ingelheim)

Glund S, *et al*. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet*. 2015;**386**:680–690
Pollack C. V., *et al*. Idarucizumab for Dabigatran Reversal. *NEJM*. 2015;**373**:511-520.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

CONCLUSIONS

Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects. (Funded by Portola Pharmaceuticals and others; ANNEXA-A and ANNEXA-R ClinicalTrials.gov numbers, NCT02207725 and NCT02220725.)

	Rivaroxaban (Xarelto; Bayer HealthCare/Janssen Pharmaceuticals)	Apixaban (Eliquis; Bristol-Myers Squibb/Pfizer)	Edoxaban (Lixiana; Daiichi Sankyo)	Dabigatran etexilate (Pradaxa; Boehringer Ingelheim)	Warfarin (generic)
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor	Vitamin K antagonist
Currently approved for VTE treatment in Europe and the USA?	Yes	Yes	No	Yes	Yes
Time to maximum concentration h	2–4	3–4	1–2	0.5–2	Several days
Half-life h	5–13	~12	8–10	12–14	~40
Proportion of unchanged drug excreted renally %	33[#]	27	35	85	Minor only
VTE treatment approach and dose	Single drug; 15 mg twice daily for 3 weeks, then 20 mg once daily	Single drug; 10 mg twice daily for 7 days, then 5 mg twice daily	Dual drug; after median 7 days of parenteral anticoagulation, 60 mg once daily	Dual drug; after 5–10 days of parenteral anticoagulation, 150 mg twice daily	Dual drug; start alongside parenteral anticoagulant, discontinue latter after ⩾5 days when INR ⩾2 for ⩾2 days, adjust dose to maintain INR 2–3
Dose adjustments for VTE treatment	None	No reduced dose tested in phase III trials	30 mg once daily tested in patients with CrCl 30–50 mL·min^{-1} or body weight ⩽60 kg or receiving concomitant strong P-gp inhibitors	No reduced dose tested in phase III trials	Frequent, guided by the INR
Incidence of clinically relevant/major bleeding in VTE treatment studies %	10.3/1.1 (EINSTEIN PE) and 8.1/0.7 (EINSTEIN DVT) as a single drug	4.3/0.6 (AMPLIFY) as a single drug	8.5/1.4 (Hokusai-VTE) after parenteral induction	5.6/1.6 (RE-COVER) after parenteral induction	Up to 11.4/2.2 in studies of direct OACs after parenteral induction
Reversal in bleeding emergency	PCC, aPCC or rFVIIa suggested for rivaroxaban, apixaban and dabigatran (specific antidotes in development)				PCC (vitamin K is slow)
Food effect	No interactions; take rivaroxaban 15 mg and 20 mg doses with food	No interaction; apixaban, edoxaban and dabigatran can be taken with or without food			Affected by many common foods, *e.g.* cranberry juice and vegetables containing high levels of vitamin K
Relevant drug interactions	Factor Xa inhibitors: strong inhibitors of CYP3A4 and P-gp: azole antimycotics (*e.g.* ketoconazole) and HIV protease inhibitors (*e.g.* ritonavir)			Dabigatran: strong P-gp inhibitors and inducers	Multiple

Rivaroxaban (Xarelto; Bayer HealthCare/ Janssen Pharmaceuticals)	Apixaban (Eliquis; Bristol-Myers Squibb/ Pfizer)	Edoxaban (Lixiana; Daiichi Sankyo)	Dabigatran etexilate (Pradaxa; Boehringer Ingelheim)	Warfarin (generic)
Age <18 years	Age <18 years	To be confirmed (not yet licensed for any indication in Europe)	Age <18 years	Hypersensitivity to warfarin or excipients
CrCl <15 mL·min^{-1}	CrCl <15 mL·min^{-1}		CrCl <30 mL·min^{-1}	Haemorrhagic stroke
Hypersensitivity to the active substance or excipients	Hepatic disease associated with coagulopathy and clinically relevant bleeding risk		Hypersensitivity to the active substance or any of the excipients	Clinically significant bleeding
Clinically significant active bleeding or lesions at risk of clinically significant bleeding	Severe hepatic impairment or dialysis		Clinically significant active bleeding or a lesion or condition at significant risk of major bleeding	Use within 72 h of surge with risk of severe bleeding
Concomitant strong inhibitors of both CYP3A4 and P-gp	Elevated liver enzymes (ALT/AST >2×ULN) or total bilirubin ⩾1.5×ULN		Hepatic impairment or liver disease expected to impact survival	Use within 48 h post-partum
Concomitant dronedarone	Hypersensitivity to active substance or excipients		Concomitant treatment with other anticoagulants (except when switching) or systemic ketoconazole, cyclosporine, itraconazole, tacrolimus or dronedarone	Pregnancy or breast feeding
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child–Pugh B or C	Clinically significant active bleeding		Pregnancy or breast feeding	Drugs where interactio lead to a significantly increased risk of bleedi (multiple)
Malignant neoplasms at high risk of bleeding	Concomitant strong inhibitors of both CYP3A4 and P-gp			
Pregnancy or breast feeding	Increased bleeding risk for other reasons			
	Pregnancy or breast feeding			

DOACs and obesity

- The 2016 ISTH recommendations suggested not to use DOAC in patients with a BMI>40 kg/m^2 or weight > 120 kg, in whom VKA would be more appropriate.
- Conversely, few participants of DOAC phase III trials had weights <50kg, in whom the efficacy and safety of these anticoagulant are therefore mostly unknown.

Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14(6):1308-13

DOACs and drug interactions

JAMA | Original Investigation

Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation

Shang-Hung Chang, MD, PhD; I-Jun Chou, MD; Yung-Hsin Yeh, MD; Meng-Jiun Chiou, MSc; Ming-Shien Wen, MD; Chi-Tai Kuo, MD; Lai-Chu See, PhD; Chang-Fu Kuo, MD, PhD

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using data from the Taiwan National Health Insurance database and including 91 330 patients with nonvalvular atrial fibrillation who received at least 1 NOAC prescription of dabigatran, rivaroxaban, or apixaban from January 1, 2012, through December 31, 2016, with final follow-up on December 31, 2016.

CONCLUSIONS AND RELEVANCE Among patients taking NOACs for nonvalvular atrial fibrillation, concurrent use of amiodarone, fluconazole, rifampin, and phenytoin compared with the use of NOACs alone, was associated with increased risk of major bleeding. Physicians prescribing NOAC medications should consider the potential risks associated with concomitant use of other drugs.

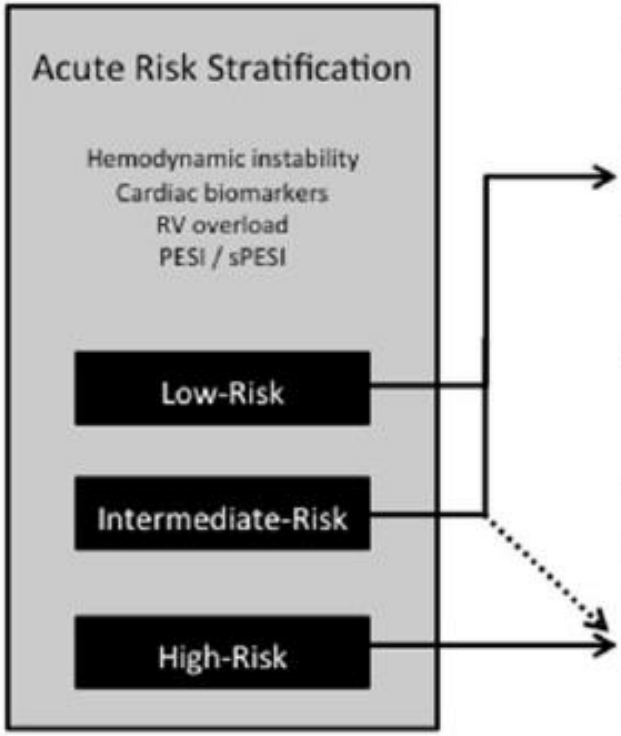
JAMA. 2017;318(13):1250-1259. doi:10.1001/jama.2017.13883

Recommendations for pulmonary embolism in pregnancy

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**
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**

Recommendations for pulmonary embolism in cancer

Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	**IIa C**
Negative D-dimer levels have the same negative diagnostic value as in noncancer patients.	**IIa 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**



ANTITHROMBOTIC AGENTS			
	INITIATION	EARLY MAINTENANCE (3-6M)	SECONDARY PREVENTION
Rivaroxaban	15 mg bid (21d)	20 mg od	20 mg od
Apixaban	10 mg bid (7d)	5 mg bid	2.5 mg bid
Edoxaban	IV or SC heparin (≥ 5d)	60 mg od *	60 mg od *
Dabigatran	IV or SC heparin (≥ 5d)	150 mg bid	150 mg bid
VKA	IV or SC heparin (≥ 5d)	INR 2.0-3.0	INR 2.0-3.0
LMWH (cancer) Dalteparin Tinzaparin	200 U/kg SC od (1m) 175 U/kg SC od	150 U/kg SC od 175 U/kg SC od	150 U/kg SC od 175 U/kg SC od
Aspirin	-	-	100mg od

Primary reperfusion
Fibrinolytics, catheter-directed techniques, surgical embolectomy, ECMO

Take away messages

- ✓ PE is the third most common cardiovascular disease after heart attack and stroke.
- ✓ Correct diagnosis, risk stratification and individualized treatment can reduce PE mortality.
- ✓ The management of acute PE is tailored to its predicted associated short-term mortality risk, and in the vast majority of cases relies simply on fast and efficient anticoagulation.

Take away messages

- ✓ DOAC have become the preferred anticoagulant agent in most situations, because of their effectiveness, favourable bleeding profile and lack of need for monitoring.
- ✓ When secondary long-term prevention of recurrent VTE after PE is decided, the anticoagulant agent must be chosen according its efficacy and safety profile, the patient's comorbidities and preferences.