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Pulmonary Embolism

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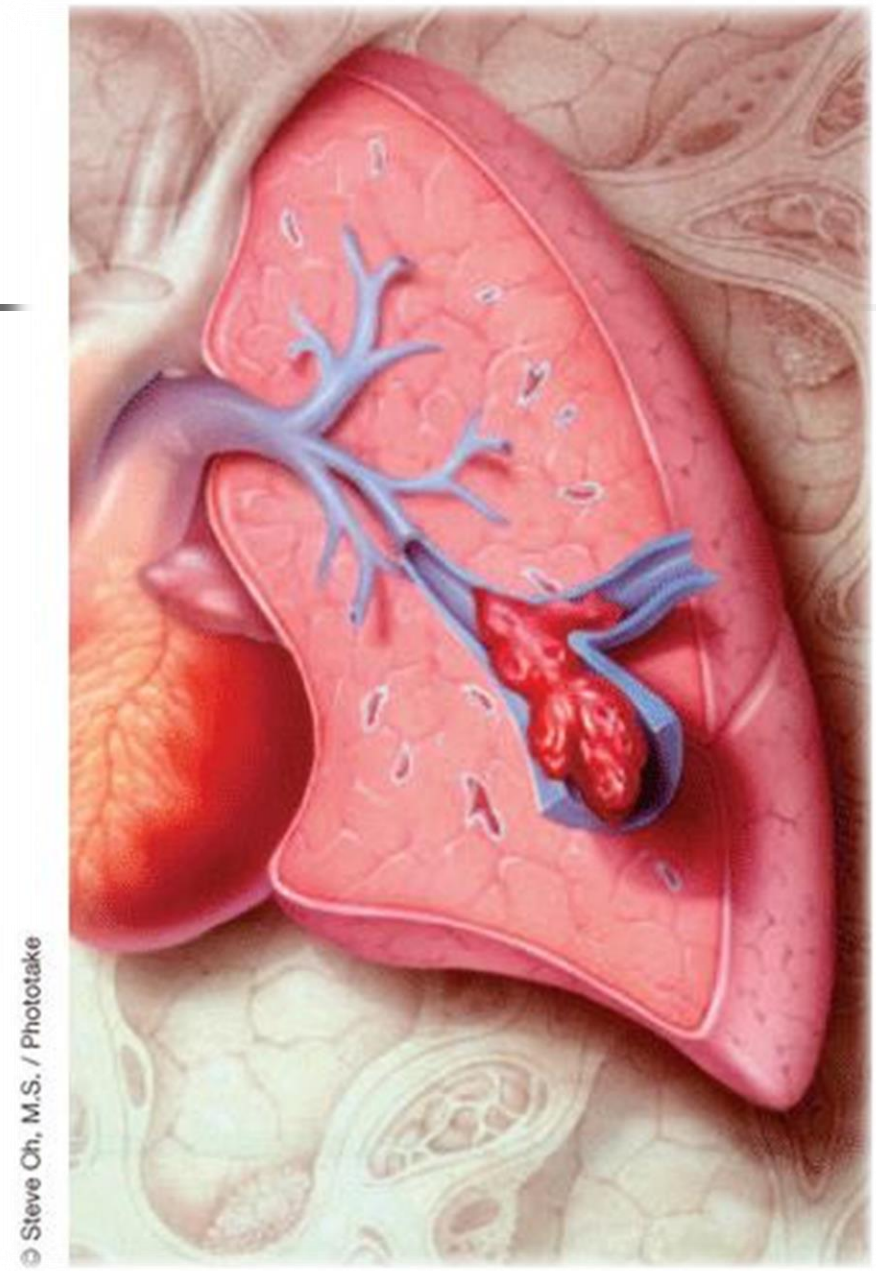
Objectives

- Epidemiology
- Pathophysiology
- Diagnosis
- Massive PE
- Treatment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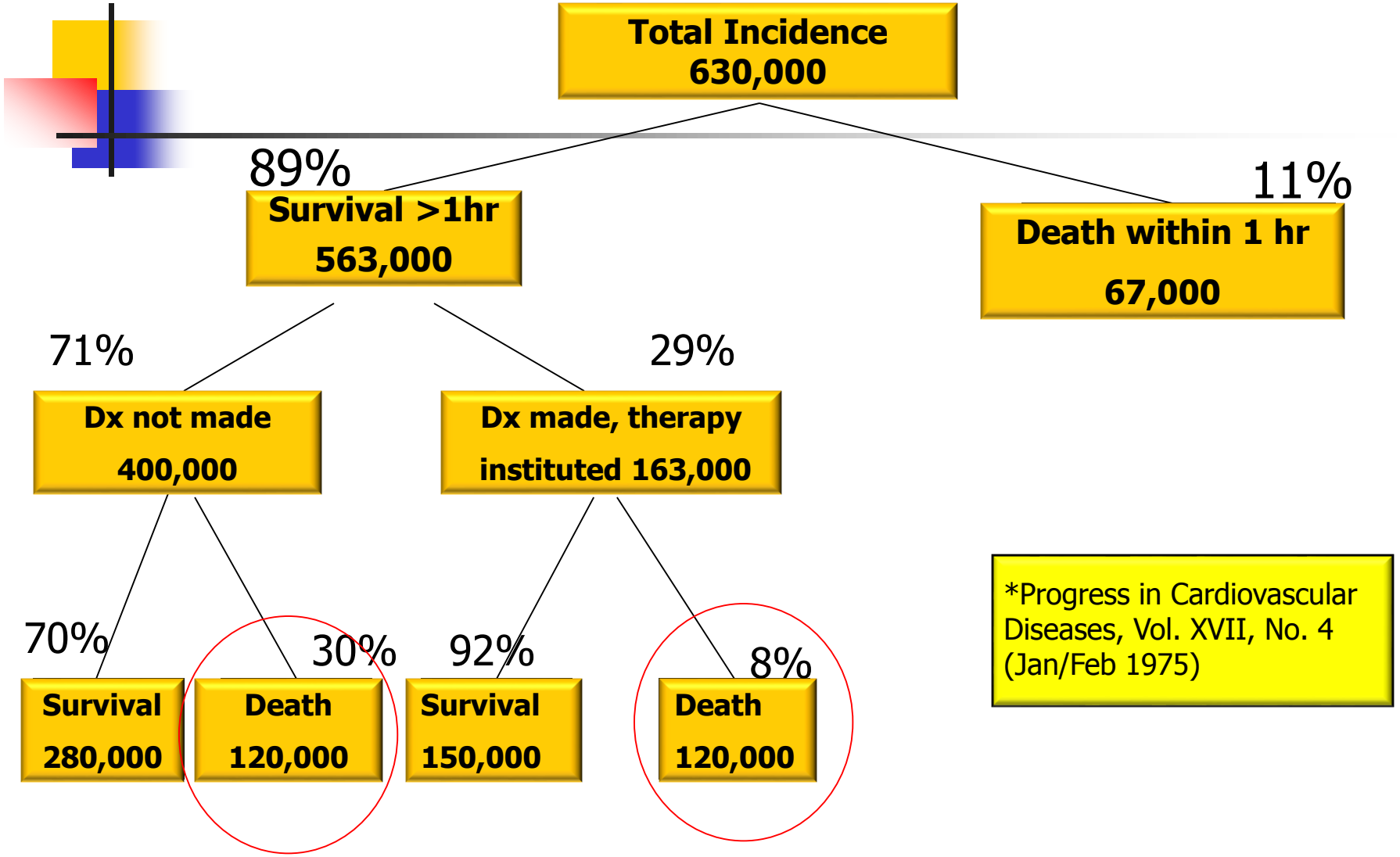
Edpidemiology

- 50,000 individuals die from PE each year in USA
- The incidence of PE in USA is 500,000 per year

Incidence of Pulmonary Embolism Per Year in the United States*



*Progress in Cardiovascular Diseases, Vol. XVII, No. 4 (Jan/Feb 1975)

Epidemiology

- Over **317,000** deaths were related to VTE in six countries of the European Union (with a total population of **454.4 million**) in 2004

- Of these cases,
  - **34%** presented with sudden fatal PE
  - **59%** were deaths resulting from PE that remained undiagnosed
  - Only **7%** of the patients who died early were correctly diagnosed with PE before death.

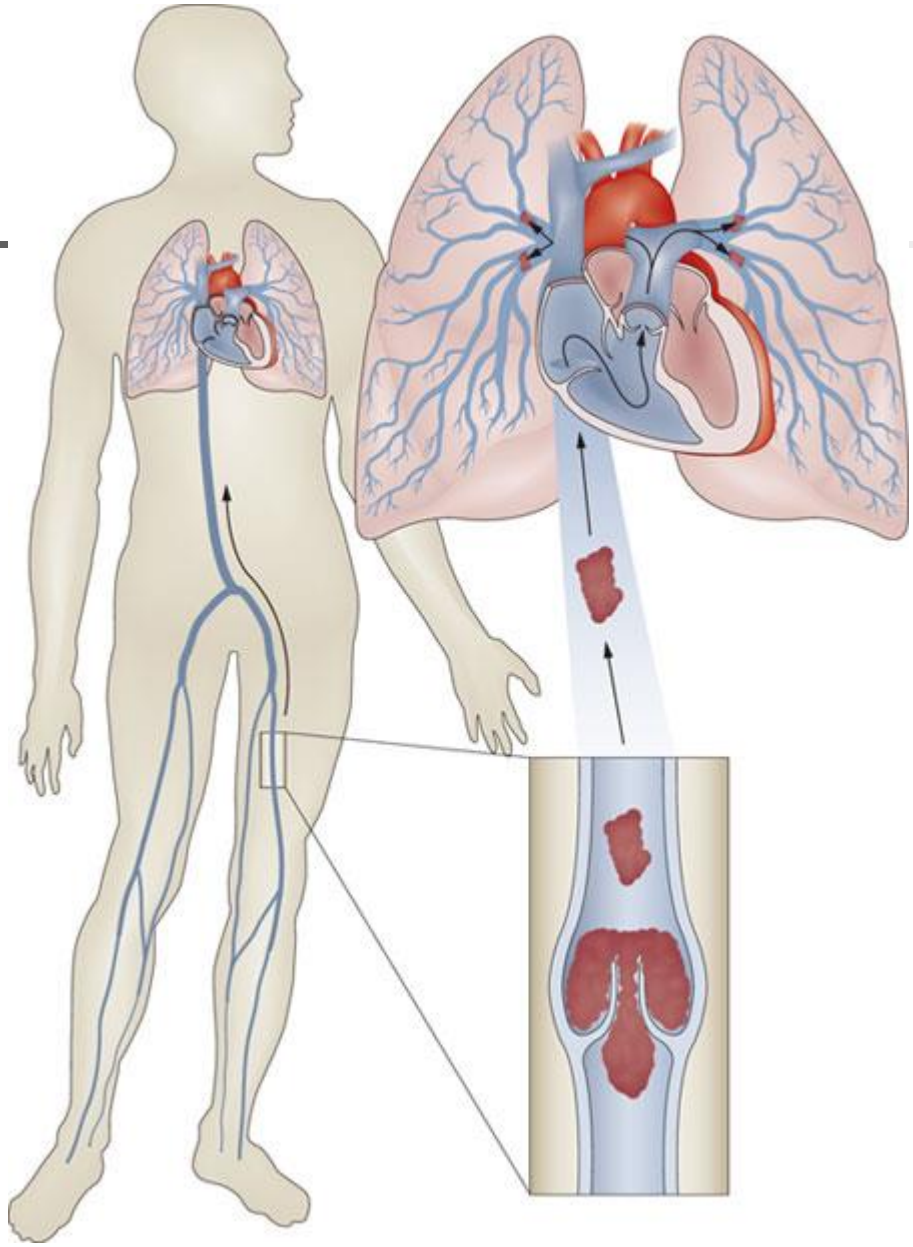
Thromb Haemost 2007;98(4):756–764

Risk factor for venous thrombosis

- Stasis
- Injury to venous intima
- Alterations in the coagulation-fibrinolytic system

Source of emboli

- Deep venous thrombosis (>95%)
- Other veins:
  - Renal
  - Uterine
  - Right cardiac chambers



Risk factors for DVT

- General anesthesia
- Lower limb or pelvic injury or surgery
- Congestive heart failure
- Prolonged immobility
- Pregnancy
- Postpartum
- Oral contraceptive pills
- Malignancy
- Obesity
- Advanced age
- Coagulation problems

Clinical features

- Sudden onset dyspnea
- Pleuritic chest pain
- Hemoptysis
- Clinical clues cannot make the diagnosis of PE; their main value lies in suggesting the diagnosis

Clinical features

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

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

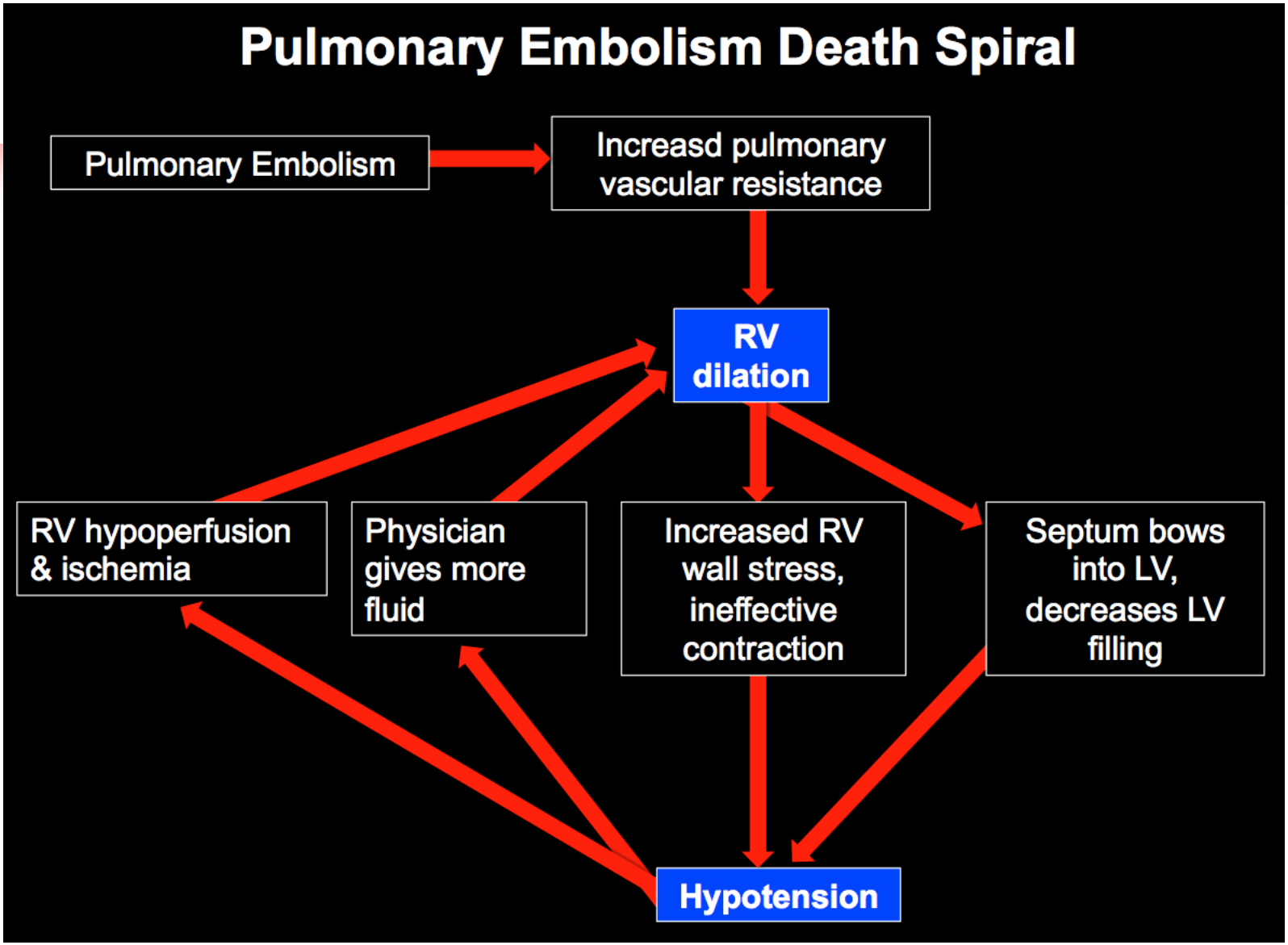
DVT = deep vein thrombosis.

J Am Coll Cardiol 2011;57(6):700–706

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Deep vein thrombosis	Swelling	28	88*
	Pain	26	56
	Tenderness	—	55
	Warmth	—	42
	Redness	—	34
	Homan's sign	4	13
	Palpable cord	—	6

Massive Pulmonary Embolism

- It is a catastrophic entity which often results in acute right ventricular failure and death
- Frequently undiscovered until autopsy
- Fatal PE typically leads to death within one to two hours of the event


Pulmonary Embolism Death Spiral
Pulmonary Embolism
Increasd pulmonary vascular resistance
RV dilation
RV hypoperfusion & ischemia
Physician gives more fluid
Increased RV wall stress, ineffective contraction
Septum bows into LV, decreases LV filling
Hypotension

Pathophysiology

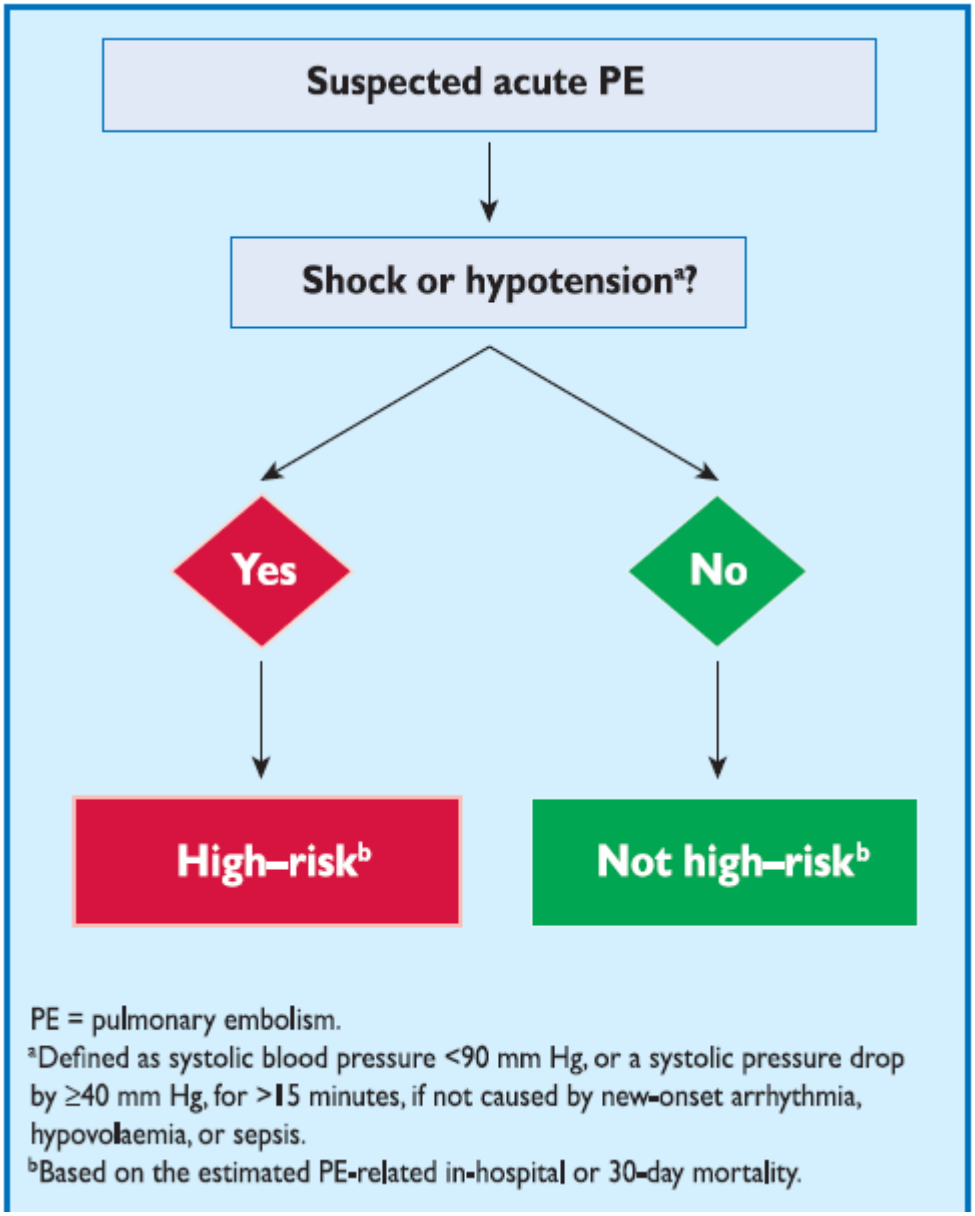
- Massive PE causes an increase in PVR $\rightarrow$ right ventricular outflow obstruction $\rightarrow$ decrease left ventricular preload $\rightarrow$ Decrease CO

- In patients without cardiopulmonary disease, occlusion of 25-30 % of the vascular bed $\rightarrow$ increase in Pulmonary artery pressure (PAP)

- Hypoxemia ensues $\rightarrow$ stimulating vasoconstriction $\rightarrow$ increase in PAP

Pathophysiology

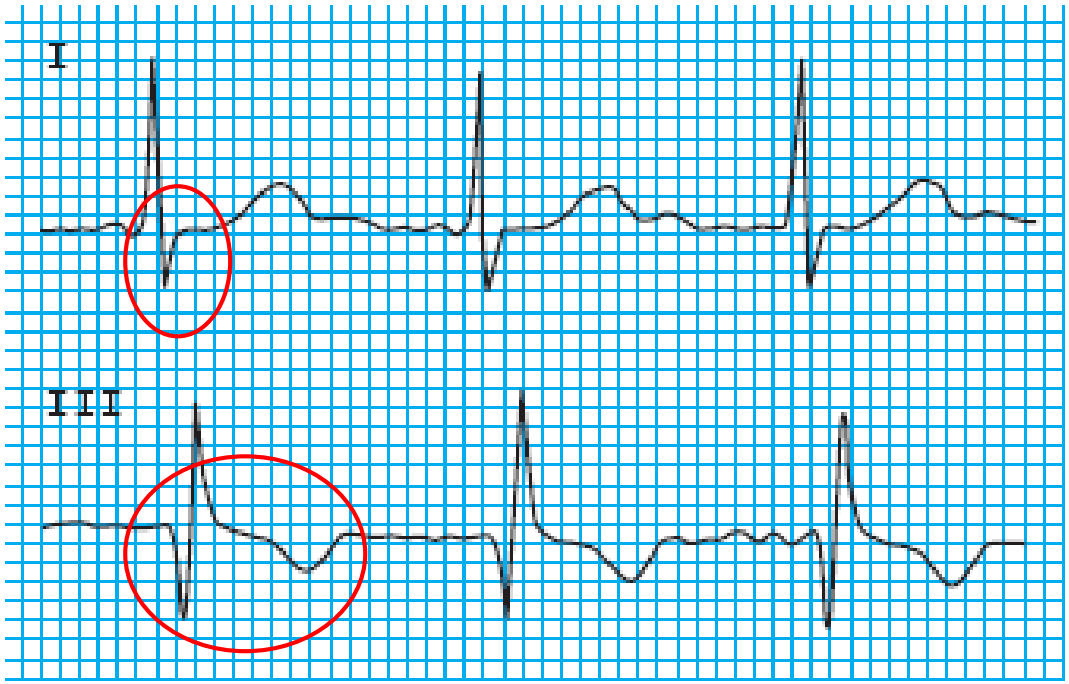
- More than 50% of the vascular bed has to be occluded before PAP becomes substantially elevated
- When obstruction approaches 75%, the RV must generate systolic pressure in excess of 50mmHg to preserve pulmonary circulation
- The normal RV is unable to accomplish this acutely and eventually fails


Suspected acute PE
Shock or hypotension[a]?
Yes
No
High–risk[b]
Not high–risk[b]
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.

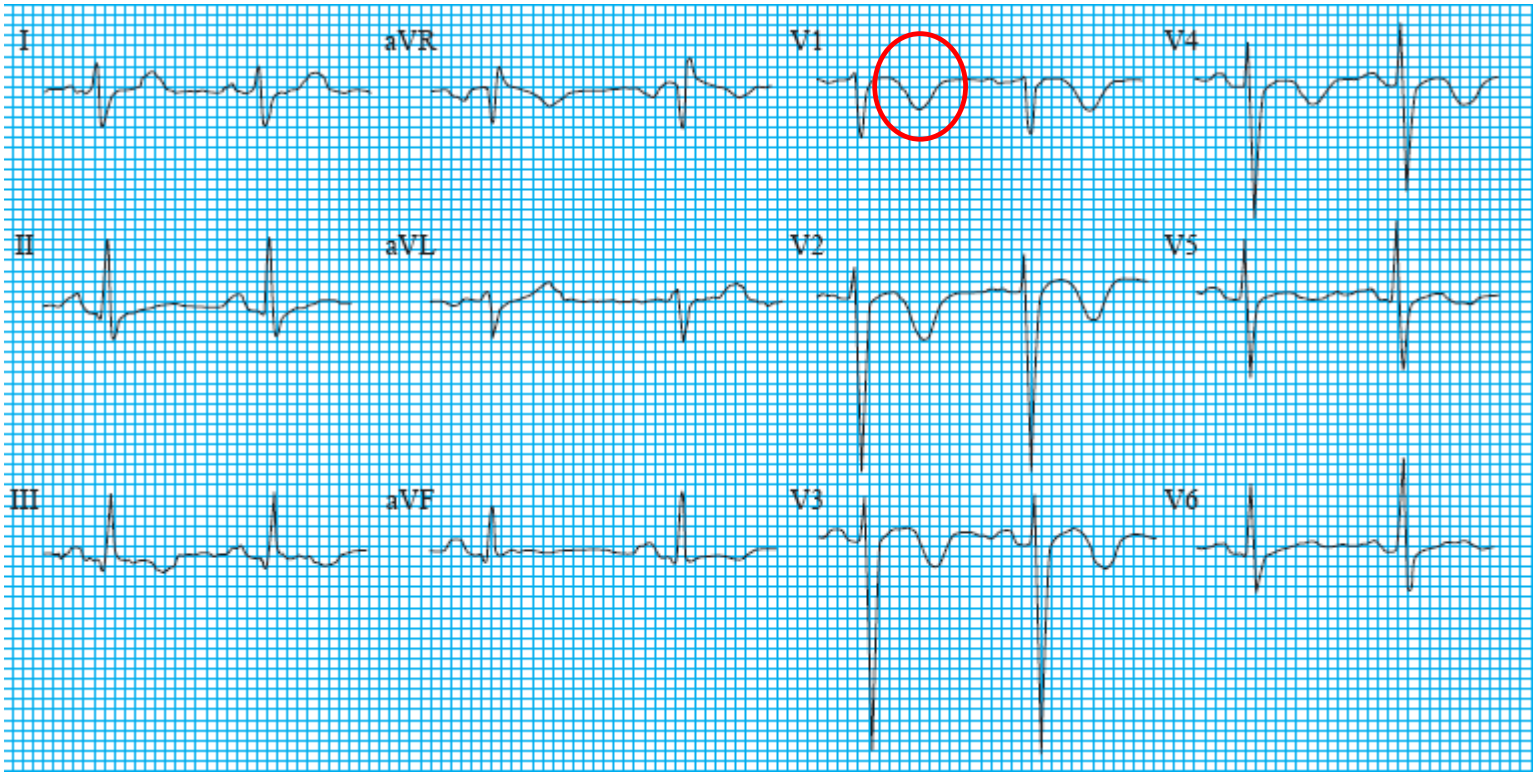
Diagnosis

- **ECG**
- **CXR**
- ABG:
- **ECG**
- **D-dimer**
- **Spiral CT**
- **V/Q**
- **Echo**
- **Angio**

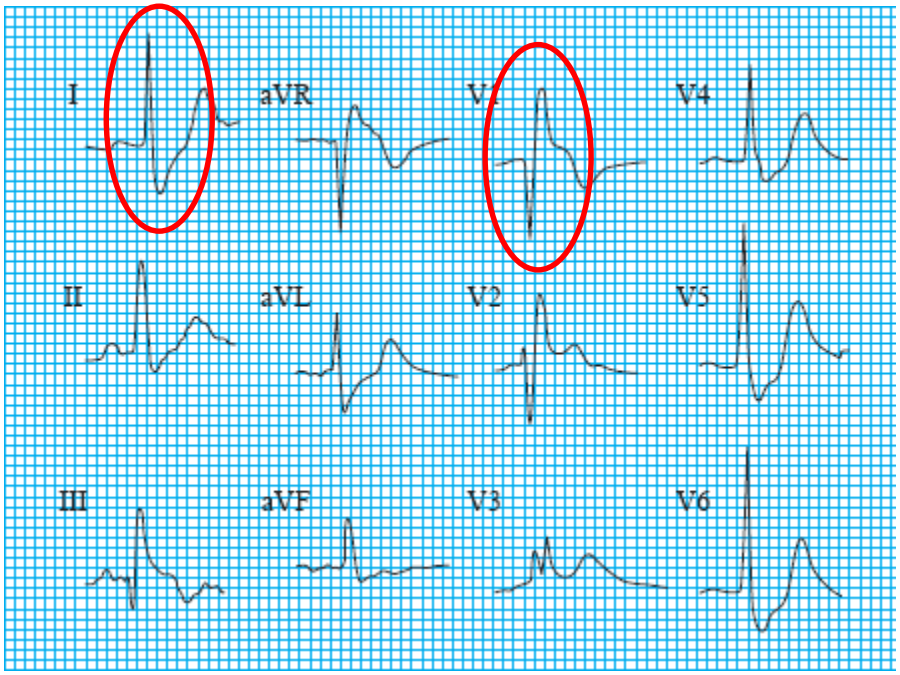
S1 Q3 T3 Pattern



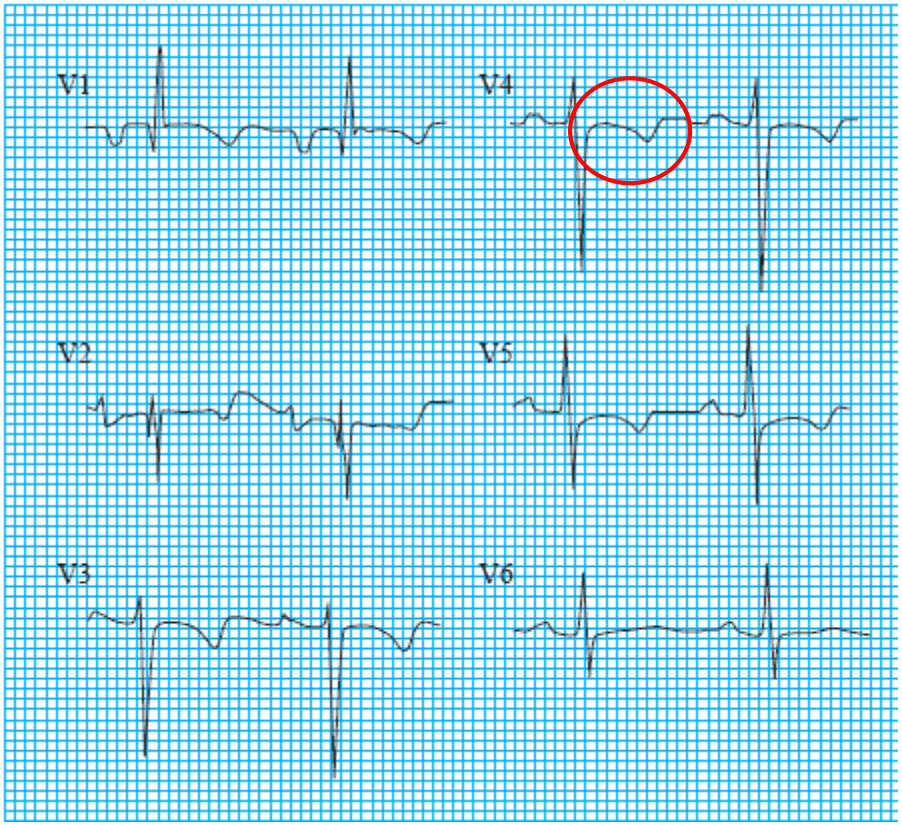
T-wave inversion



Rt. Bundle Branch Block



Rt. Ventricular Strain

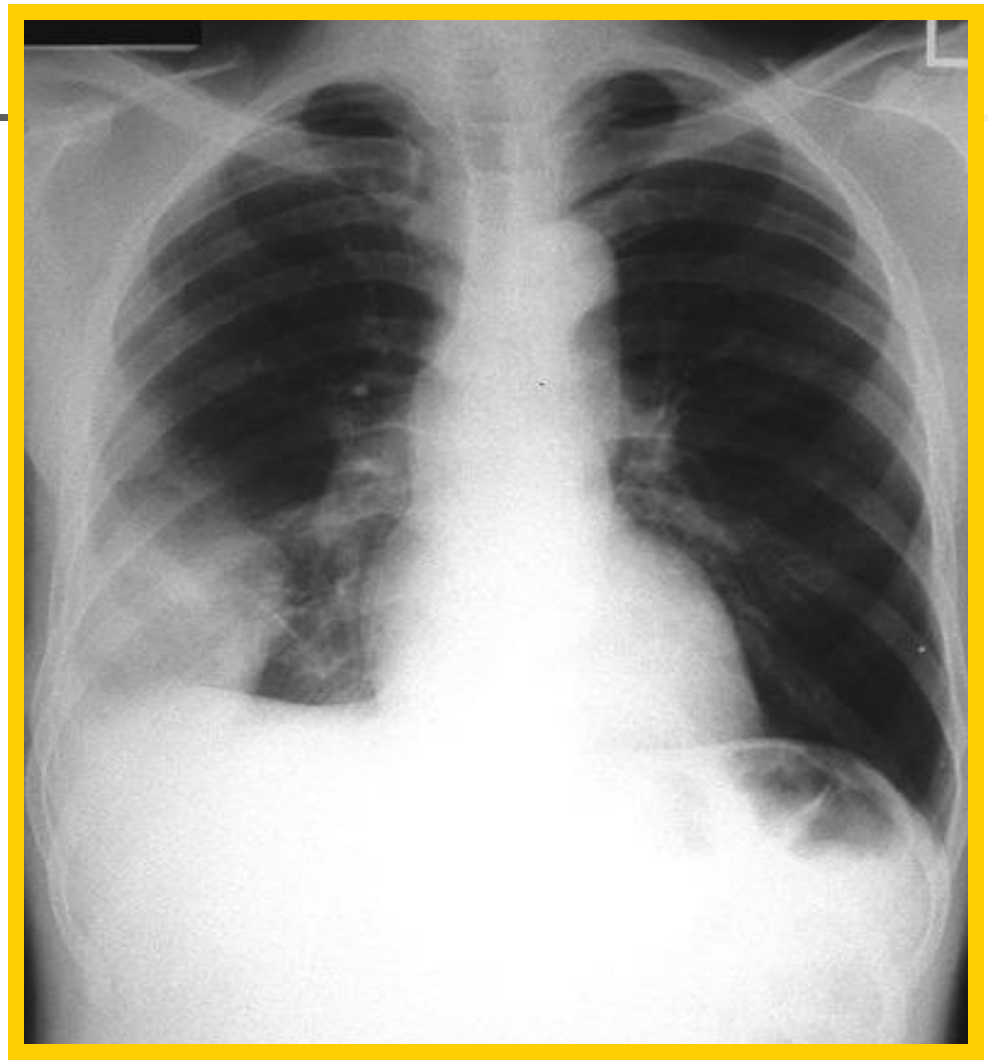


Diagnosis

The diagnosis of massive PE should be explored whenever oxygenation or hemodynamic parameters are severely compromised without explanation

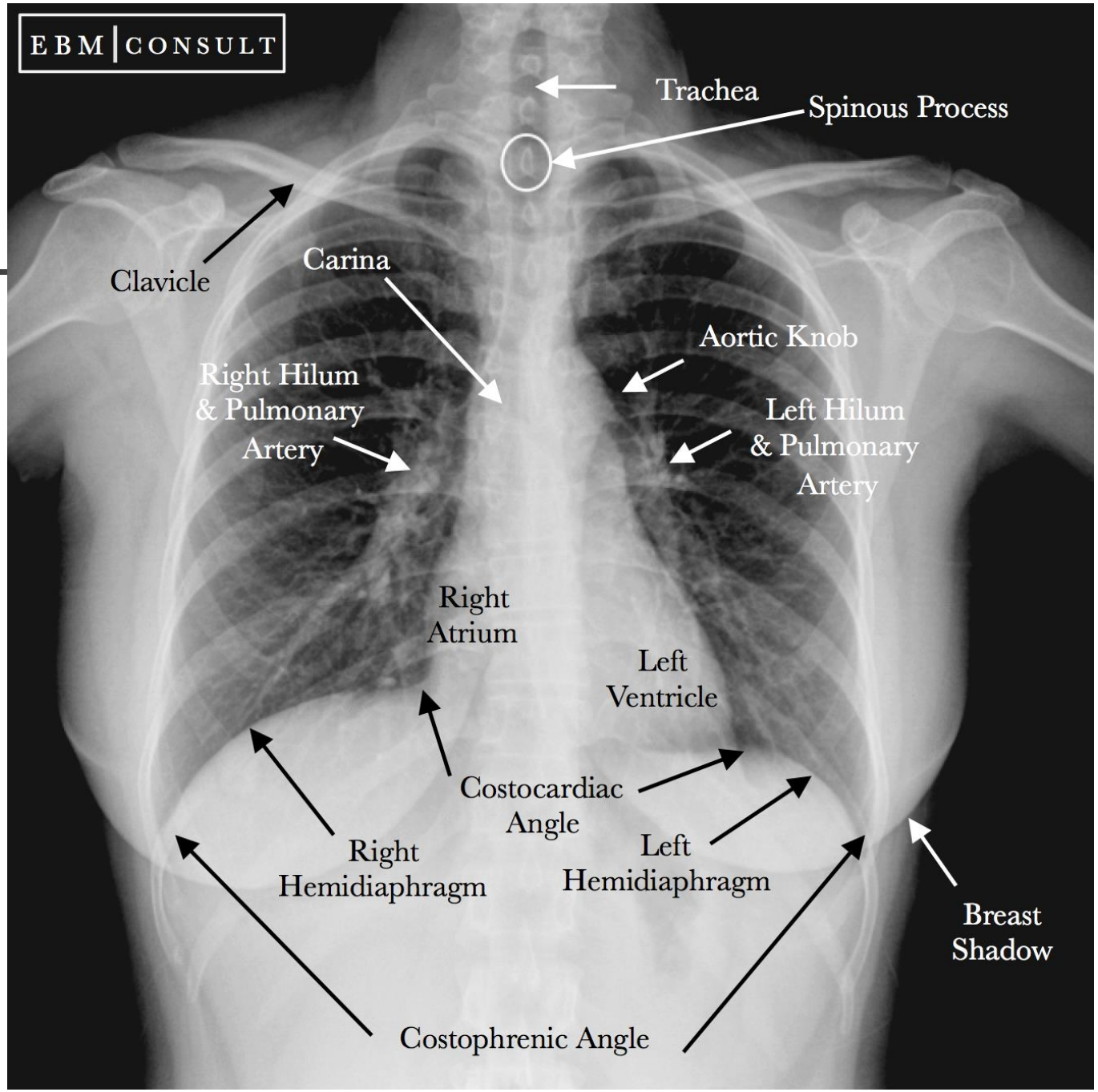
- CXR
- ABG:
  - Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE
- V/Q
- Spiral CT
- Echo
- Angio

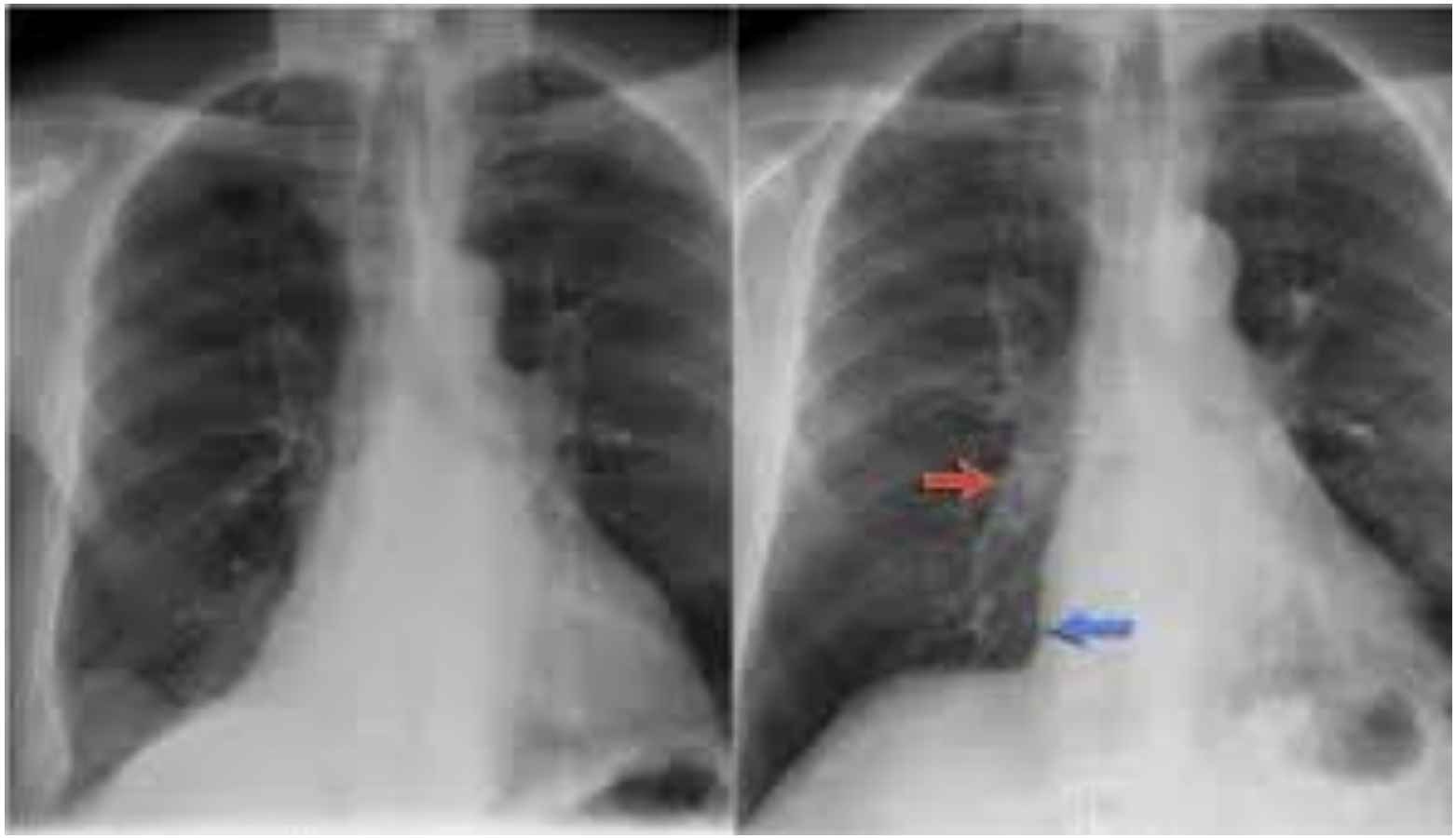
Chest radiograph showing pulmonary infarct in right lower lobe

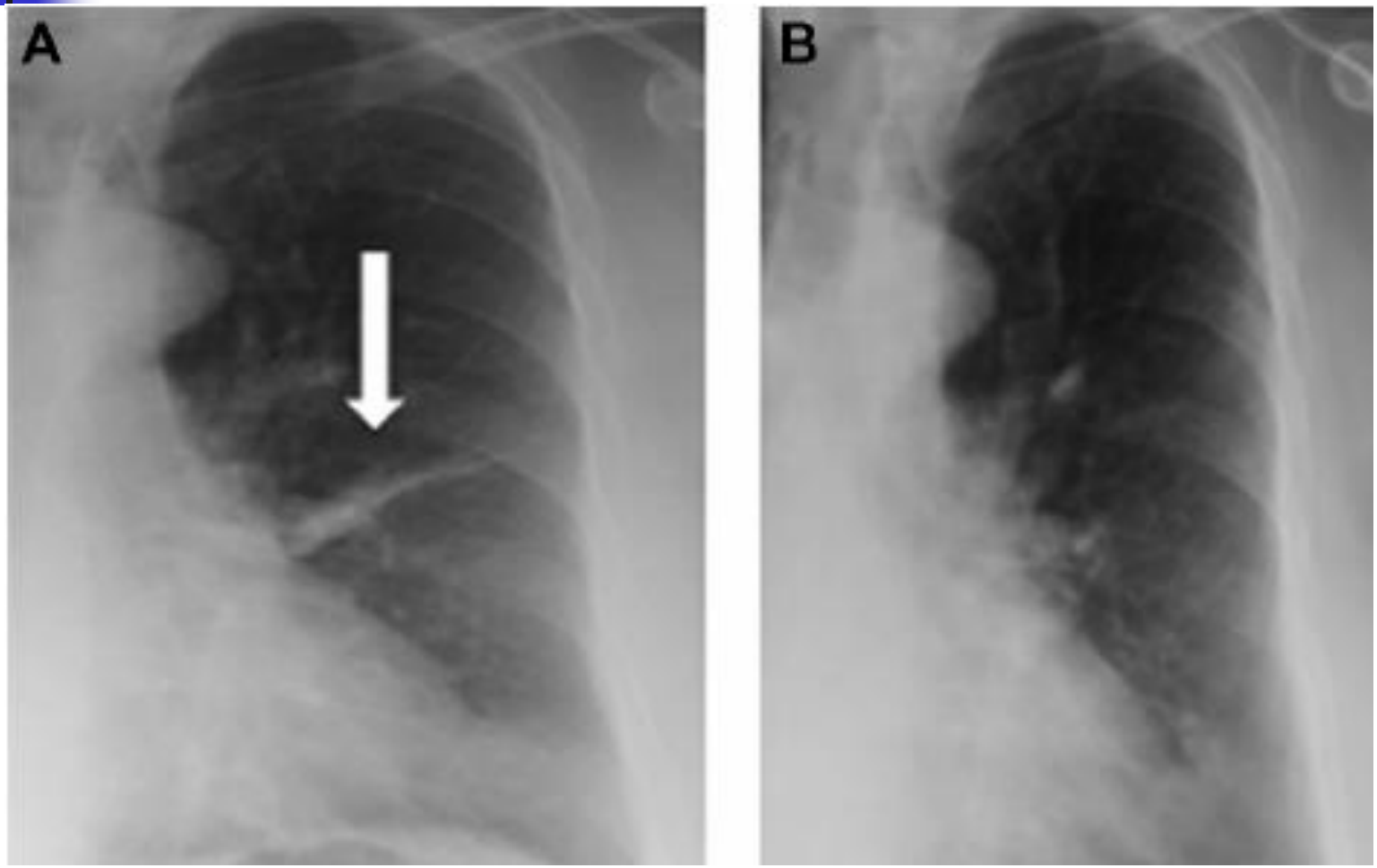


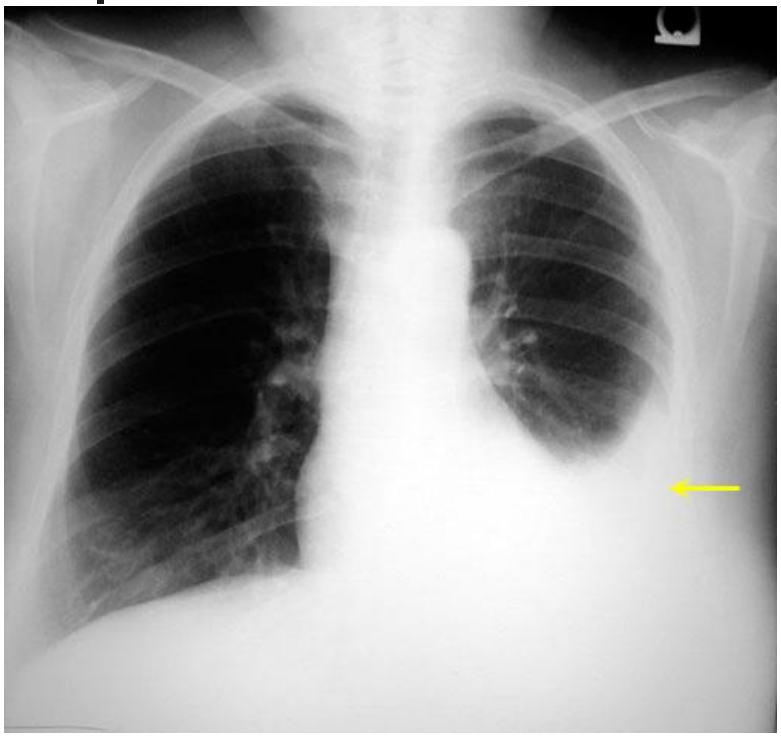
Chest radiographic findings in patients with pulmonary embolism

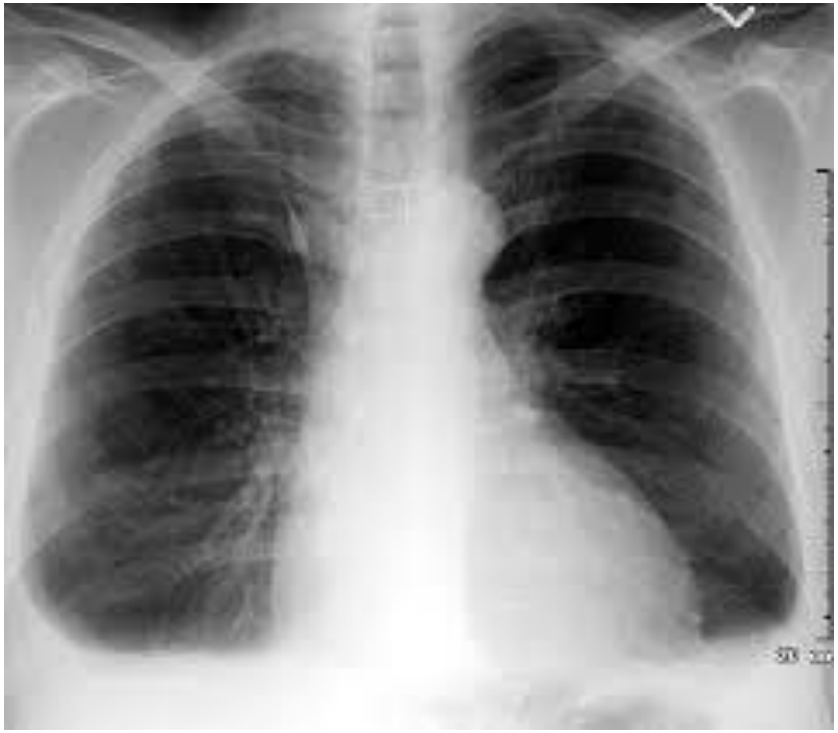
	COPD, % (n= 21)	No prior cardiopulmonary disease, % (n= 117)
Atelectasis or pulmonary parenchymal abnormality	76	68
Pleural effusion	52	48
Pleural-based opacity	33	35
Elevated diaphragm	14	24
Decreased pulmonary vascularity	38	21
Prominent central pulmonary artery	29	15
Cardiomegaly	19	12
Westermark's sign*	5	7
Pulmonary edema	14	4


EBM | CONSULT
Trachea
Spinous Process
Clavicle
Carina
Aortic Knob
Right Hilum & Pulmonary Artery
Left Hilum & Pulmonary Artery
Right Atrium
Left Ventricle
Costocardiac Angle
Right Hemidiaphragm
Left Hemidiaphragm
Breast Shadow
Costophrenic Angle

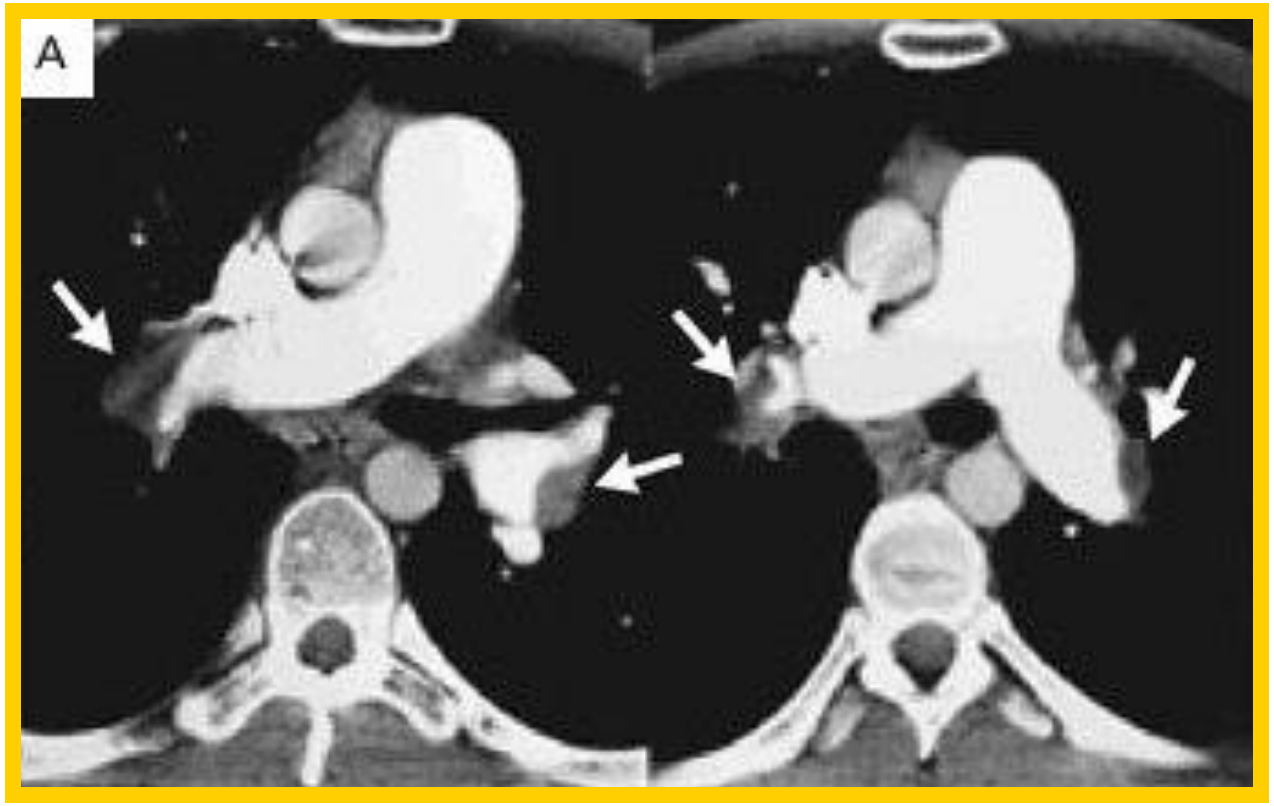



A
B

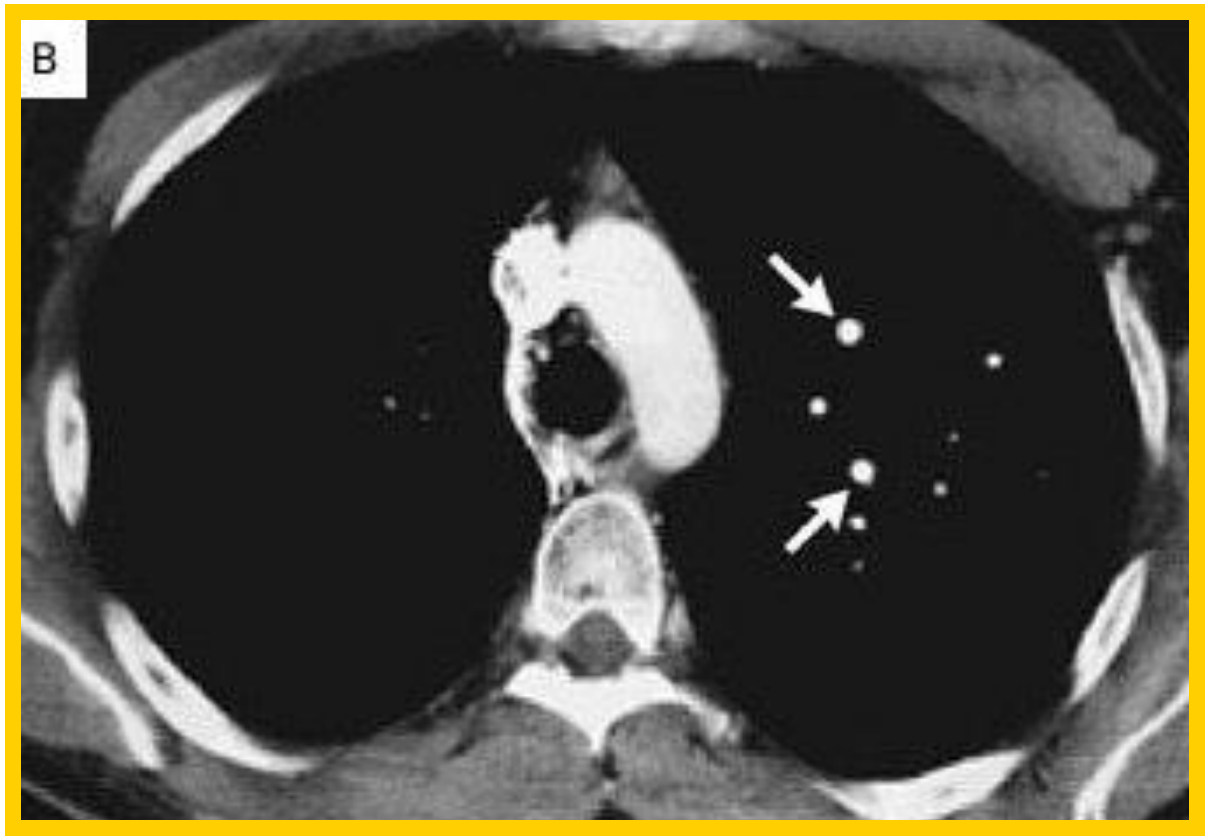




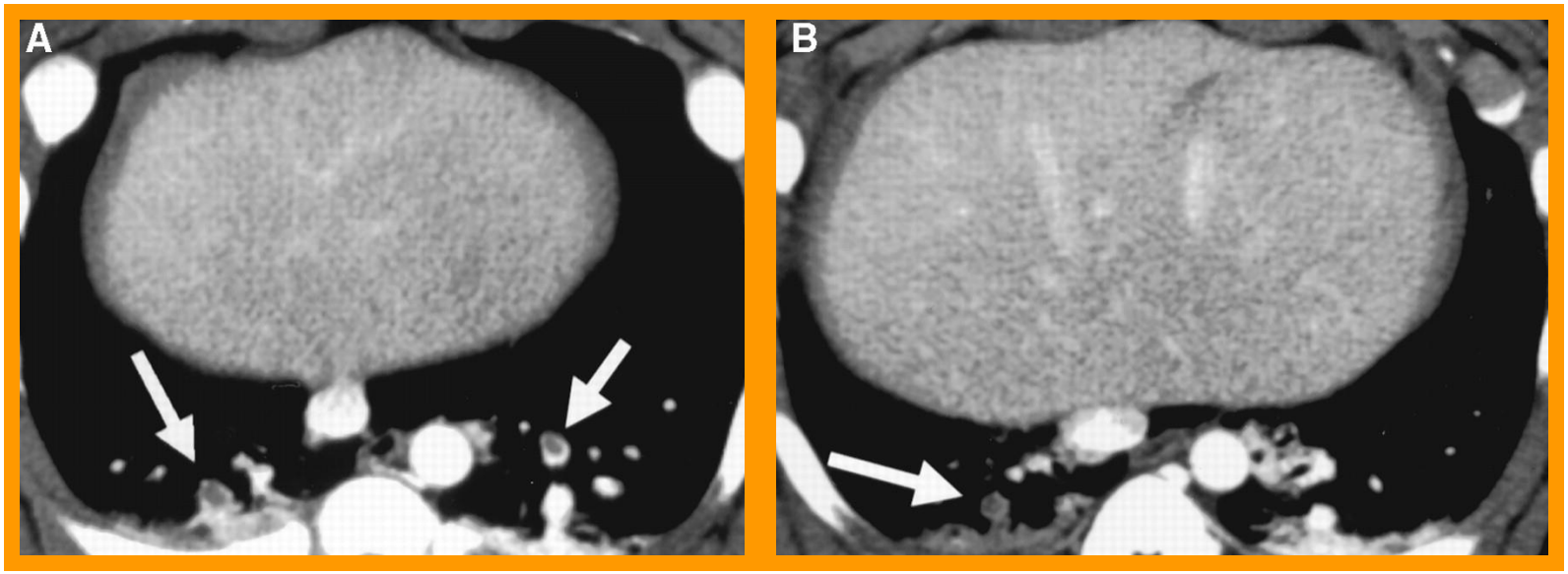
Spiral CT

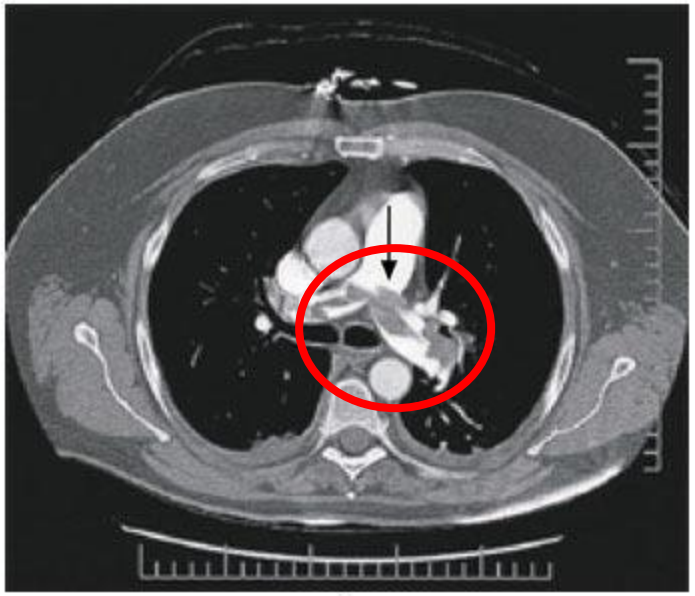


Spiral CT



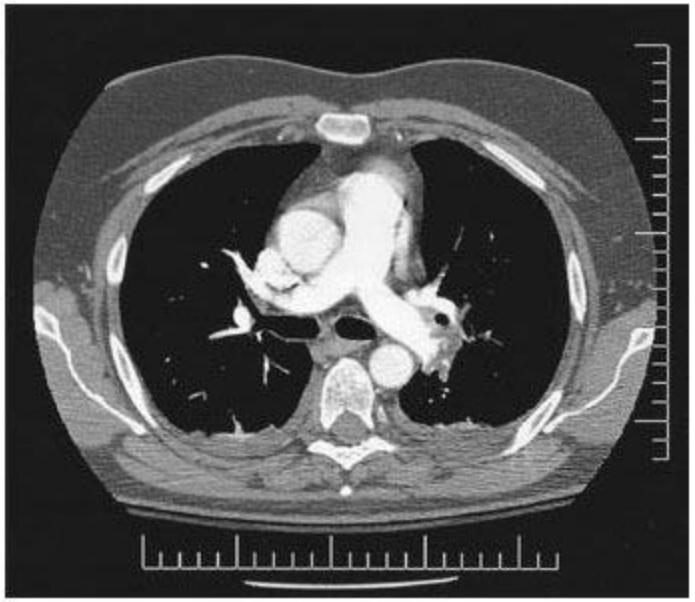
Spiral CT





A

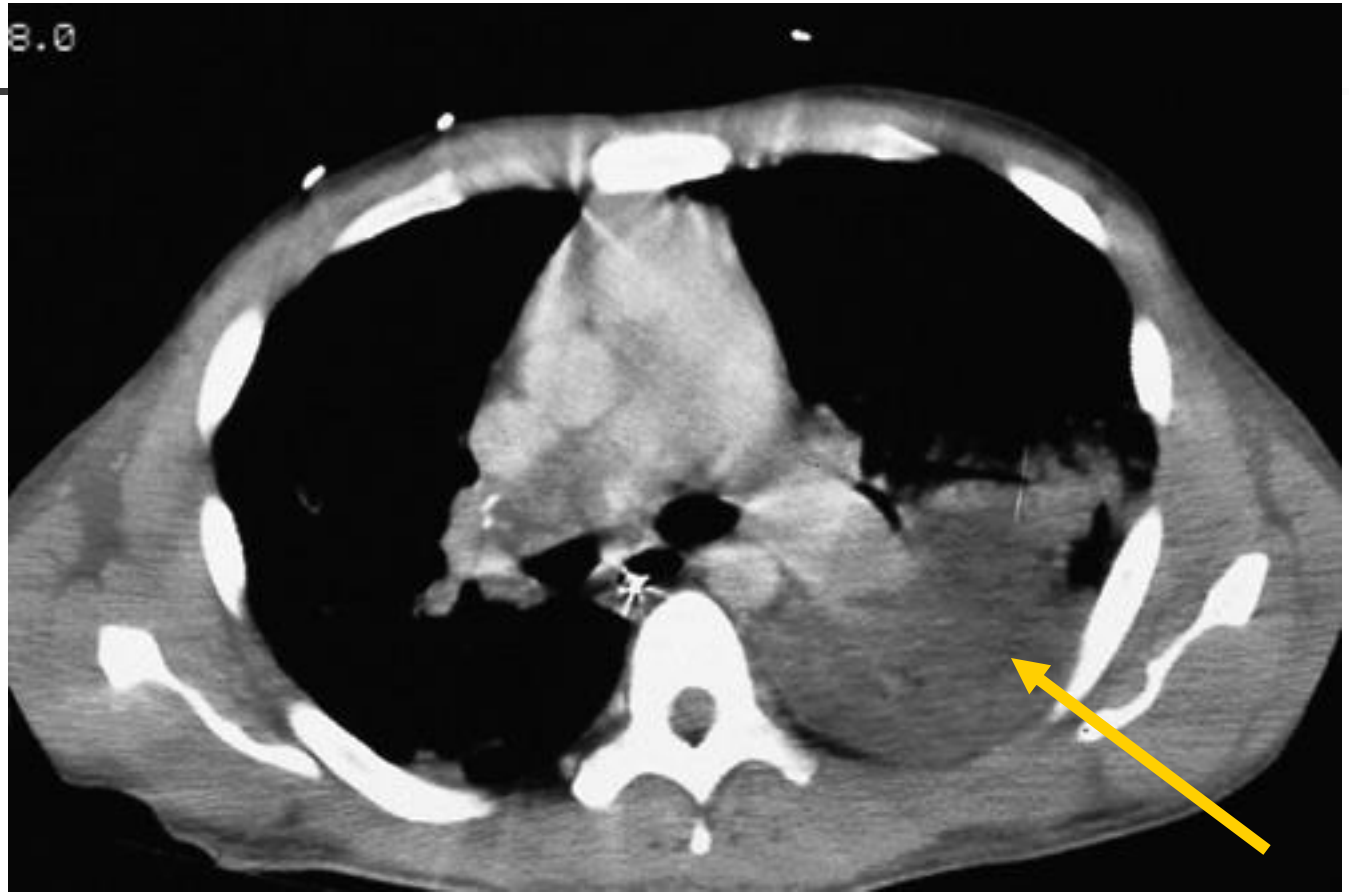
Before



B

After

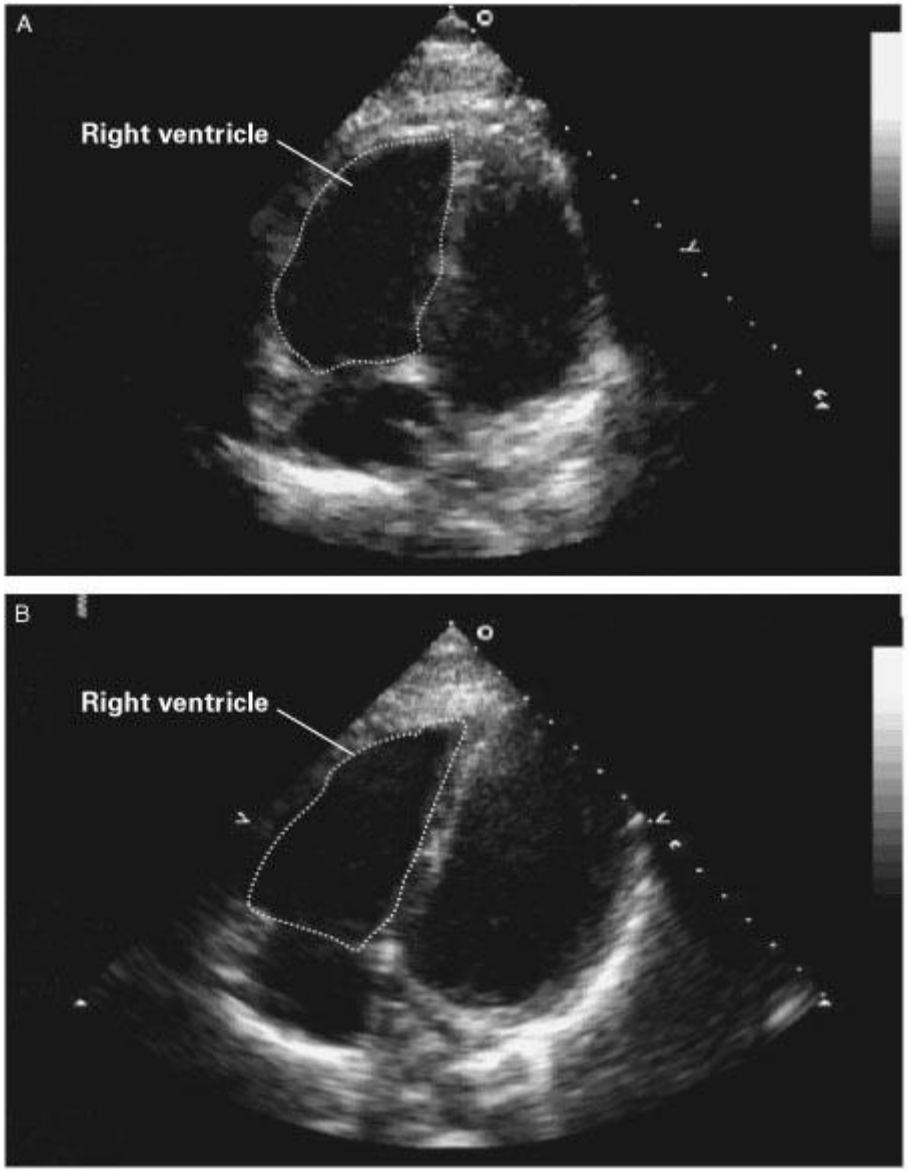
Tomographic scan showing infarcted left lung, large clot in right main pulmonary artery



Computed tomographic pulmonary angiography (Spiral CT)

- Data suggest that a negative Spiral CT is an adequate criterion for excluding PE in patients with a non-high clinical probability of PE

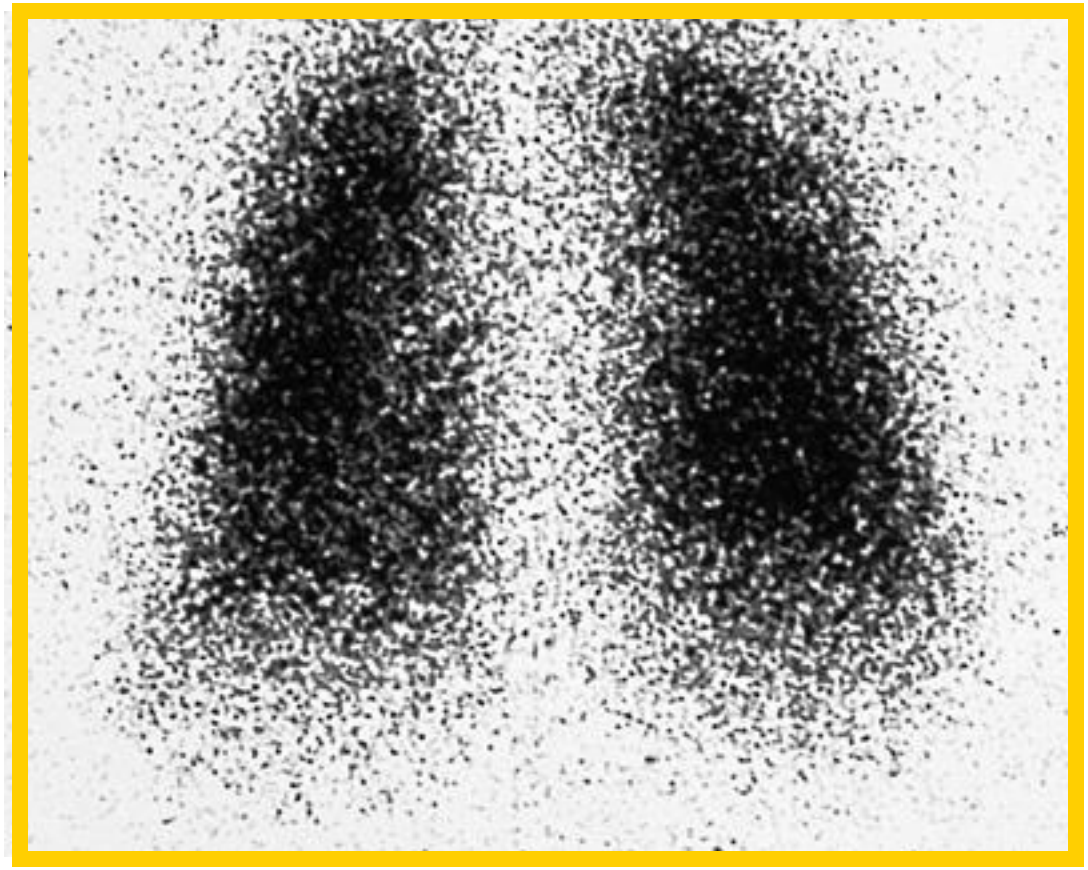
European Heart Journal (2014) 35, 3033–3080



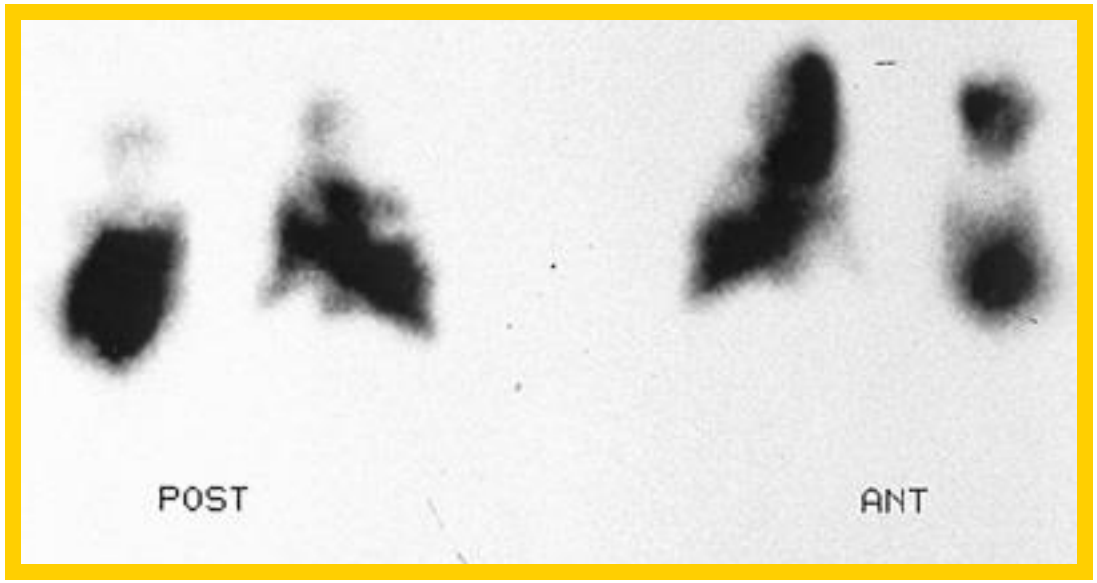
Before

After

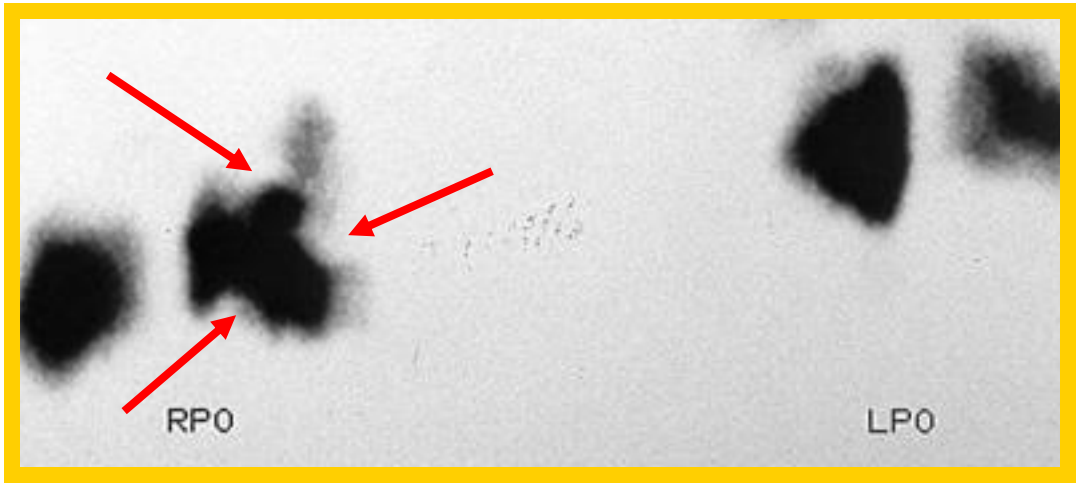
High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan

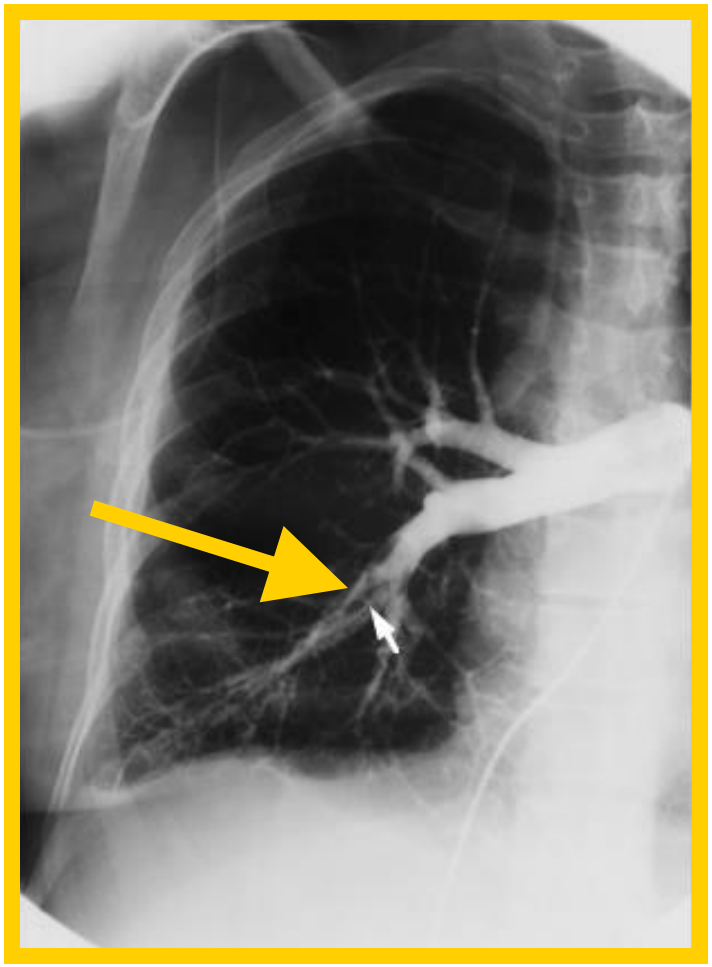


Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) results

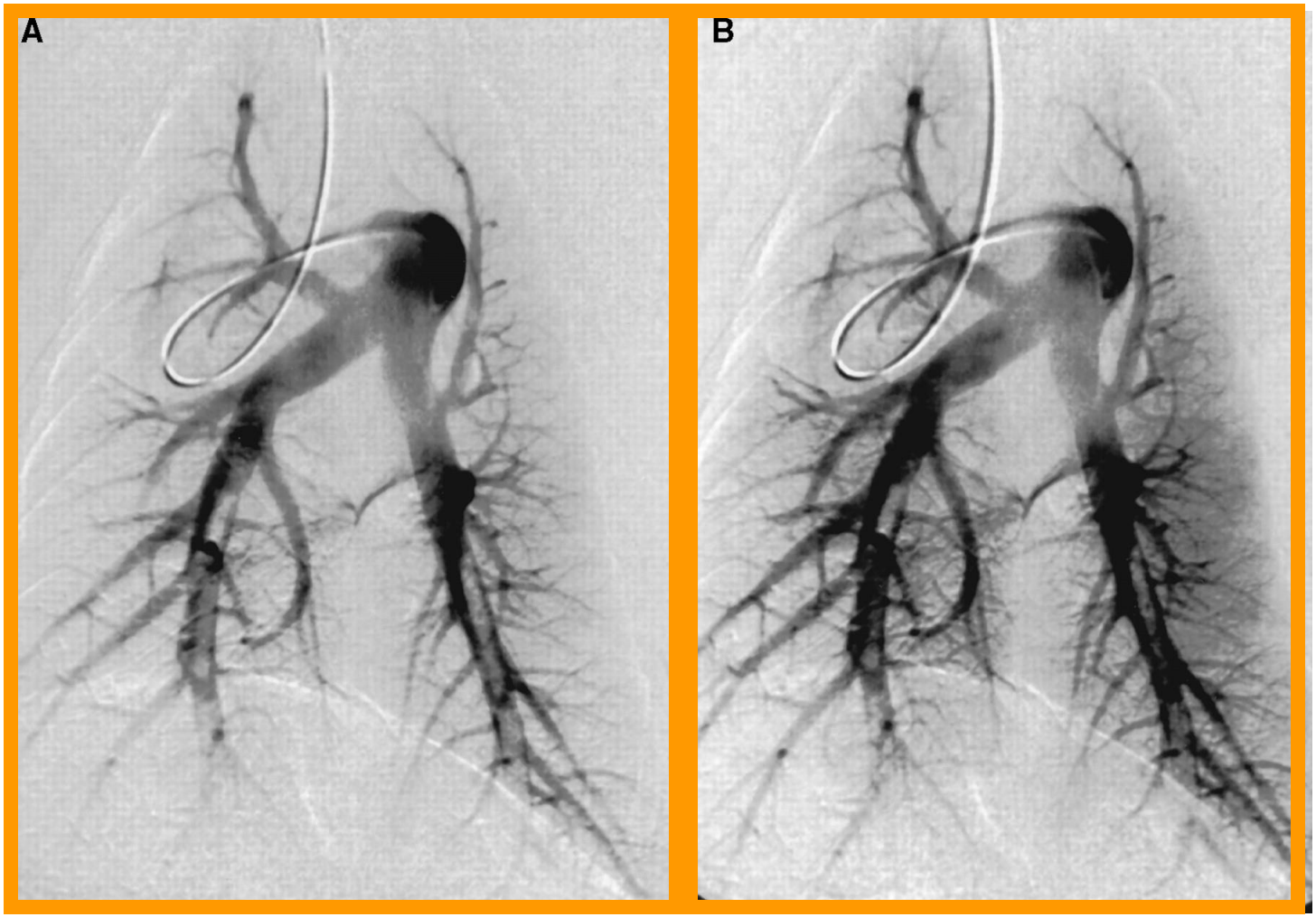
Prospective investigation of pulmonary embolism diagnosis results

Scan category	PE present	PE absent	PE uncertain	No angiogram	Total
High probability	102	14	1	7	124
Intermediate probability	105	217	9	33	364
Low probability	39	199	12	62	312
Near normal or normal	5	50	2	74	131
Total	251	480	24	176	931

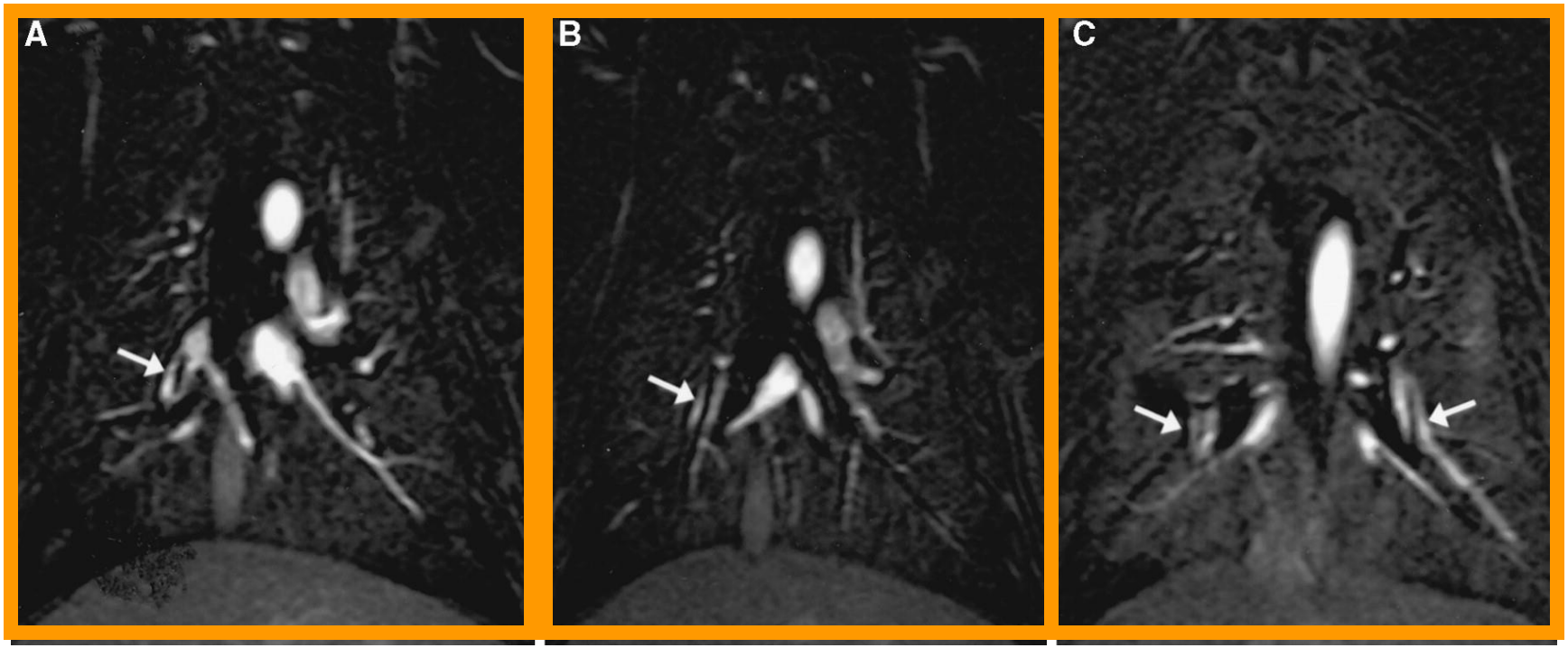
Pulmonary angiogram



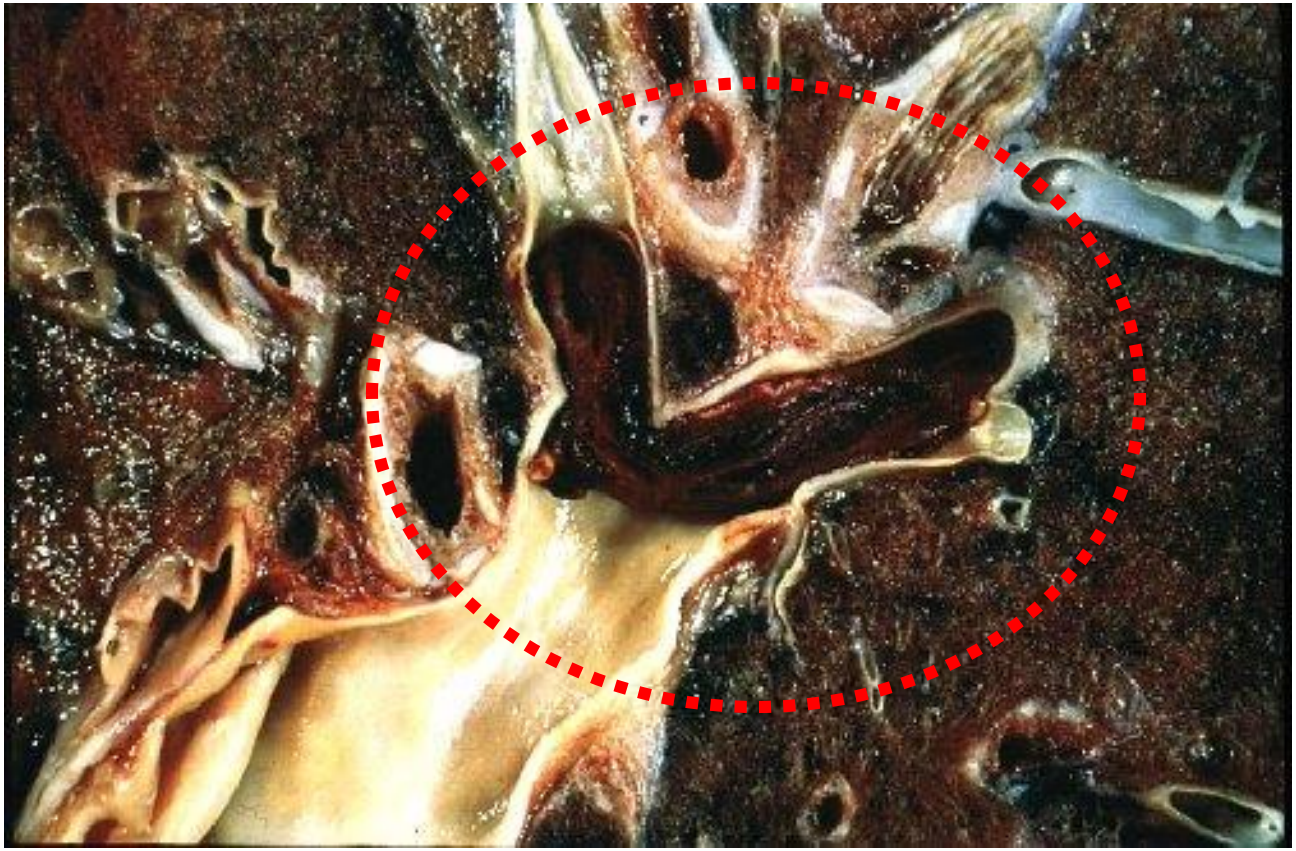
Pulmonary Angiogram



MRA with contrast



PULMONARY EMBOLISM



Dosage and monitoring of anticoagulant therapy

- **After initiating heparin therapy, repeat APTT every 6 h for first 24 h and then every 24 h when therapeutic APTT is achieved**
- **Warfarin 5 mg/d can be started on day 1 of therapy; there is no benefit from higher starting doses**
- **Platelet count should be monitored at least every 3 d during initial heparin therapy**
- **Heparin is usually continued for 5–7 d**
- **Heparin can be stopped after 4–5 d of warfarin therapy when INR is in 2.0–3.0 range**

Important drug interactions with warfarin

Drugs that decrease warfarin requirement	Drugs that increase warfarin requirement
Phenylbutazone	Barbiturates
Metronidazole	Carbamazepine
Trimethoprim-sulfamethoxazole	Rifampin
Amiodarone	Penicillin
Second- and third-generation cephalosporins	Griseofulvin
Clofibrate	Cholestyramine
Erythromycin	
Anabolic steroids	
Thyroxine	

Complications of anticoagulation

	Complication	Management
Heparin	Bleeding	Stop heparin infusion. For severe bleeding, the anticoagulant effect of heparin can be reversed with intravenous protamine sulfate 1 mg/100 units of heparin bolus or 0.5 mg for the number of units given by constant infusion over the past hour; provide supportive care including transfusion and clot evacuation from closed body cavities as needed.

Complications of anticoagulation

	Complication	Management
Heparin	**Heparin-induced thrombocytopenia and thrombosis**	Carefully monitor platelet count during therapy. Stop-heparin for platelet counts <75,000. Replace heparin with direct inhibitors of thrombin-like desirudin if necessary. These agents do not cause heparin-induced thrombocytopenia. Avoid platelet transfusion because of the risk for thrombosis.

Complications of anticoagulation

	Complication	Management
Heparin	Heparin-induced osteoporosis (therapy >1 mo)	LMWHs may have lower propensity to cause osteoporosis as compared with unfractionated heparin; consider LMWH if prolonged heparin therapy is necessary.

Complications of anticoagulation

Warfarin

Complication	Management
Bleeding	Stop therapy. Administer vitamin K and fresh-frozen plasma for severe bleeding; provide supportive care including transfusion and clot evacuation from closed body cavities as needed
Skin necrosis (rare)	Supportive care.
Teratogenicity	Do not use in pregnancy or in patients planning to become pregnant.

Table 11 Overview of phase III clinical trials with non-vitamin K-dependent new oral anticoagulants (NOACs) for the acute-phase treatment and standard duration of anticoagulation after VTE

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran		Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[254]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban		Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[256]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban		Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Endoxaban		Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

b.i.d. = bis in die (twice daily); CRNM = clinically relevant non-major; DVT = deep vein thrombosis; o.d. = omni die (once daily); PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism.

European Heart Journal (2014) 35, 3033–3080

Approved thrombolytics for pulmonary embolism

- **Recombinant tissue-plasminogen activator**

  100 mg as a continuous peripheral intravenous infusion administered over 2 h

- **Streptokinase**

  250,000 IU as loading dose over 30 min, followed by 100,000 U/h for 24 h

- **Urokinase**

  4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h for 12-24 h

Indications and contraindications for thrombolytic therapy in pulmonary embolism

Indications

Hemodynamic instability

Hypoxia on 100% oxygen

Right ventricular dysfunction by echocardiography

Contraindications

Relative

Recent surgery within last 10 d

Previous arterial punctures within 10 d

Neurosurgery within 6 mo

Bleeding disorder (thrombocytopenia, renal failure, liver failure)

Ophthalmologic surgery within 6 wk

Hypertension >200 mm Hg systolic or 110 mm Hg diastolic

Placement of central venous catheter within 48 h

Hypertensive retinopathy with hemorrhages or exudates

Intracerebral aneurysm or malignancy

Cardiopulmonary resuscitation within 2 wk

Cerebrovascular disease

Major internal bleeding within the last 6 mo

Pregnancy and the 1st 10 d postpartum

Infectious endocarditis

Severe trauma within 2 mo

Pericarditis

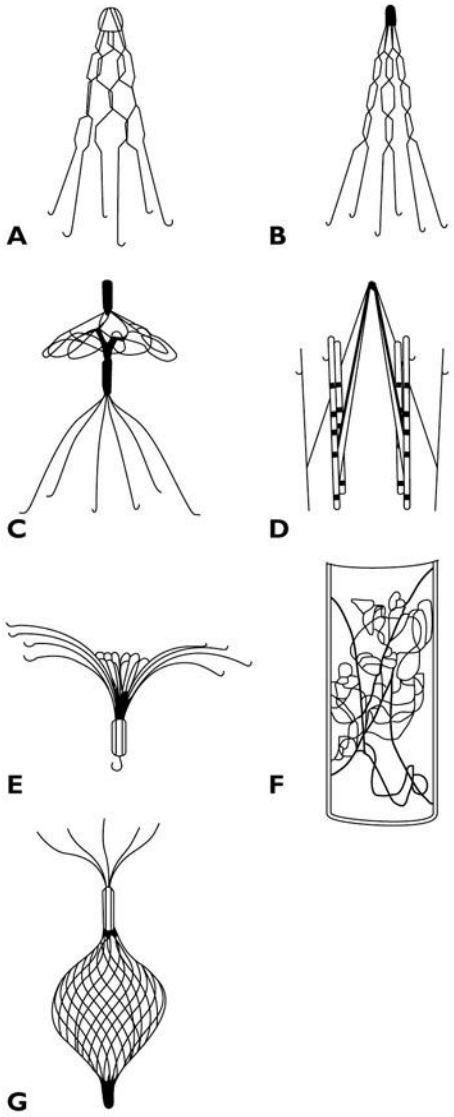
Absolute

Active internal bleeding

Other Treatment Modalities

- Surgical embolectomy
- Percutaneous catheter-directed treatment

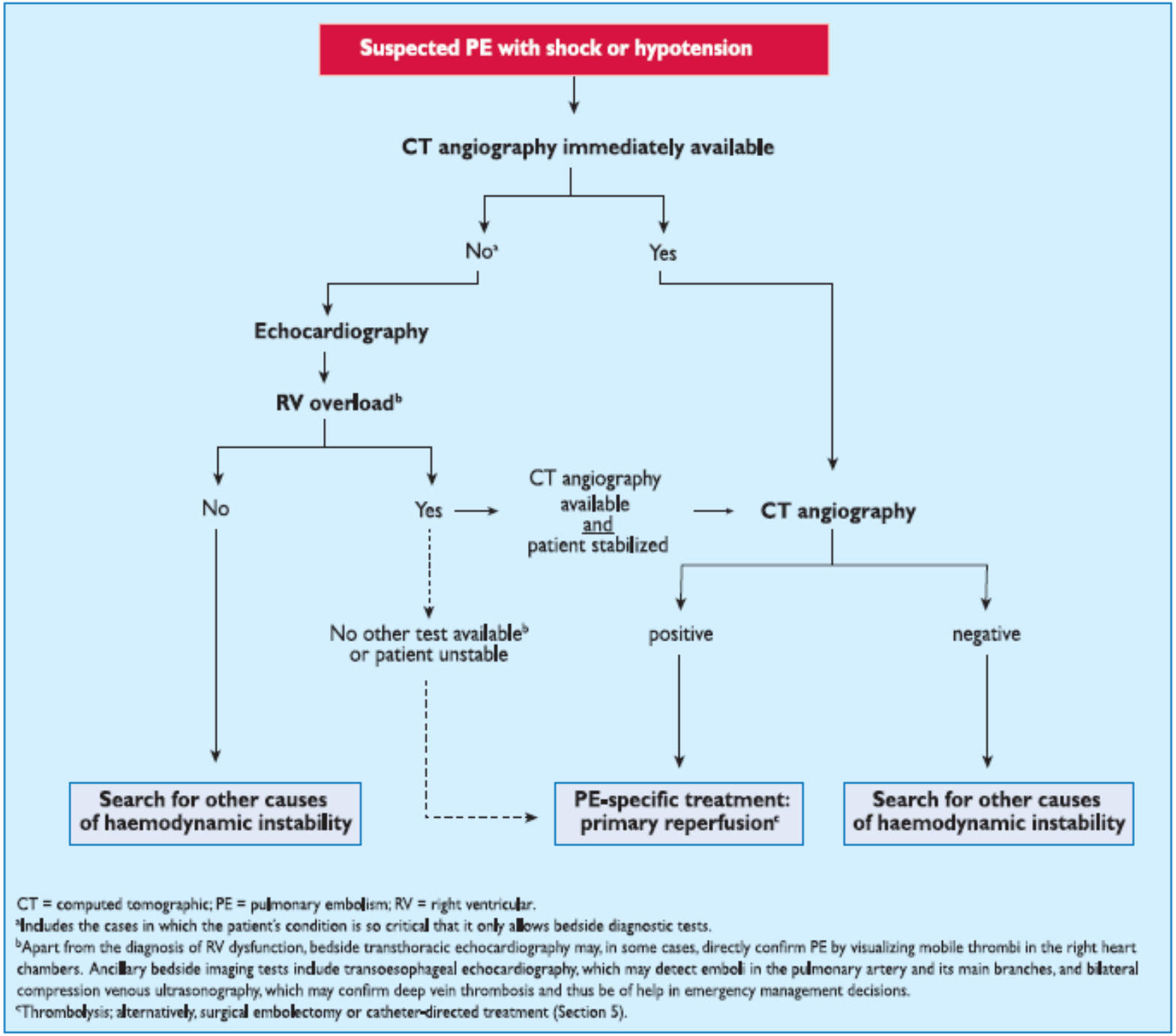
Various inferior vena caval filters



Indications for inferior vena caval (IVC) filters

Indications for inferior vena caval filter placement

- Anticoagulation contraindicated (eg, patients with multiple trauma, active bleeding)
- Failure of antithrombotic therapy
- Complications from anticoagulant therapy preclude further use
- Prophylaxis against embolism from preexisting deep vein thrombosis in patients with poor cardiopulmonary reserve
- Prophylaxis against embolism in patients at high risk to develop deep vein thrombosis
- Patients with recurrent pulmonary embolism undergoing thromboendarterectomy



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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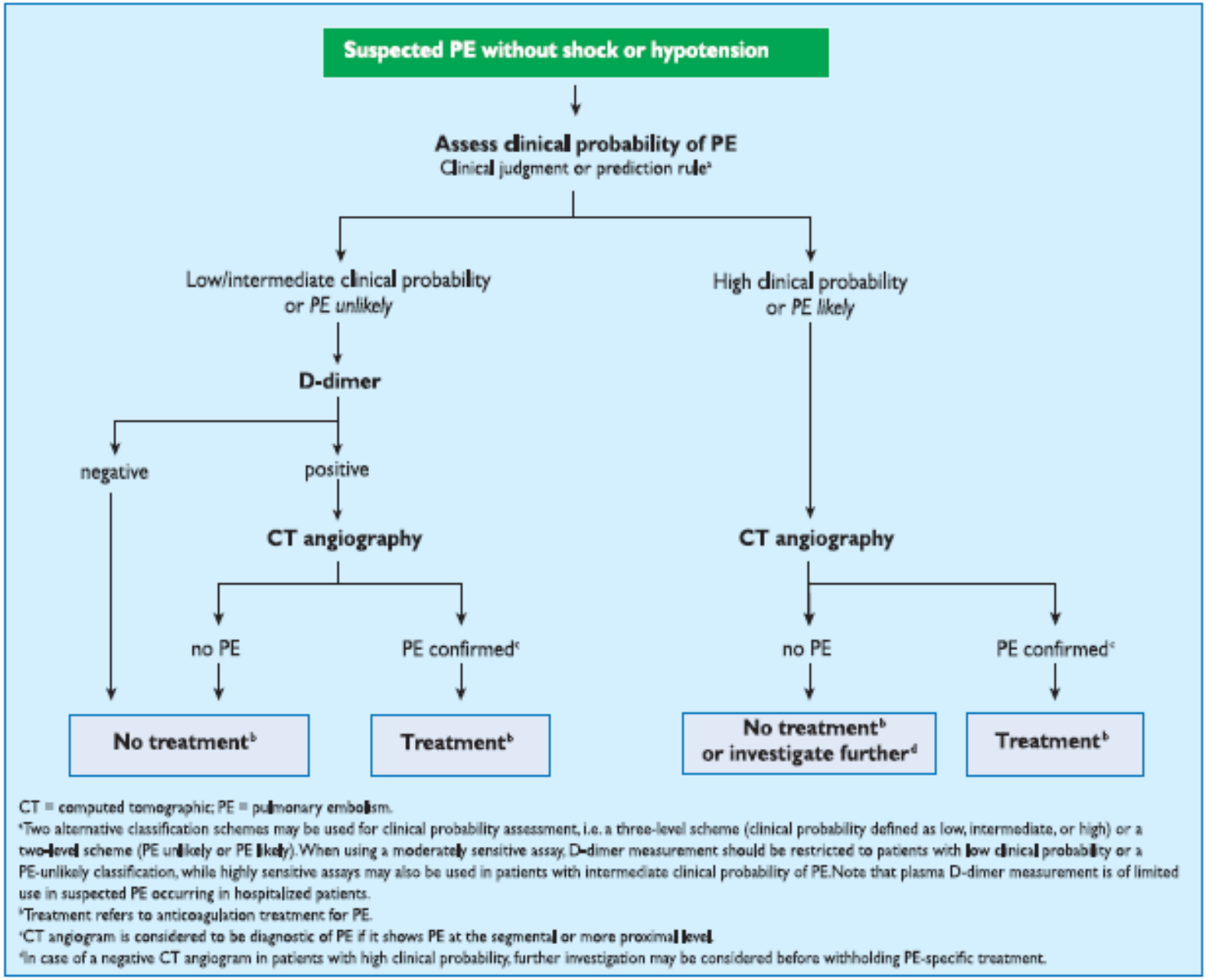

CT = computed tomographic; PE = pulmonary embolism.

[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.

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Conclusions

- PE is common and under-recognized serious medical problem
- Early diagnosis and treatment is essential for good outcome
- High index of suspicion is needed in high risk patients