Pulmonary Embolism

/*Pulmonary hypertension*

Khaled Al Oweidat, MD

PE

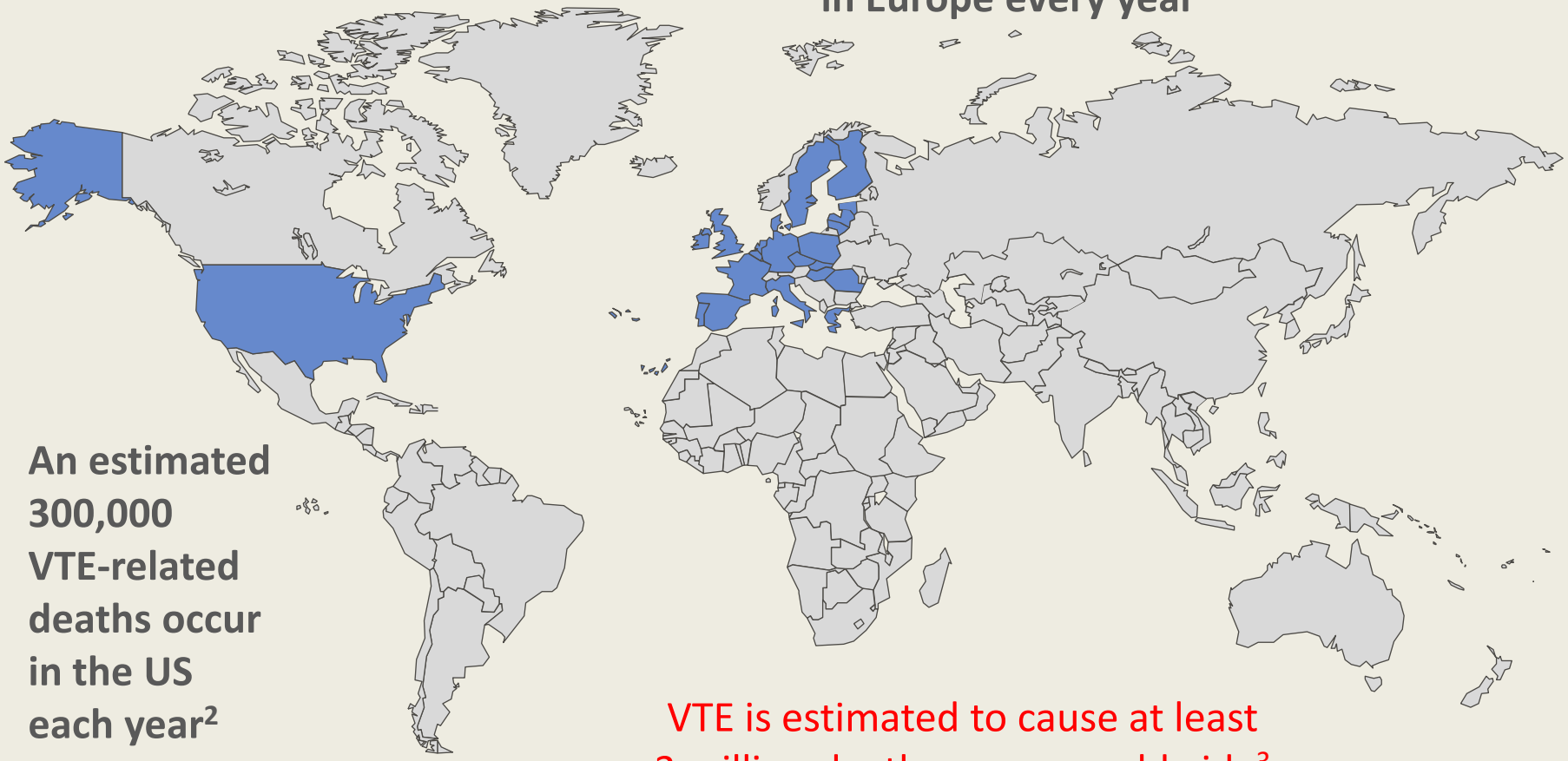
- Introduction
- Source of emboli
- Pathogenesis & Risk factors
- S&S
- Management approach:
  - - Assess clinical probability
  - -Assess risk of mortality
  - -Investigation
    - * Diagnostic
    - *Non diagnostic (helpful test)
  - -Treatment (medications and duration of treatment)

Introduction

- Partial or complete **occlusion** of a pulmonary arterial branch by blood clot(thrombus or multiple thrombi).
- Deep vein thrombosis and PE are different presentations of the same underlying pathophysiological event, venous thromboembolism **(VTE).**

VTE Is a Leading Cause of Death Worldwide

VTE is estimated to cause >500,000 deaths in Europe every year[1]



An estimated 300,000 VTE-related deaths occur in the US each year[2]

VTE is estimated to cause at least 3 million deaths a year worldwide[3]

1. Cohen AT *et al*, *Thromb Haemost* 2007;98:756–764; 2. Heit JA *et al, Blood* 2005;106:Abstract 910;
3. ISTH Steering Committee for World Thrombosis Day *J Thromb Haemost* 2014;12:1580–1590

Source of emboli

- **Thrombotic**

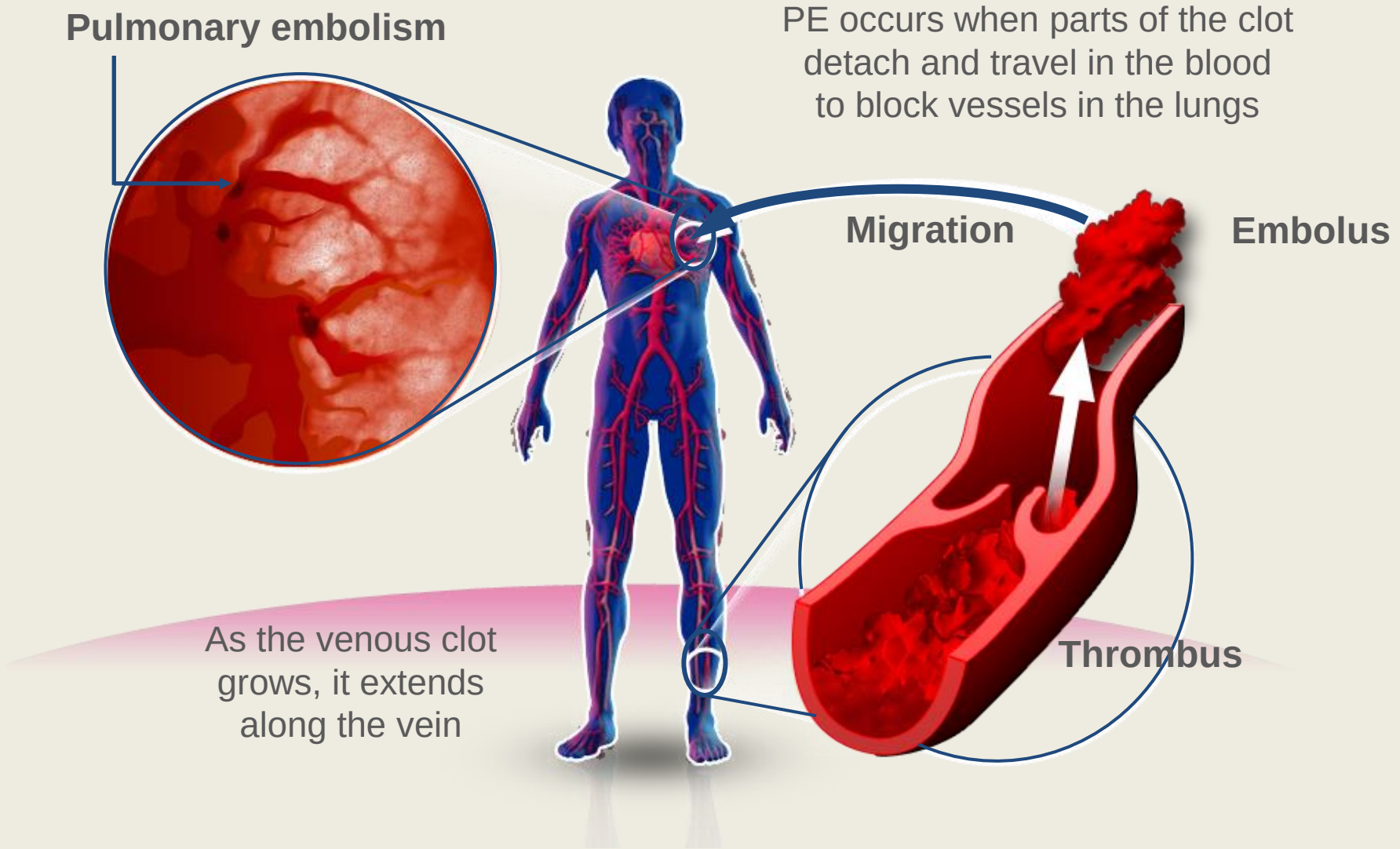
- Most cases (80–95 percent) as a result of thrombus **originating** in the lower extremity

- Most thrombi originate in the deep veins of the calf and propagate proximally to the popliteal and femoral veins.

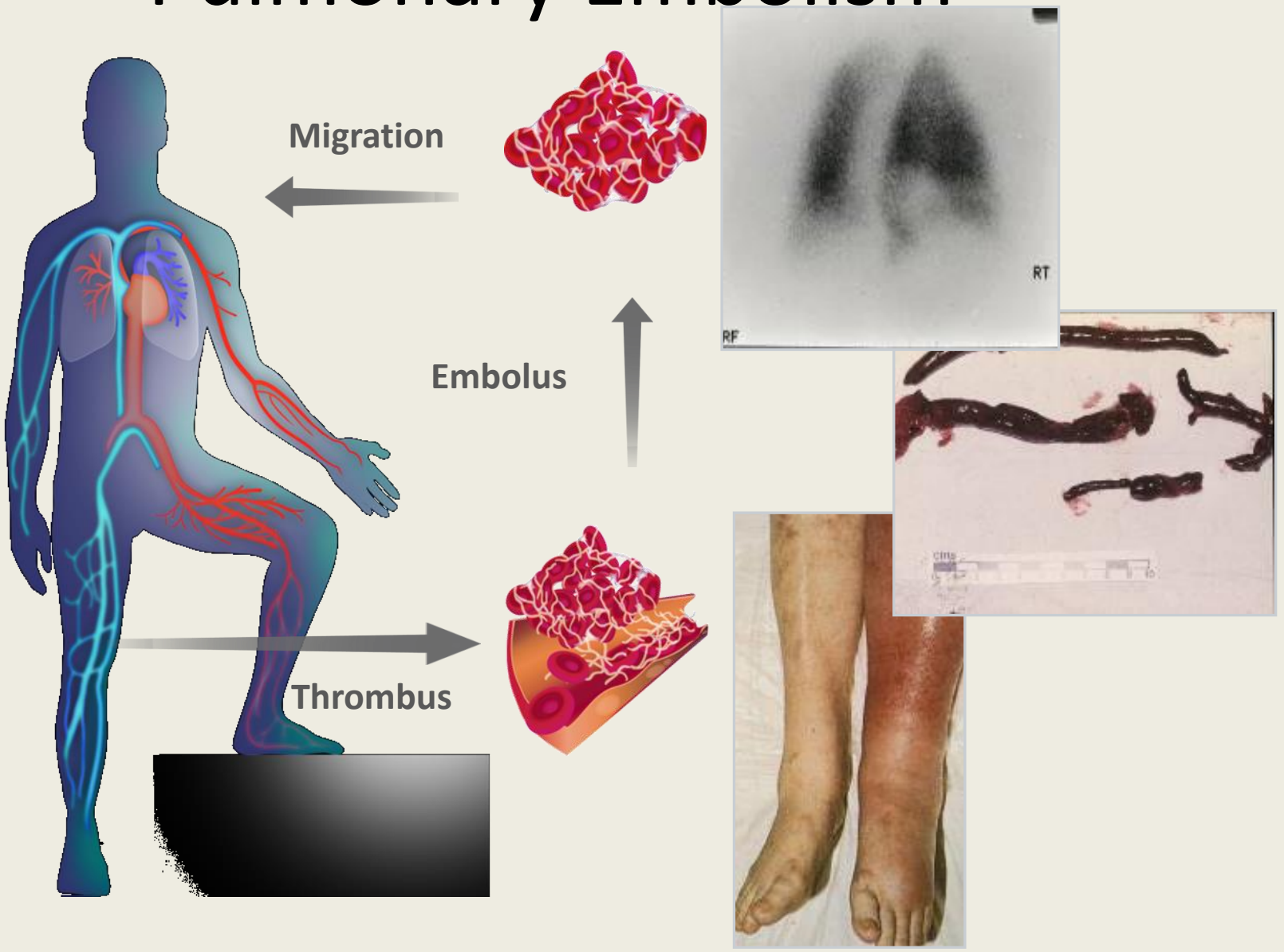
- Calf-limited(**below knee**) thrombi pose a minimal embolic risk

- Emboli may also originate from **atypical sites** such as upper-extremity thrombosis associated with central venous catheters or intravascular cardiac 2*devices, or may be associated with thoracic outlet obstruction or effort thrombosis

VTE: Deep Vein Thrombosis and Pulmonary Embolism



VTE: Deep Vein Thrombosis and Pulmonary Embolism



Non thrombotic

BOX 61-2 Causes of Nonthrombotic Pulmonary Emboli

Fat Embolism
Amniotic fluid embolism
Air Embolism
- Venous
- Arterial

Tumor embolism
Septic pulmonary embolism

Table 3 Predisposing factors for VTE (1)

Strong risk factors (OR >10)
Fracture of lower limb
Previous VTE
Spinal cord injury
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)

VTE = venous thromboembolism.

Table 3 Predisposing factors for VTE (2)

Moderate risk factors (OR 2–9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)

VTE = venous thromboembolism.

(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Table 3 Predisposing factors for VTE (3)

Moderate risk factors (cont'd)
In vitro fertilization
Oral contraceptive therapy
Postpartum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia

VTE = venous thromboembolism.

Table 3 Predisposing factors for VTE (4)

Weak risk factors (OR <2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

VTE = venous thromboembolism.

TABLE 61-1 Inherited Thrombophilias

	Prevalence (%)				
Disorder	General Population	Patients with VTE	Inheritance	Relative Risk	Clinical Features
AT deficiency	0.2	1–3	AD	20	VTE, heparin resistance
Protein C deficiency	0.2–0.4	3–5	AD	10	VTE
Protein S deficiency	0.03–0.1	1–5	AD	10	VTE and ATE
Factor V Leiden	5	10–50	AD	5	VTE and ATE
Prothrombin G20210A	2–5	6–18	AD	3	VTE
Hyperhomocysteinemia	5	10	Not known	3	VTE and premature ASCVD
Elevated factor VIII	11	25	Not known	5	VTE

(Data from Franchini M, Veneri D, Salvagno GL, *et al:* Inherited thrombophilia. Crit Rev Clin Lab Sci 2006;43:249–290.)
AT, Antithrombin; *VTE*, venous thromboembolism, *ATE*, arterial thromboembolism, *ASCVD*, atherosclerotic cardiovascular disease.

Once detached from their point of origin, emboli travel via the systemic venous system, through the right chambers of the heart, and **eventually reach the pulmonary arterial system**.

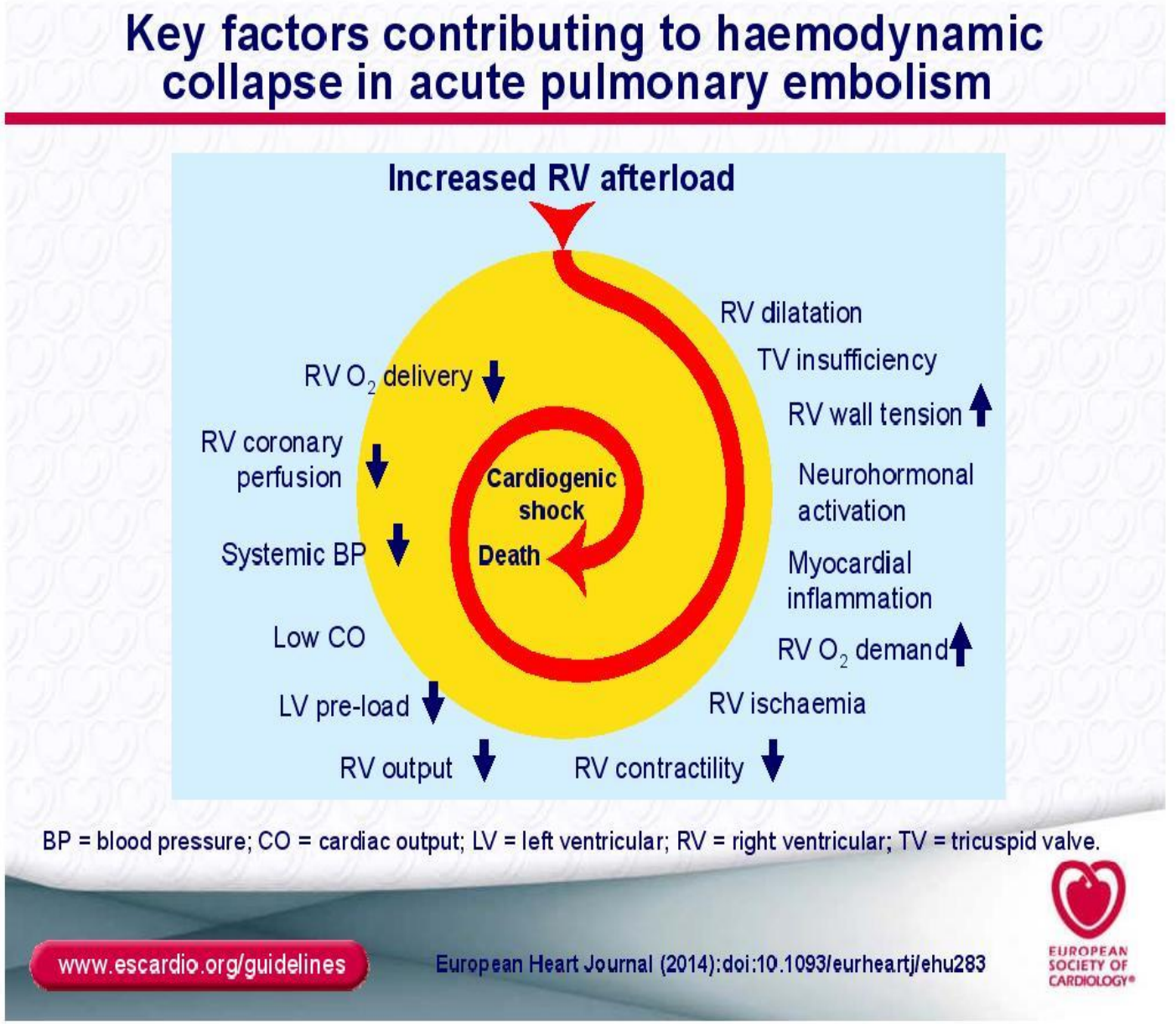
Physiologic effects and clinical consequences of pulmonary thromboembolism **vary widely**, ranging from asymptomatic disease to hemodynamic collapse and death

- **Major factors that determine the outcome include:**

- ❑ **Size and location** of emboli
- ❑ Coexisting cardiopulmonary **diseases**
- ❑ Secondary humoral mediator release and vascular hypoxic **responses**
- ❑ The rate of **resolution** of emboli.

European Heart Journal, 2019

Hemodynamic consequences



Gas exchange abnormality

- Gas exchange abnormalities…
  - **Hypoxemia**
  - **Increased A–a gradient.**
  - **<u>V/Q mismatch</u>**.
  - Increased dead space
  - Respiratory alkalosis from hyperventilation

    - **Often a sign of increased dead space and impaired minute ventilation**
    - ***may suggest massive PE***

S&S

TABLE 61-3 Frequency of Signs and Symptoms in Acute Pulmonary Embolism

Symptoms	Frequency (%)
Dyspnea	73
Pleuritic chest pain	66
Cough	37
Leg swelling	33
Hemoptysis	13
Wheezing	9
Chest pain	4
Signs	
Respiratory rate $\geq$20/min	70
Crackles	51
Heart rate $\geq$100/min	30
Third or fourth heart sound	26
Loud pulmonary component of second heart sound	23
Temperature $>$ 38.5° C	7
Pleural rub	3

TABLE 61-2 Differential Diagnosis of Acute Pulmonary Embolism

Pneumonia or bronchitis	Rib fracture
Asthma or exacerbation of chronic obstructive lung disease	Pulmonary edema/ Congestive heart failure
Pleuritis	Thoracic malignancy
Pericarditis/Cardiac tamponade	Pulmonary hypertension
Pneumothorax	Myocardial infarction
Musculoskeletal pain	Aortic dissection
Costochondritis	Anxiety

Management approach

- Assess clinical probability
- Assess risk of mortality
- Investigation
  - Diagnostic
  - Non diagnostic (helpful test)
- Treatment (medications and duration of treatment)

Assessment of pre-test probability

Clinical prediction rules for pulmonary embolism		
	Clinical decision rule points	
Wells rule	**Original version**	**Simplified version**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 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

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

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Assessment of pre-test probability (cont'd)

Clinical prediction rules for pulmonary embolism (cont.)		
	Clinical decision rule points	
Revised Geneva score	**Original version**	**Simplified version**
Previous DVT or PE	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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Assess risk of mortality

- **High Risk**:

  - Hemodynamically Unstable.
  - Early mortality is 15%.

- **Non-High Risk**

(According to RVD and Myocardial injury)

  - Intermediate Risk
  - Low Risk

Table 4 Definition of haemodynamic instability

(1) Cardiac arrest	(2) Obstructive shock	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP <90 mmHg, or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP <90 mmHg, or systolic BP drop ≥40 mmHg, either lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Table 8 Original and simplified PESI (1)

Parameter	Original version	Simplified version
Age	Age in years	1point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1point
Chronic heart failure	+10 points	1point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110b.p.m.	+20 points	1point
Systolic BP <100mmHg	+30 points	1point

BP = blood pressure; PESI = Pulmonary Embolism Severity Index.

(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Table 8 Original and simplified PESI (2)

Parameter	Original version	Simplified version
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1point

PESI = Pulmonary Embolism Severity Index.

Table 8 Original and simplified PESI (3)

	Risk strata	
	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%)	**0 points** = 30-day mortality risk 1.0% (95% CI 0.0–2.1%)
	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%)	**≥1 point(s)** = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)

PESI = Pulmonary Embolism Severity Index.

(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Table 9 Classification of PE based on early mortality risk

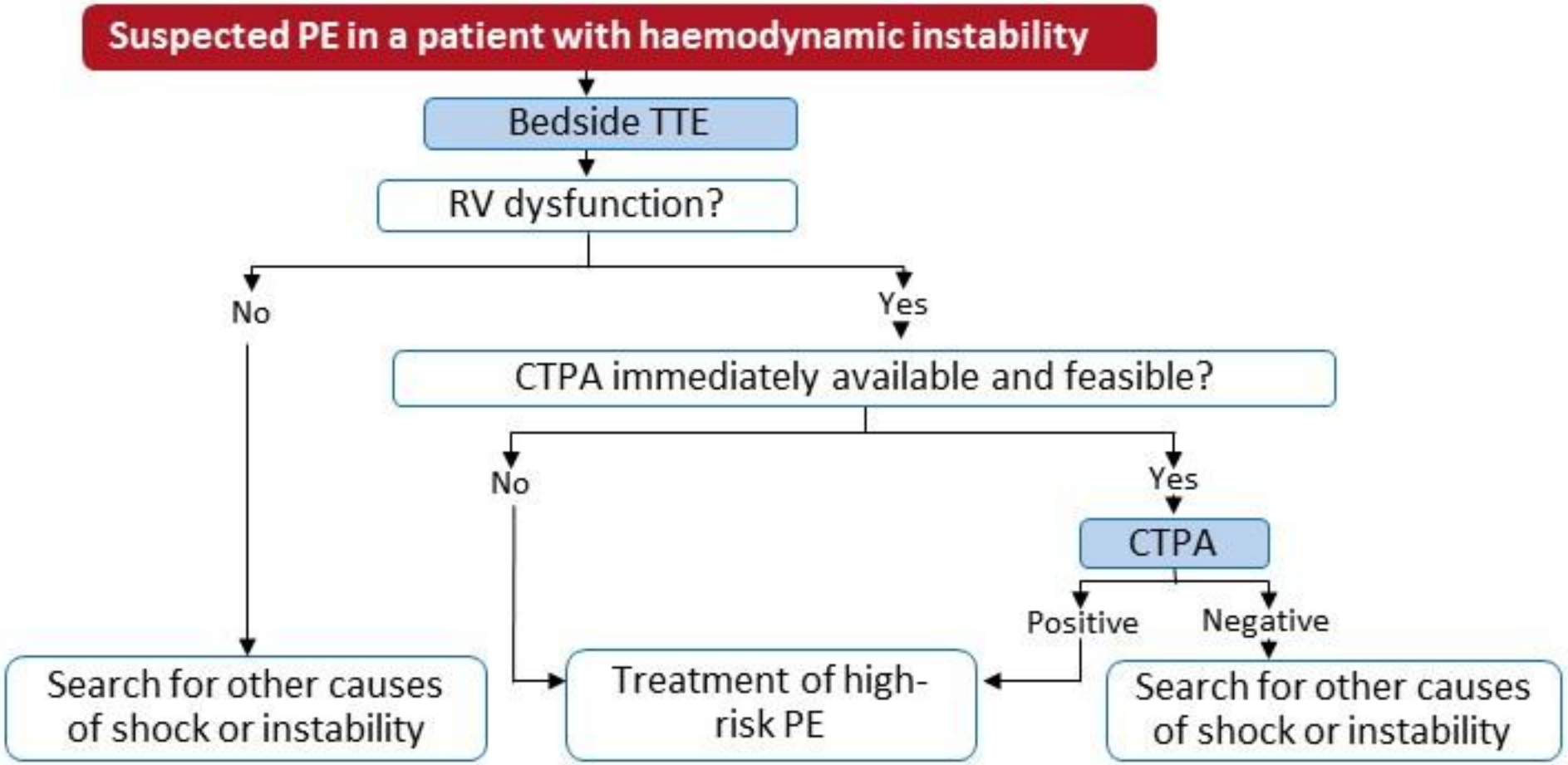
ESC European Society of Cardiology

Early mortality risk		Indicators of risk			
		Haemo-dynamic instability	Clinical parameters of PE severity/ comorbidity: PESI III–V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels
High		+	(+)	+	(+)
Interme-diate	**Intermediate–high**	-	+	+	+
	Intermediate–low	-	+	One (or none) positive	
Low		-	-	-	Assessment optional; if assessed, negative

CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; TTE = transthoracic echocardiography.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Figure 3 Diagnostic algorithm for suspected high-risk PE



CTPA = computed tomography pulmonary angiography; RV = right ventricular; TTE = transthoracic echocardiography

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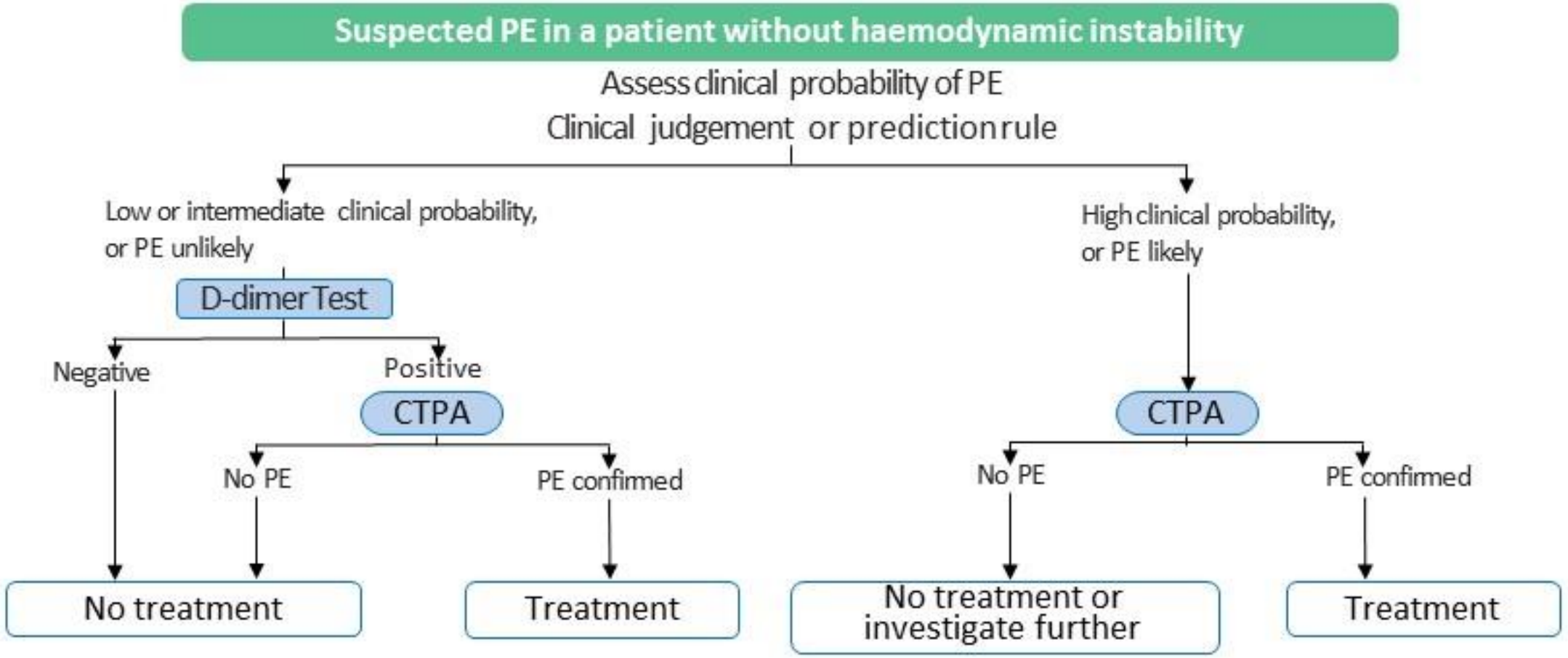
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Figure 4 Diagnostic algorithm for suspected PE without haemodynamic instability



CTPA = computed tomography pulmonary angiography

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Diagnostic investigation

- **D-dimer**

- Non specific measure of fibrinolysis

- High sensitivity (positive in presence of dx)
- High negative predictive value (dx is absent when test is negative) in the outpatient setting

-Useful in outpatient setting/emergency room, not an inpatient test for ruling out PE

- Need to be adjusted with age the optimal age-adjusted cut-off was defined as the patient's age multiplied by 10 in patients aged ⩾ 50 years.

V/Q scan

- Currently reserved for
  - Renal impairment
  - IV contrast allergies
  - Pregnancy
  - Hospital resources

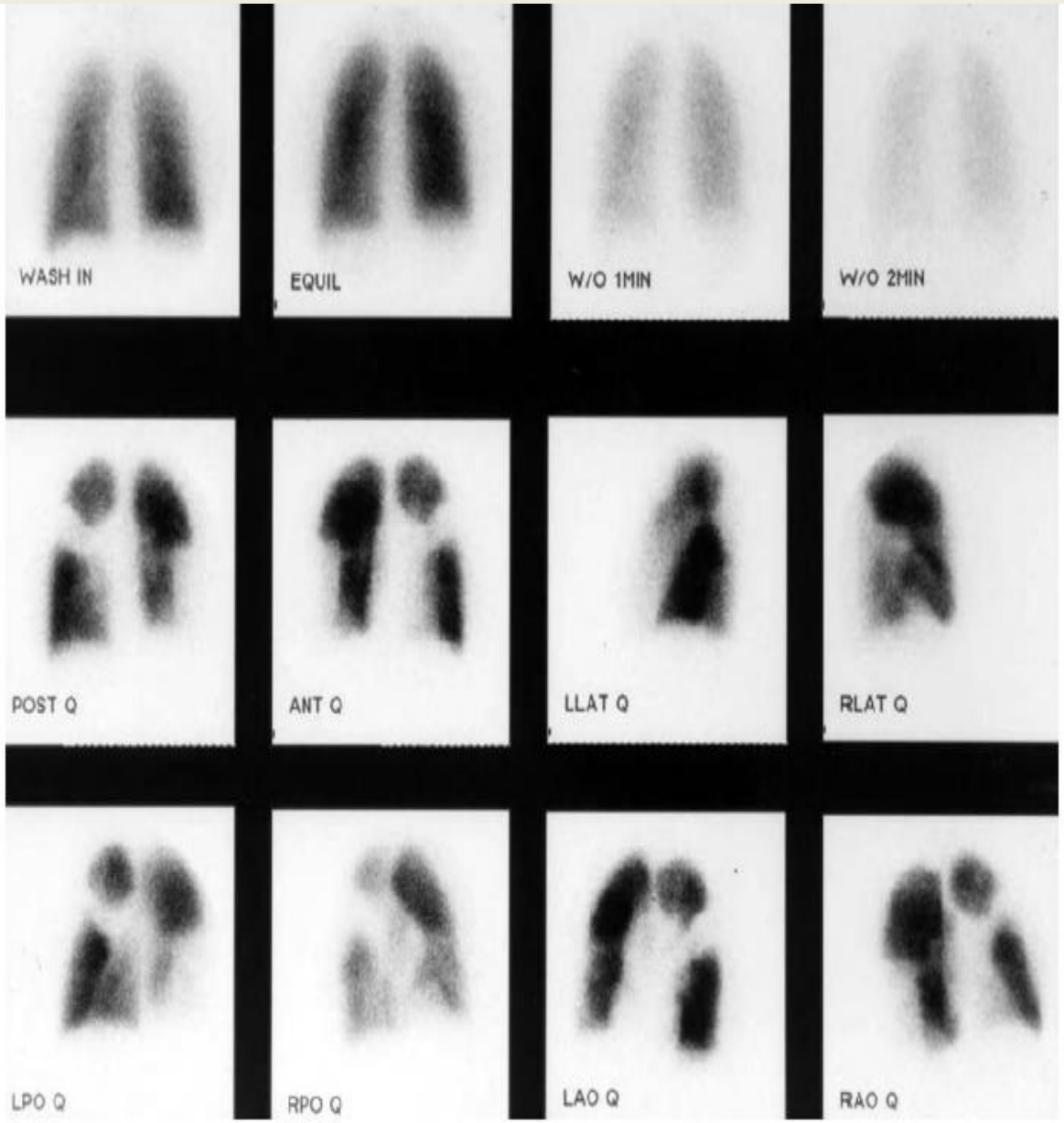


Figure 82-9 "High probability" ventilation/perfusion scan demonstrating normal ventilation and multiple mismatched segmental and larger defects.

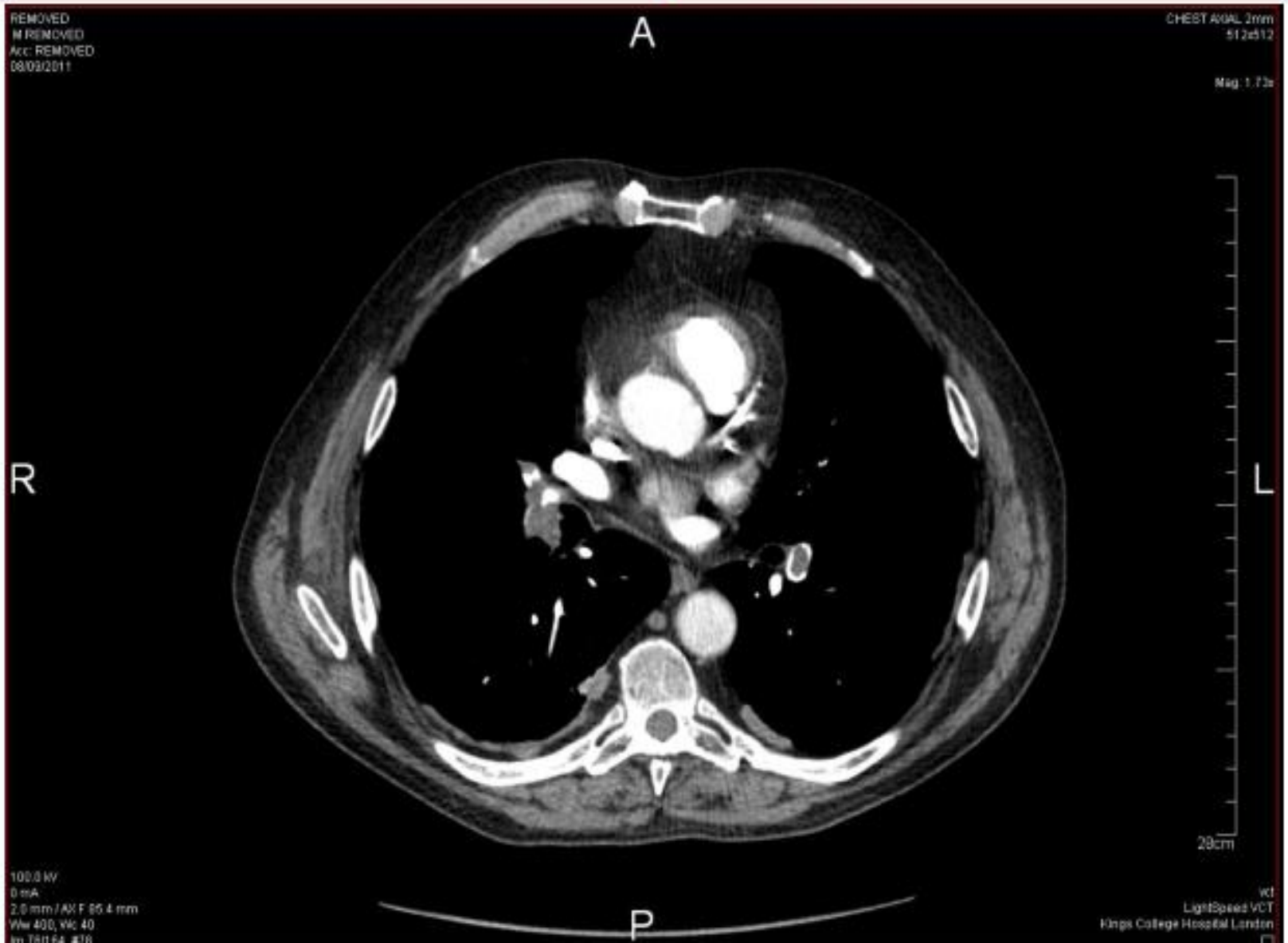
CT with PE protocol

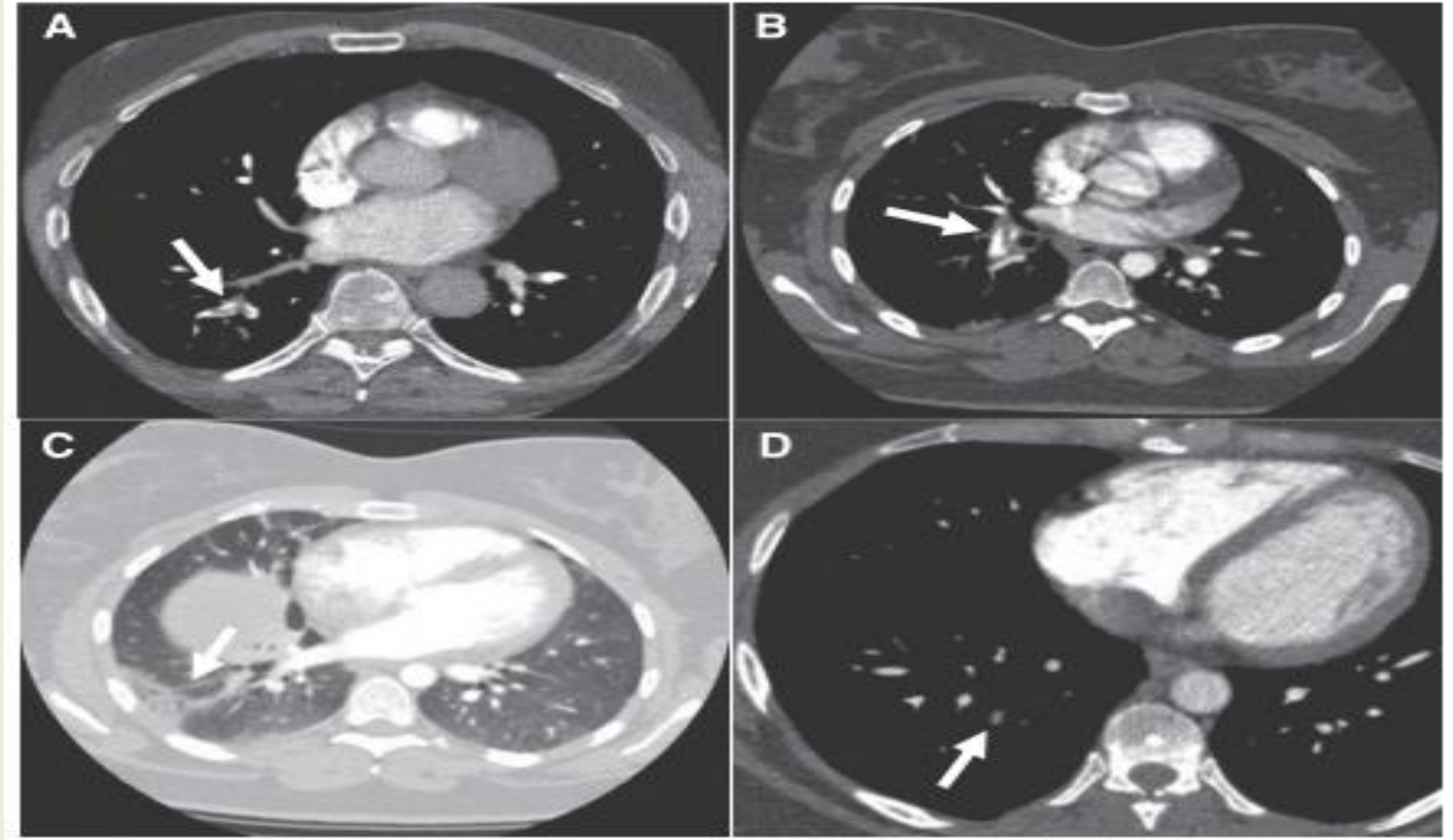
Spiral CT

- Larger dose of Contrast
- Rapid rate(timed) of contrast

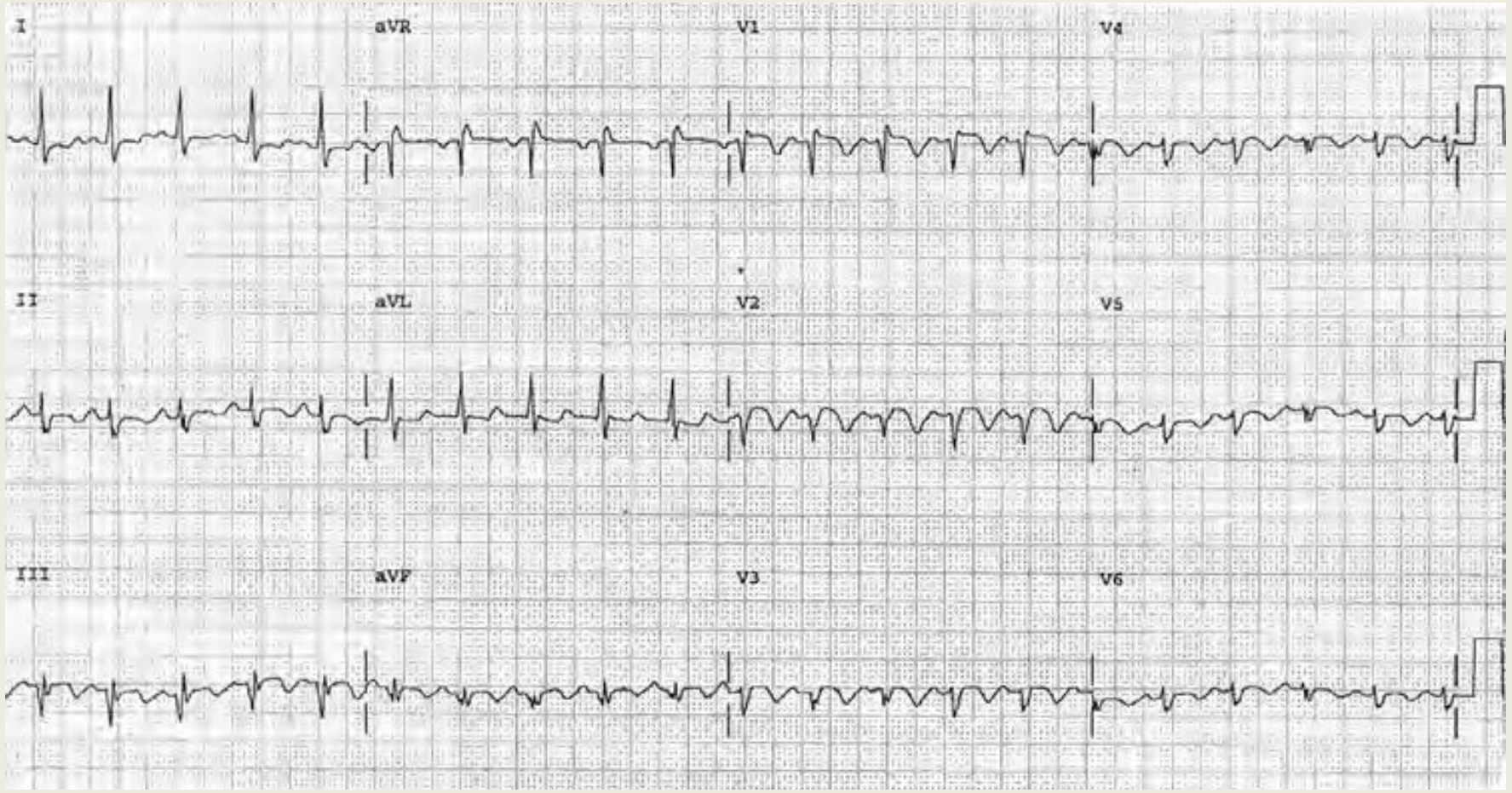
- Effective dose at pulmonary CT angiography, without significant loss of objective or subjective image quality.

Pulmonary Emboli




A
B
C
D

Electrocardiogram demonstrating findings consistent with embolism including sinus tachycardia, incomplete right bundle branch block, S1Q3T3 pattern, and inverted precordial T waves.(minority of patients)



Others

- **CXR**:

Most patients with pulmonary embolism have abnormal

but nonspecific chest radiographic findings

- **Echocardiogram**:

Suspected massive pulmonary embolism who are too ill for transportation or

have an absolute contraindication to the administration of a contrast agent.

- **Troponin** :

Increase in right heart strain .

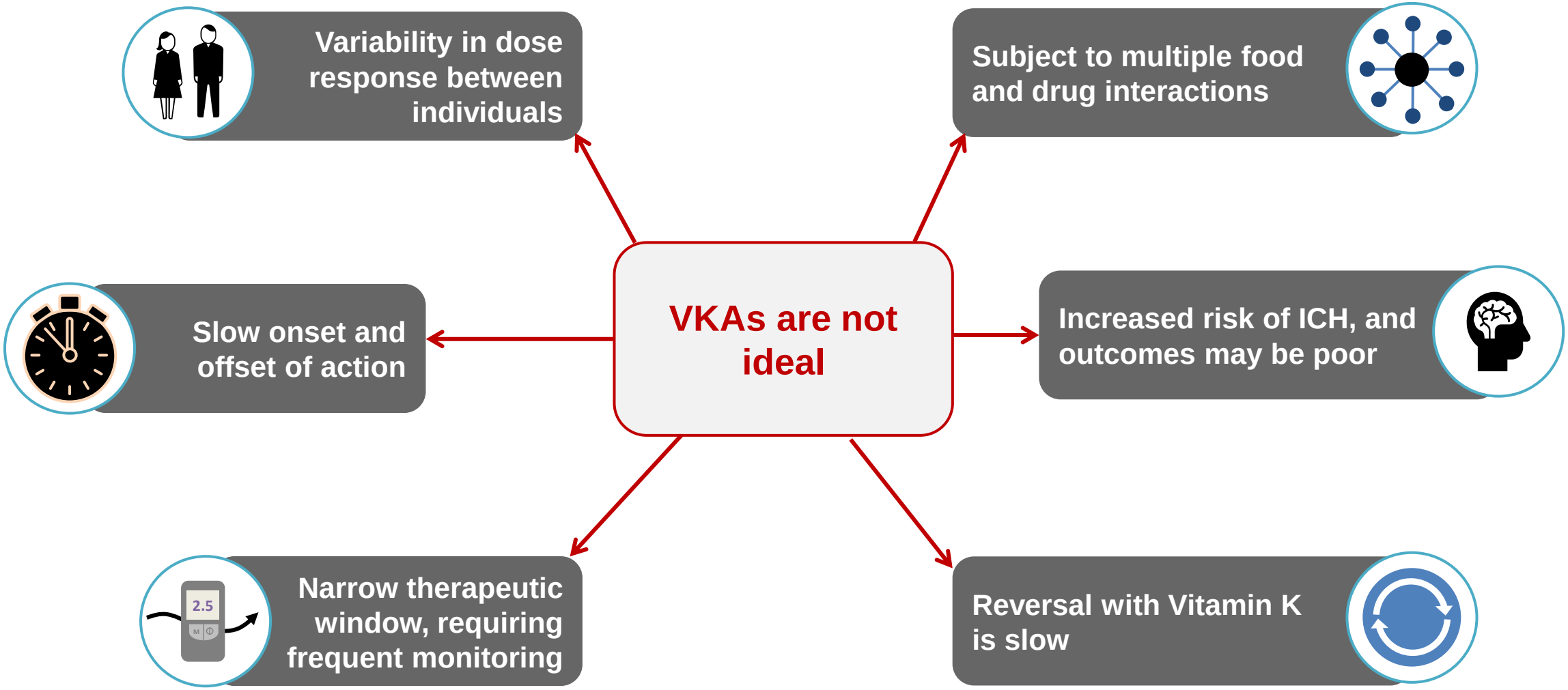
Treatment

Three phases: **Initiation phase** (5-21 days): The initial provision of anticoagulants following VTE diagnosis, **Treatment phase** (3 months): The period after initiation that completes treatment for the acute VTE event, **Extended phase** (3 months-no planned stop date):The period of anticoagulant use at full or reduced dose for the goal of secondary prevention

- **Most recent 2016 ATS guidelines, ECS 2019 , ASH 2020 , 2021 ATS update NOACs become the recommended oral treatment and alternative is VKAs(warfarin)**.
- ECS2019 recommends decrease dose of NOACs after 3-6months of treatment while ASH you can use full or reduced dose of NOACs. ATS 2021 update recommends decrease the dose of NOACs after 3 months of treatment(treatment phase)

ATS: American Thoracic Society
ESC: European Society of Cardiology
ASH: American Society of Hematology
NOAC: Novel Oral Anticoagulants
VKA: Vitamin K Antagonist

VKAs were the cornerstone of anticoagulation but they have multiple limitations



ICH, intracranial hemorrhage

Turpie. Eur Heart J 2008;29:155; Khoo et al. Int J Clin Pract 2009;63:630; Fang et al. Stroke 2012;43:1795; Hanley et al. J Clin Pathol 2004;57:1132

TABLE 1 Non-Vitamin K-Dependent Oral Anticoagulant Agents in the Treatment and Secondary Prevention of VTE

	Dosage and Interval			
	Initial Phase	Long-Term Phase	Extended Phase	Not Recommended or Contraindicated*
Rivaroxaban†	15 mg twice daily with food for 21 days	20 mg once daily with food		• CrCl <30 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers
Dabigatran etexilate‡	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of dabigatran etexilate	150 mg twice daily		• CrCl <30 ml/min • Concomitant treatment with P-gp inhibitors in patients with CrCl <50 ml/min • Concomitant treatment with P-gp inducers (i.e., rifampin)
Apixaban	10 mg twice daily for 7 days	5 mg twice daily	2.5 mg twice daily after at least 6 months of treatment	• CrCl <15 ml/min • Severe hepatic impairment (Child-Pugh C), or hepatic disease associated with coagulopathy • Strong dual inhibitors or inducers of CYP3A4 and P-gp
Edoxaban§	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of edoxaban	60 mg once daily 30 mg once daily can be considered in patients with ≥1 of the following factors: CrCl 15–50 ml/min; body weight ≤60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole		• CrCl <15 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant treatment with rifampin

NOACs are not used

- **CKD** with Ccl less than 30 ml/min (apixaban & edoxaban can be used Ccl bet.15-30 ml/min with reduced dose)

- Moderate to severe **hepatic** impairment

- Pregnancy and lactation:

Still the use of LMWH is the standard of care in pregnant lady and VKAs can be used in lactating women

- PE with cancer :

LMWH

- Antiphospholipid syndrome :

not proved yet

Risk Factors Associated with VTE Recurrence

- Idiopathic presentation[1,2]
- Presentation of primary DVT[1]
- Increasing age[1]
- Proximal DVT[2]
- Cancer[2]
- Residual thrombus mass[3]
- Male gender[4]
- High-risk thrombophilia[1]

- Scoring systems such as the DASH score, the Vienna Prediction Model, and the ‘Men continue and HERDOO2’ score are used to predict PE.

1. Prandoni P *et al, Haematologica* 2007;92:199–205; 2. Hansson PO *et al, Arch Intern Med* 2000;160:769–774;
3. Prandoni P *et al, Ann Intern Med* 2002;137:955–960; 4. Eichinger S *et al, Circulation* 2010;121:1630–1636

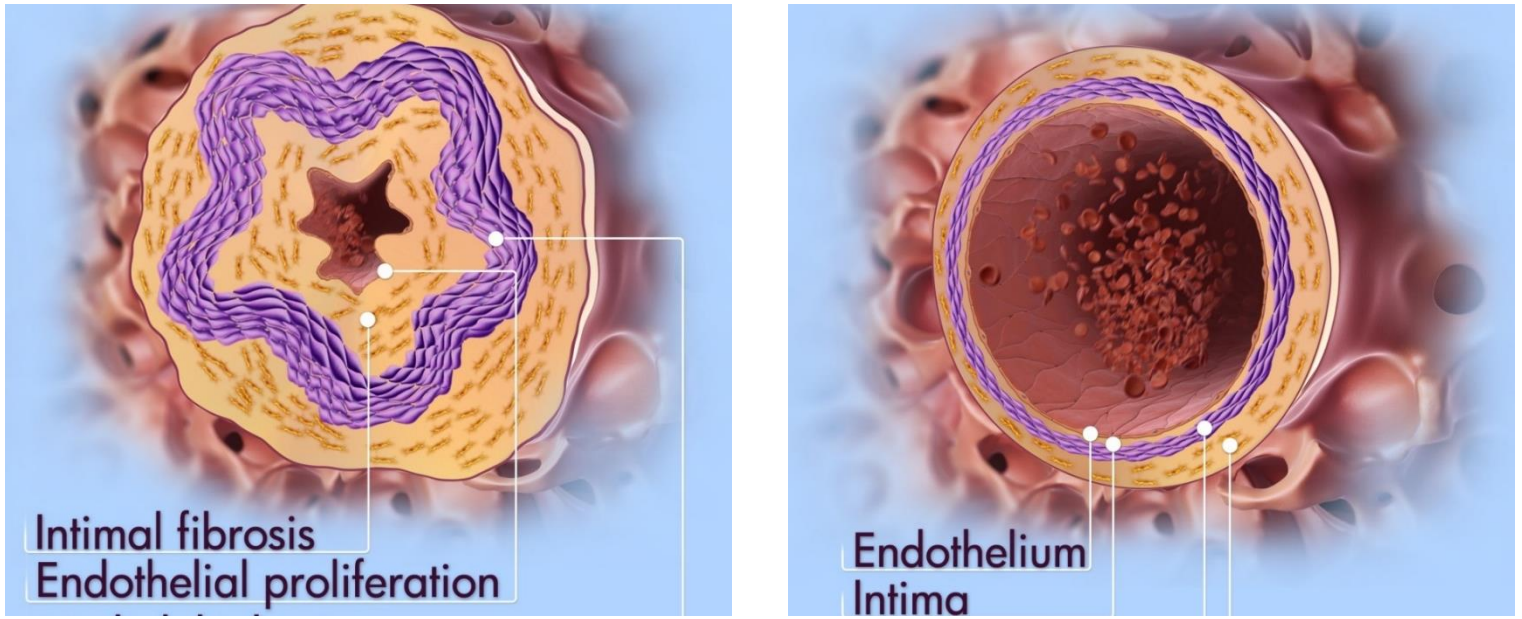
Pulmonary hypertension

Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
Combined post- and pre-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Pulmonary remodelling in PAH leads to narrowing of the artery[1]



- PAH, pulmonary arterial hypertension; SMC, smooth muscle cell.
- 1. Figure adapted from Galiè N, *et al. Eur Heart J* 2010; 31:2080-6.

Clinical classification of pulmonary hypertension (1)

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn

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(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Clinical classification of pulmonary hypertension (2)

GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (e.g. high altitude)
3.6 Developmental lung disorders

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Clinical classification of pulmonary hypertension (3)

GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multi-factorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

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Figure 1

Central illustration

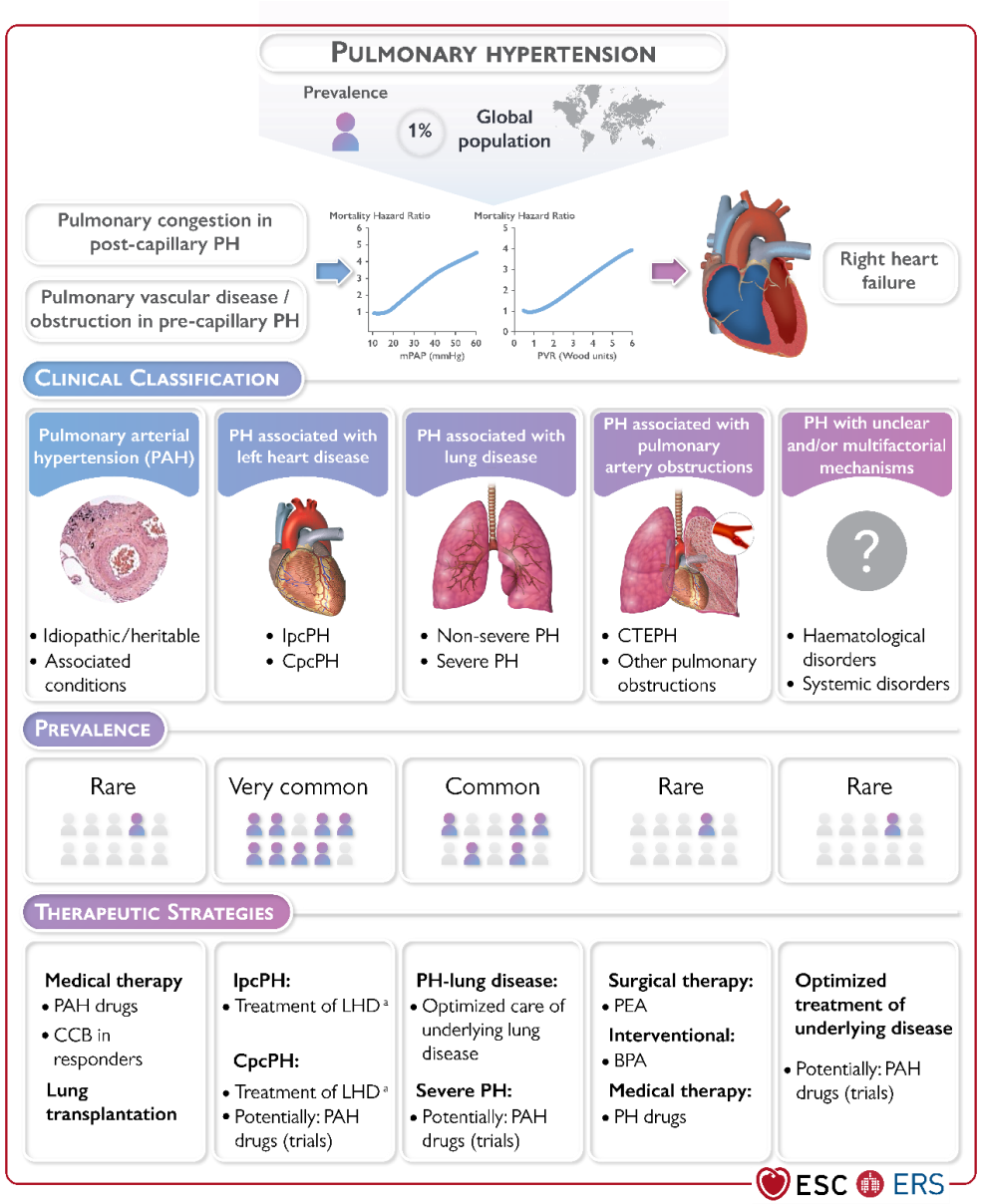

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Figure 2

Symptoms in patients with pulmonary hypertension

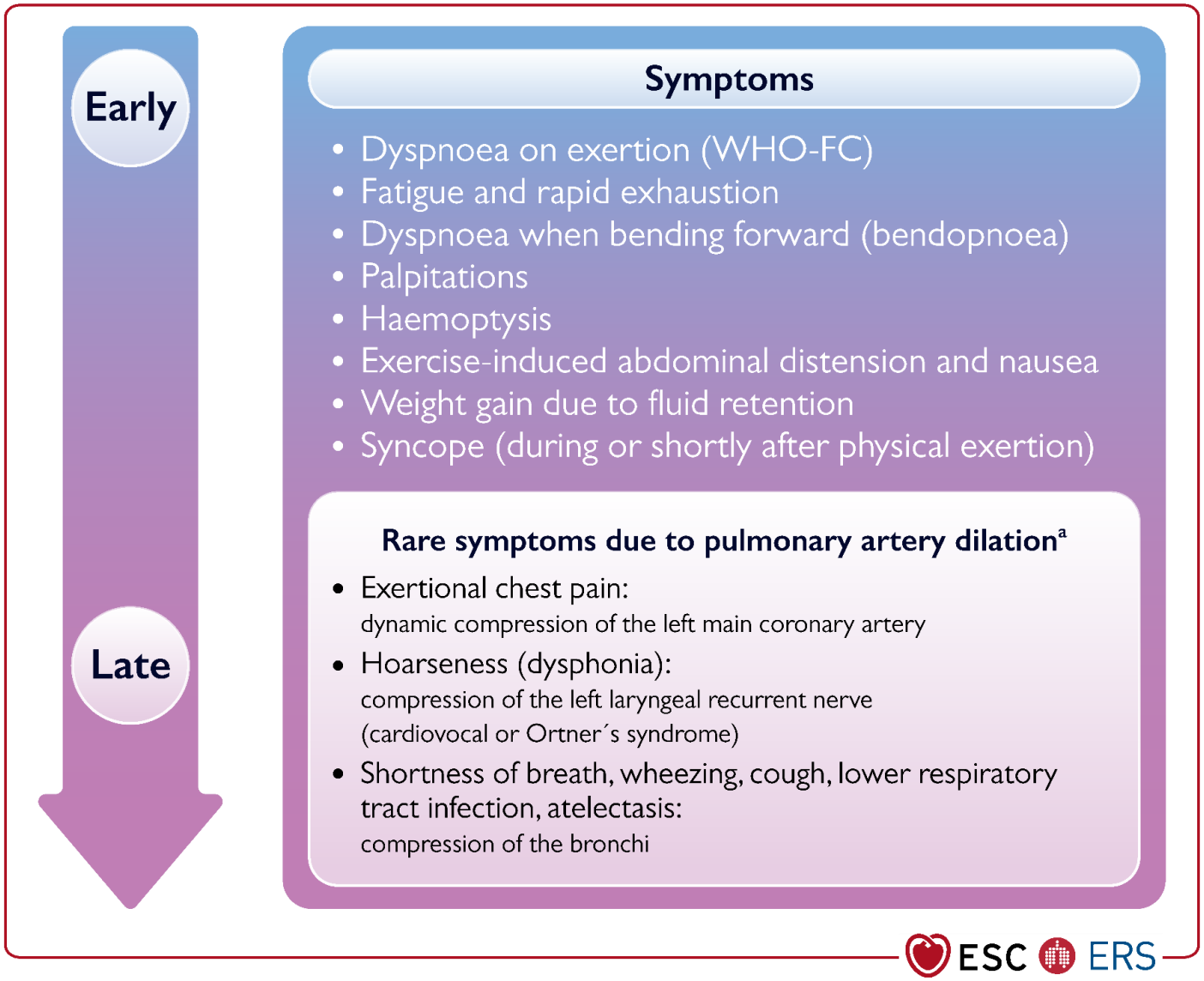

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Figure 3

Clinical signs in patients with pulmonary hypertension

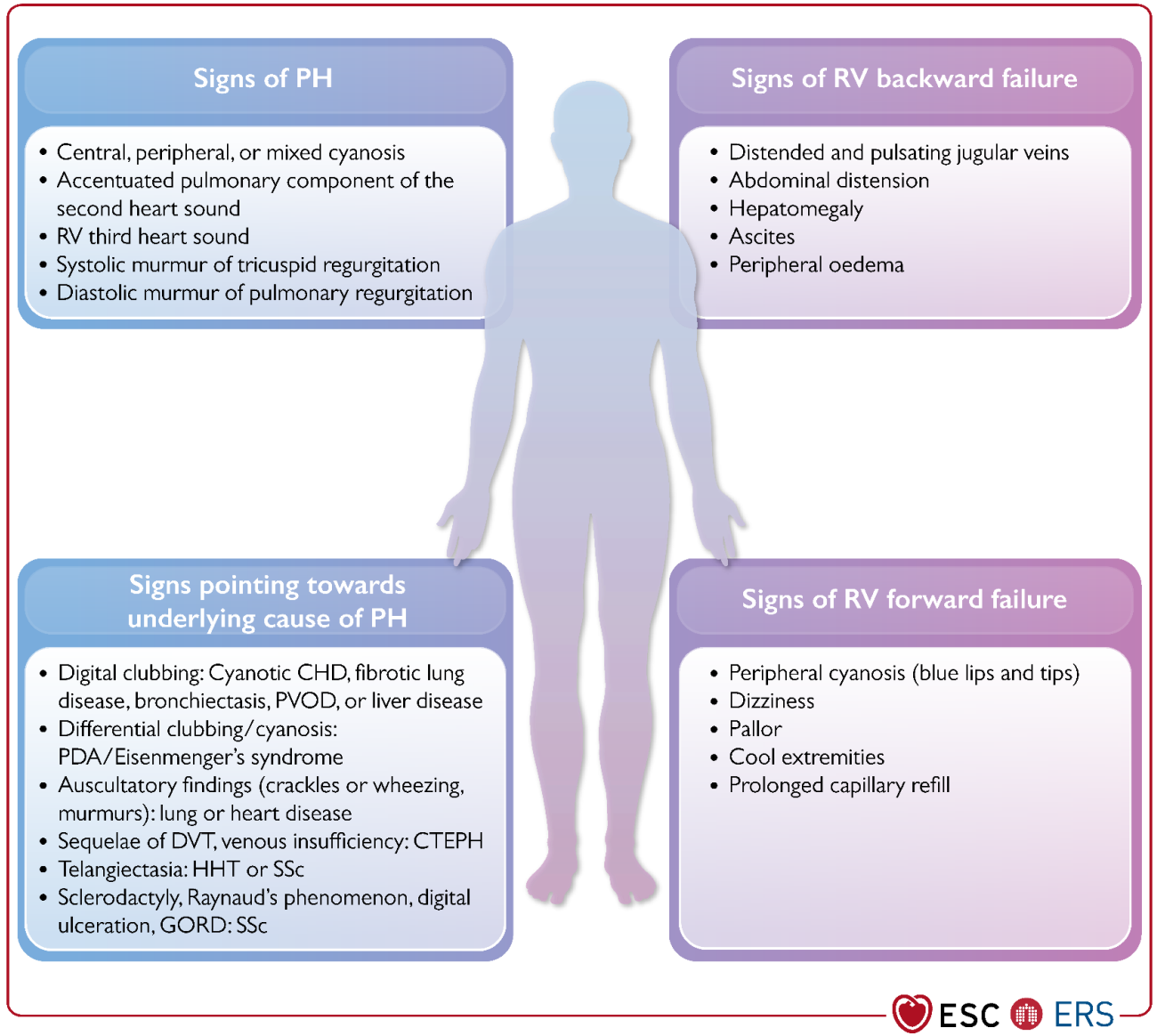

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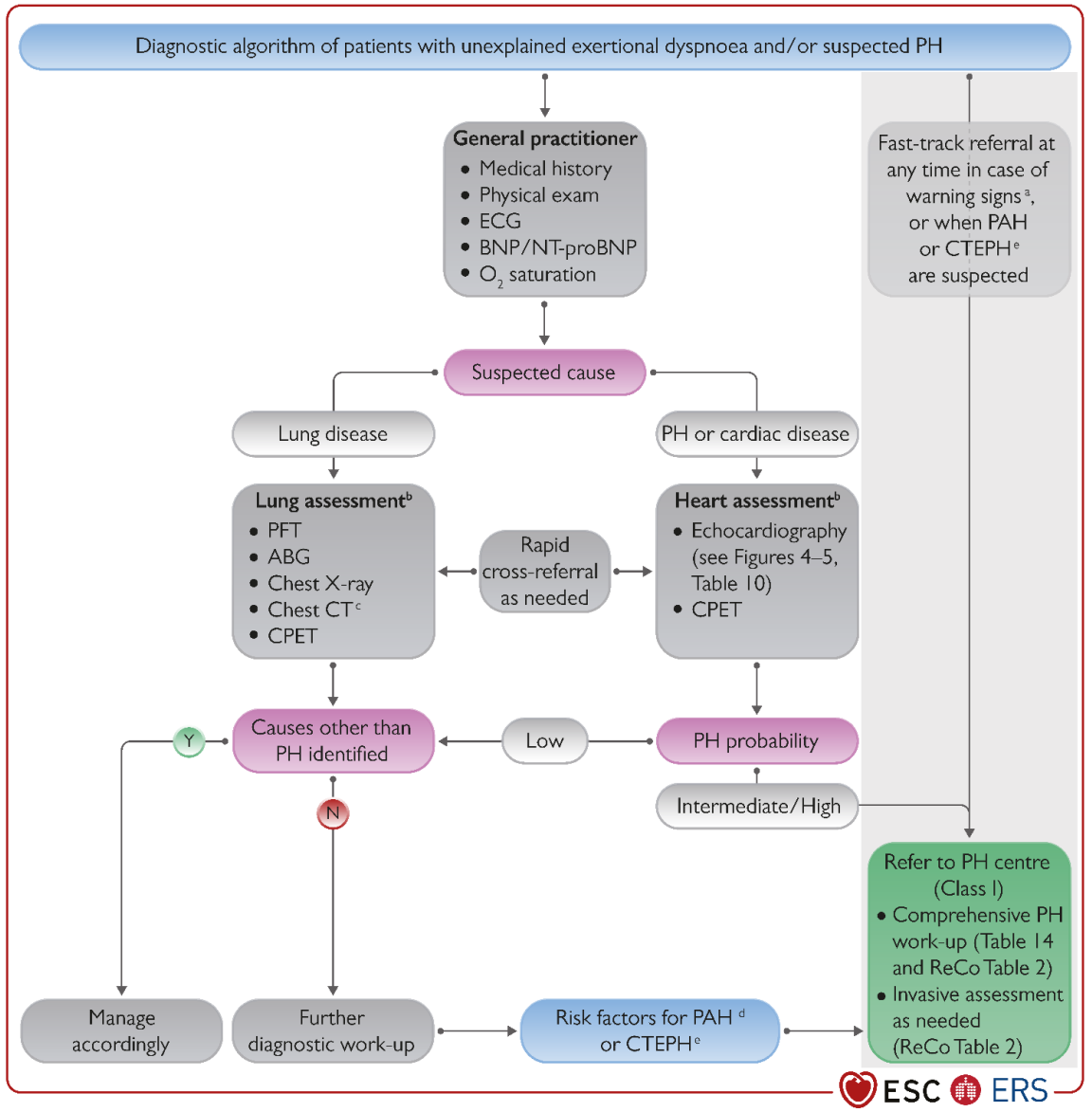
Figure 6

Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension



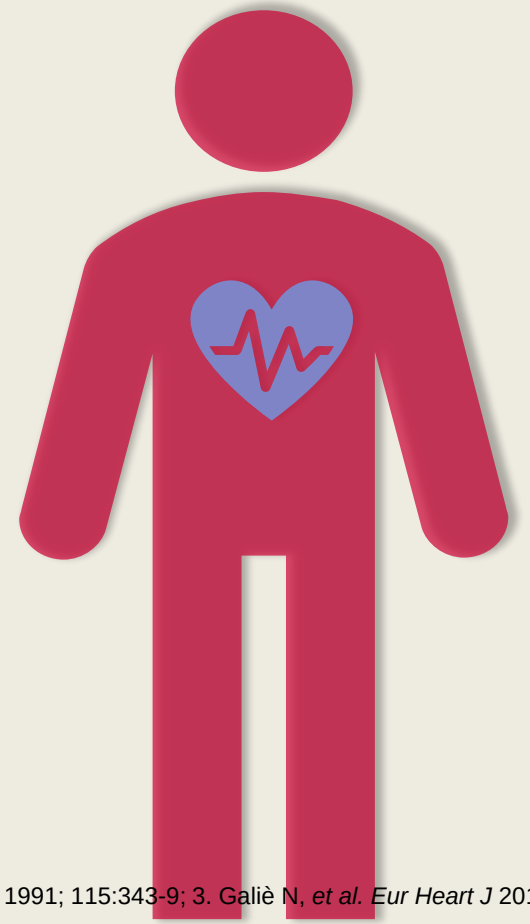
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

- **PAH is a rare, progressive disease with poor prognosis if left untreated**

Prevalence:
6.6 to 26 per million[1]

Poor short- and medium-term prognosis[2]

Severe and progressive[2]



Incidence:
1.1 to 7.6 per million[1]

Complex management[3]

Estimated median survival of 2.8 years if left untreated[2]

PAH, pulmonary arterial hypertension.

1. Hoeper MM, *et al. Int J Cardiol* 2016; 203:612-3; 2. D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9; 3. Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Thank you