Pulmonary Embolism - 2021

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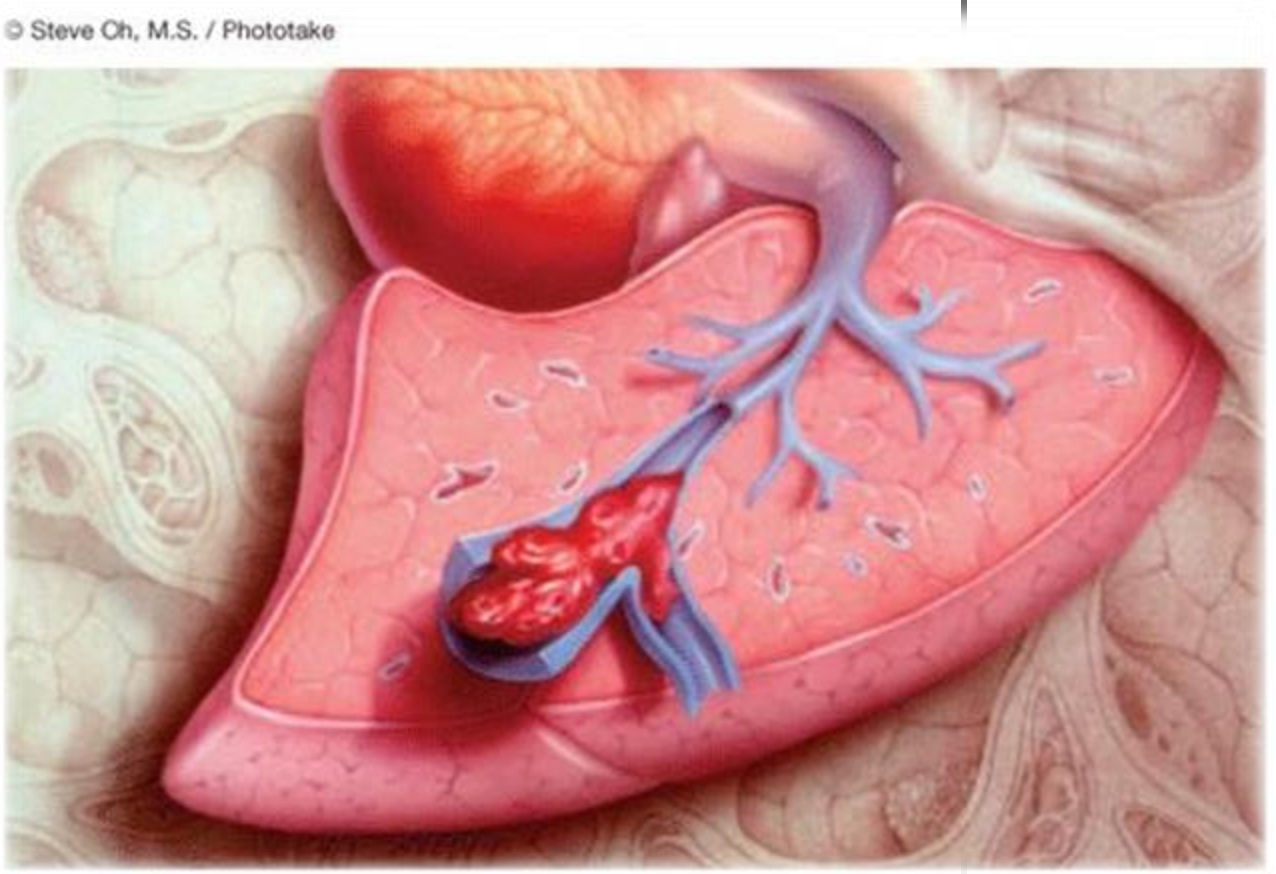
Pulmonary Embolism (PE)

Lecture Objectives:

To understand the followings:

- Prevalence of PE
- Risk factors
- Clinical features
- Pathophysiology
- Massive PE
- Diagnostic workup
- Treatment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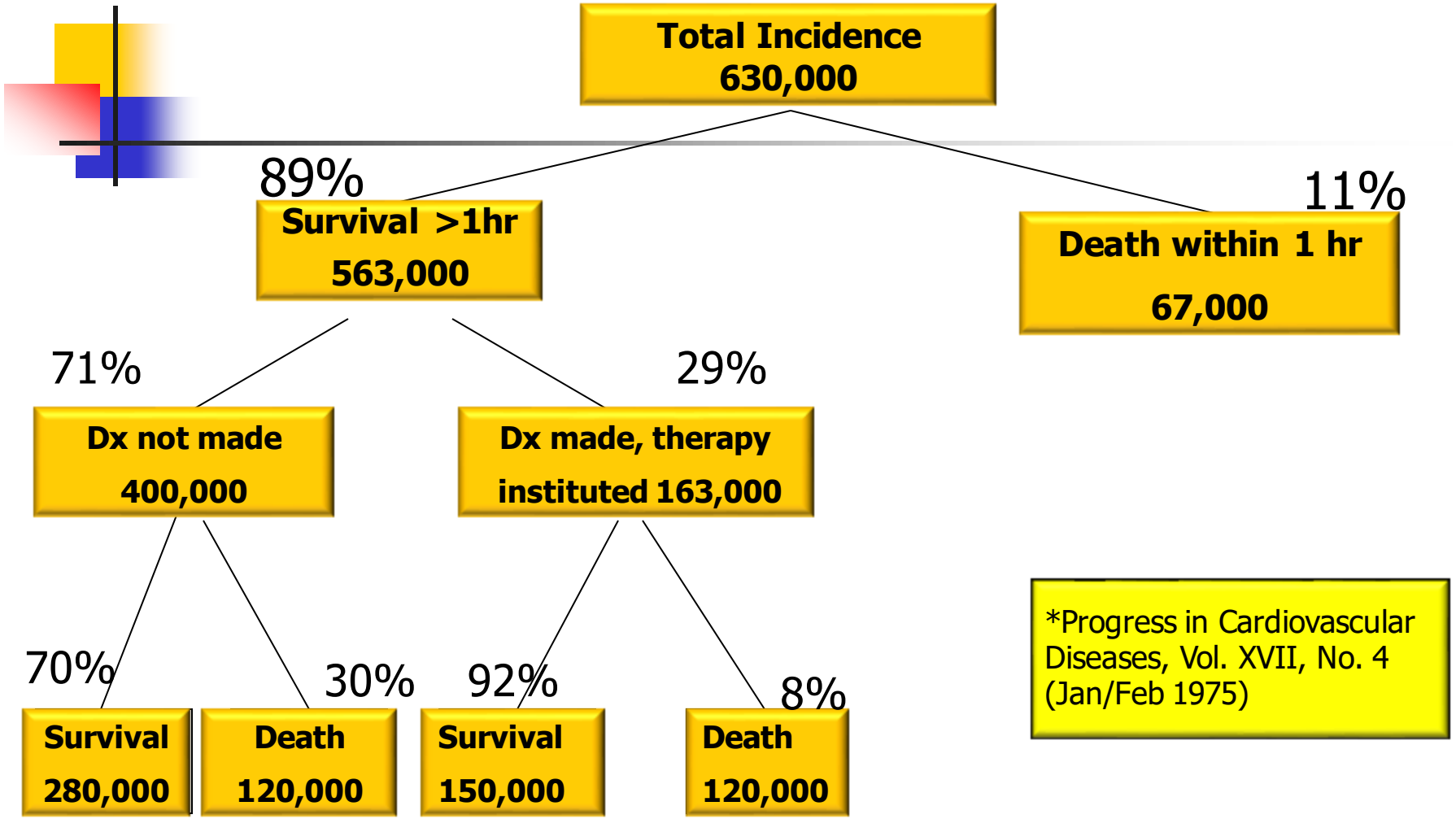
- 50,000 individuals die from PE each year in USA
- The incidence of PE in USA is 500,000 per year

Incidence of Pulmonary Embolism Per Year in the United States*



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

Incidence

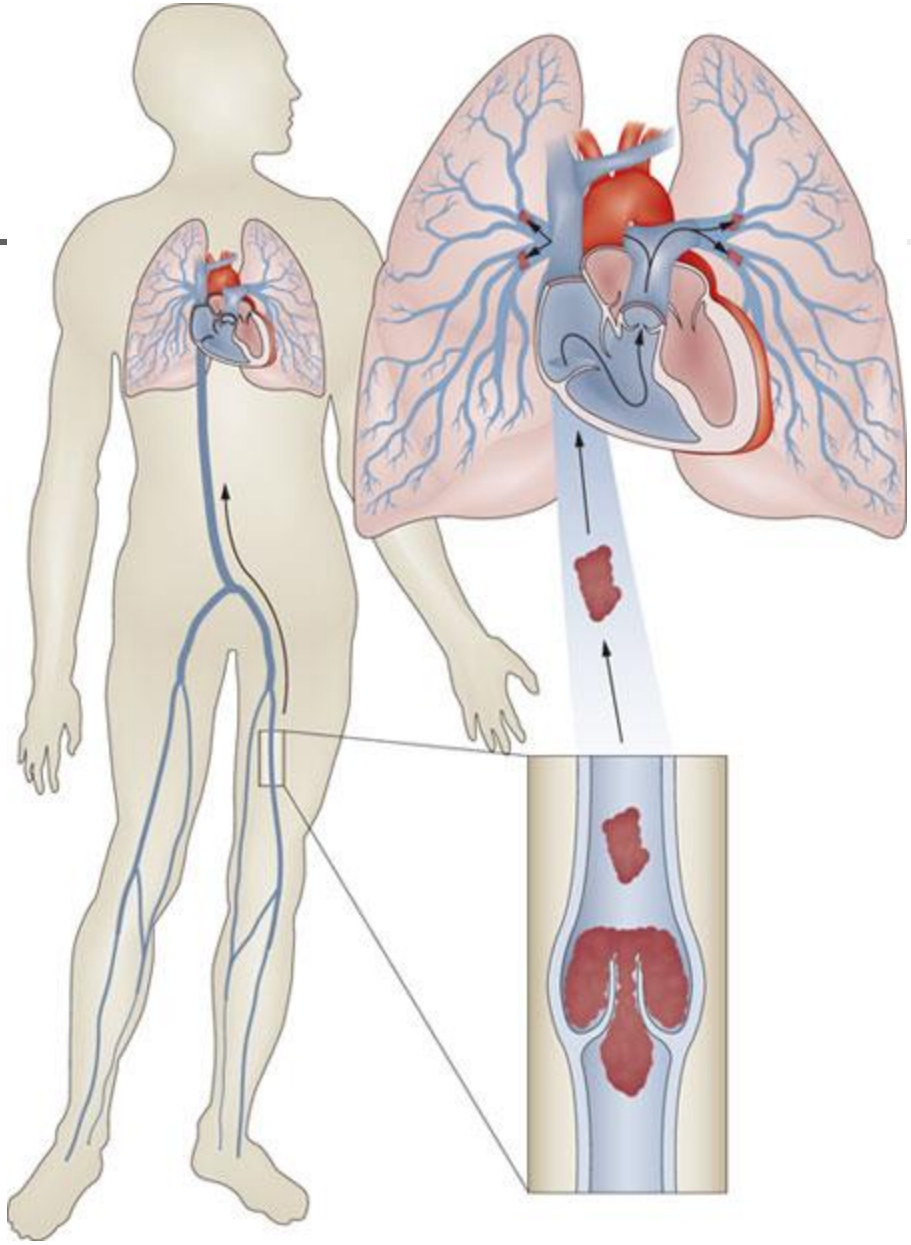
- The annual incidence of pulmonary embolism in the population is 1/1000 people,
- but this increases sharply with age,
  - 1.4 / 1000 people aged 40-49
  - 11.3 / 1000 aged 80 years or over

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

Risk factors for DVT

Box 1: Transient risk factors for venous thrombosis[16]

Strong risk factor (odds ratio >10)
- Hip or leg fracture
- Hip or leg joint replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factor (odds ratio 2-9)
- Arthroscopic knee surgery
- Central venous lines
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factor (odds ratio <2)
- Bed rest >3 days
- Immobility due to sitting (eg, prolonged road or air travel)
- Increasing age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy (antepartum)
- Varicose veins

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Risk factors

- 50%of venous thromboembolism events are associated with a transient risk factor,
- 20% are associated with cancer,
- The remainder are associated with minor or no risk factors and are thus **classified as unprovoked**

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

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary embolism	Dyspnea	73	77
	Tachypnea	70	70
	Chest pain	66	55
	Cough	37	—
	Tachycardia	30	43
	Cyanosis	1	18
	Hemoptysis	13	13
	Wheezing	9	—
	Hypotension	—	10

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary Embolism	Syncope	—	10
	Elevated jugular venous pulse	—	8
	Temperature >38.5°C	7	—
	S-3 gallop	3	5
	Pleural friction rub	3	2

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

Clinical probability scores

Modified Geneva rule*[33]	
Age ≥65 years	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active cancer	2
Unilateral lower limb pain	3
Pain on deep palpation of lower limb and unilateral edema	4
Hemoptysis	2
Heart rate 75-94 beats/min	3
Heart rate ≥95 beats/min	5
Simplified Geneva rule†[34]	
Age >65 years	1
Surgery or fracture within 1 month	1
Active cancer	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75-94 beats/min	1
Heart rate >94 beats/min	2

Clinical probability scores

- Using modified Geneva score, <3 points indicates low probability, 4-10 points indicates intermediate probability, and>10 points indicates high probability.

- Using simplified Geneva score, ≤2 points indicates that PE is unlikely.

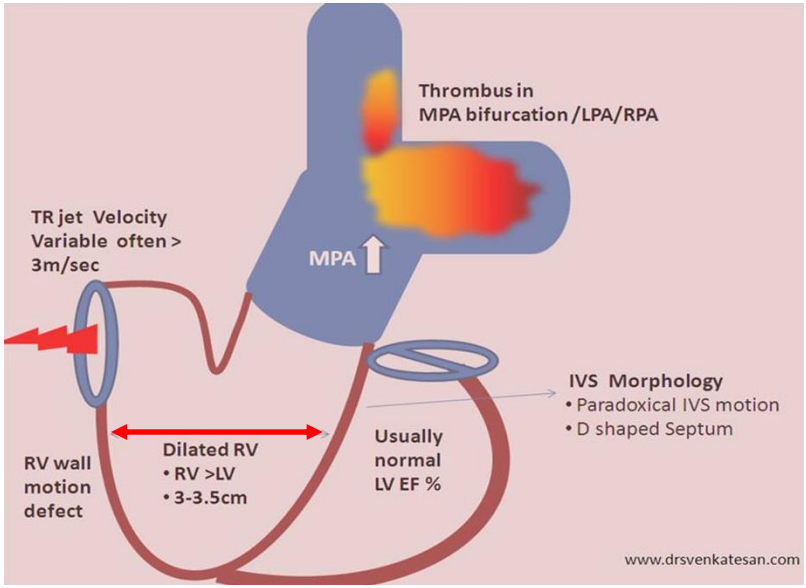
Clinical probability scores

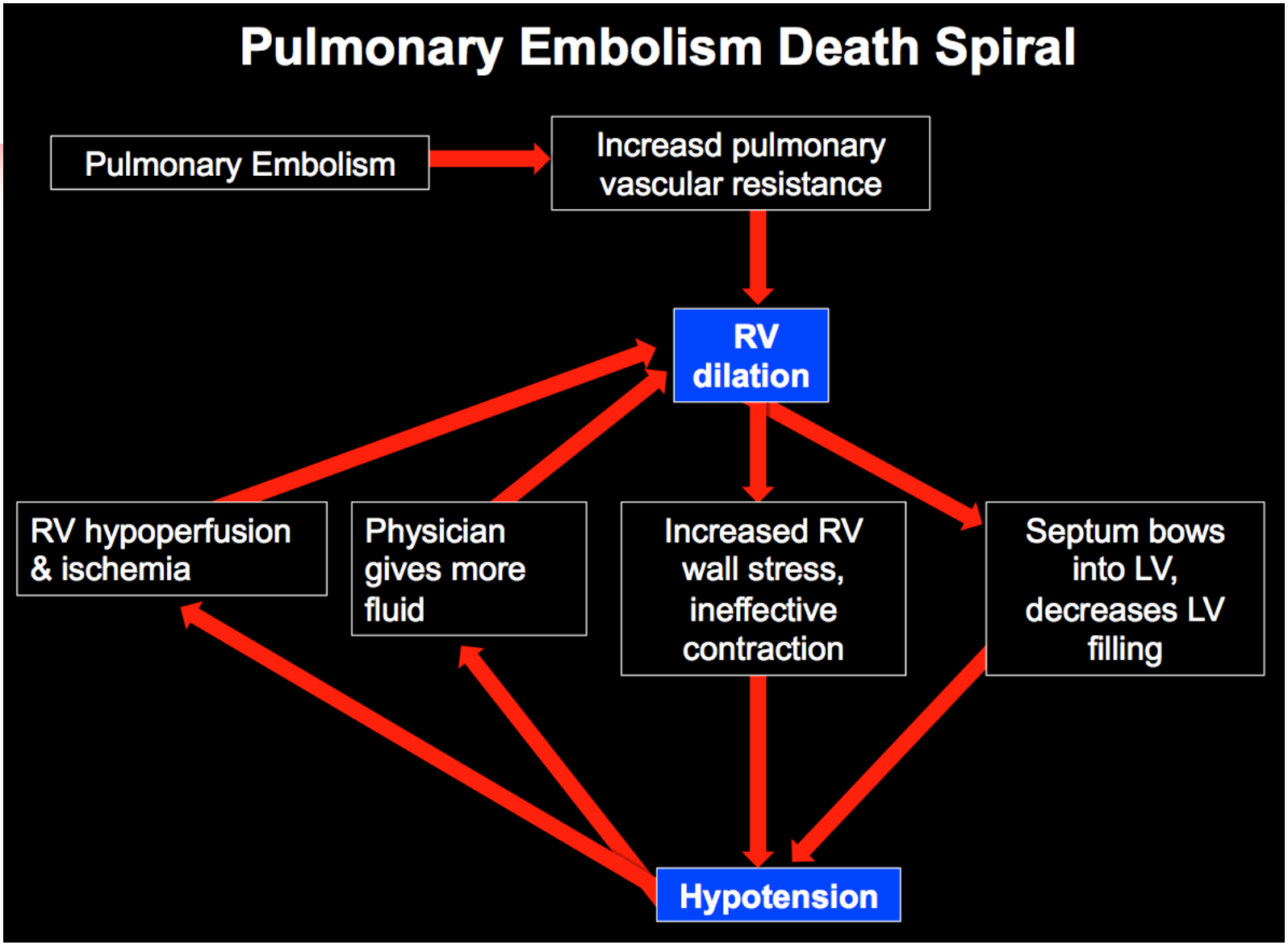
Wells rule‡[35 36]	
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization/surgery in previous 4 weeks	1.5
History of DVT or PE	1.5
Hemoptysis	1
Active cancer	1

Using traditional score, >6.0 points indicates high probability, 2.0-6.0 points indicates moderate probability,
and <2.0 points indicates low probability of PE. Using simplified score, >4 points indicates that PE is likely and
≤4 points indicates that PE is unlikely.

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

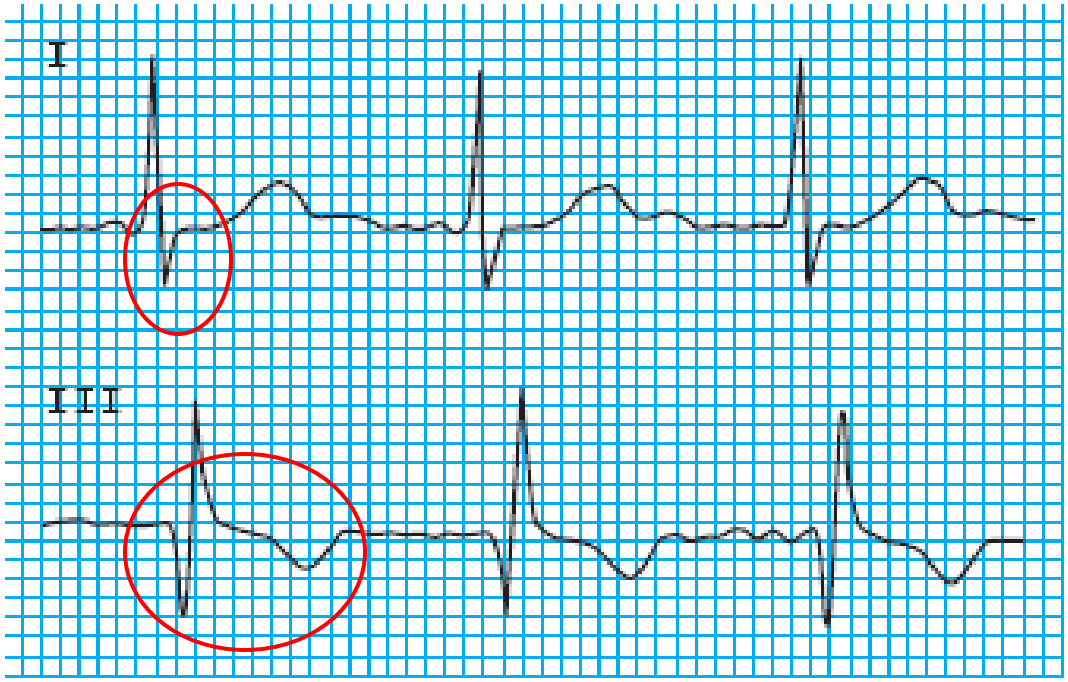



Pulmonary Embolism Death Spiral
Pulmonary Embolism
Increasd pulmonary vascular resistance
RV dilation
RV hypoperfusion & ischemia
Physician gives more fluid
Increased RV wall stress, ineffective contraction
Septum bows into LV, decreases LV filling
Hypotension

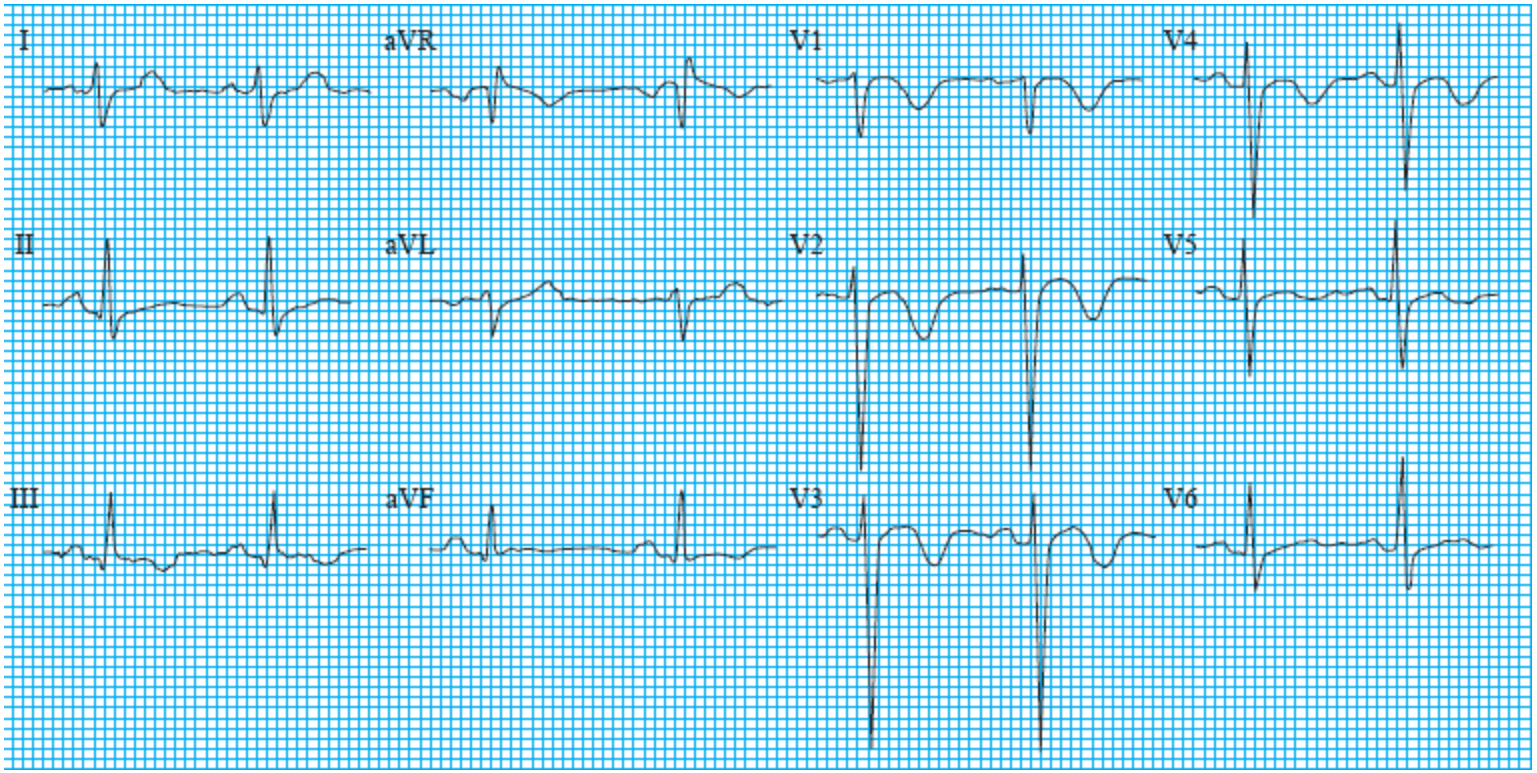
Diagnosis

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

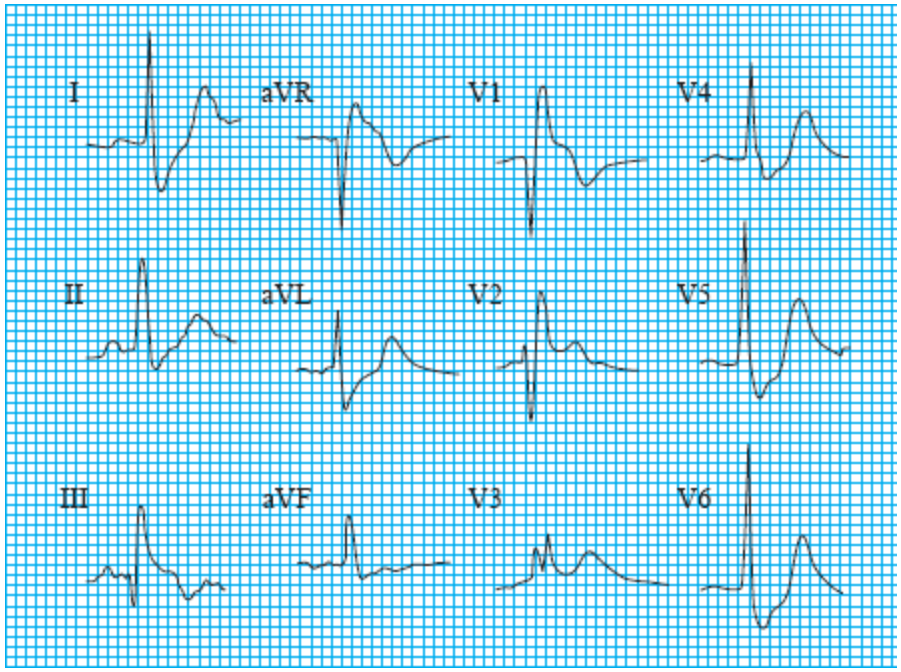
S1 Q3 T3 Pattern



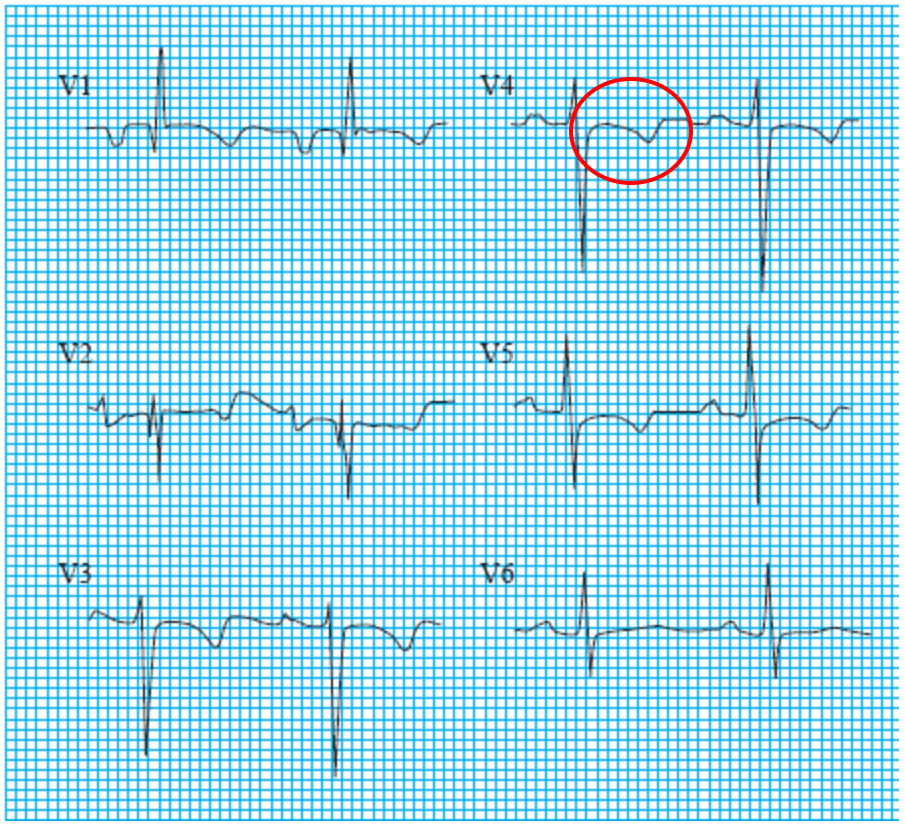
T-wave inversion



Rt. Bundle Branch Block



Rt. Ventricular Strain



D-Dimer

- The D-dimer is a degradation product of fibrinolysis and is increased in patients with acute venous thromboembolism as well other non-thrombotic disorders

- D-dimer is a sensitive but not specific diagnostic test.

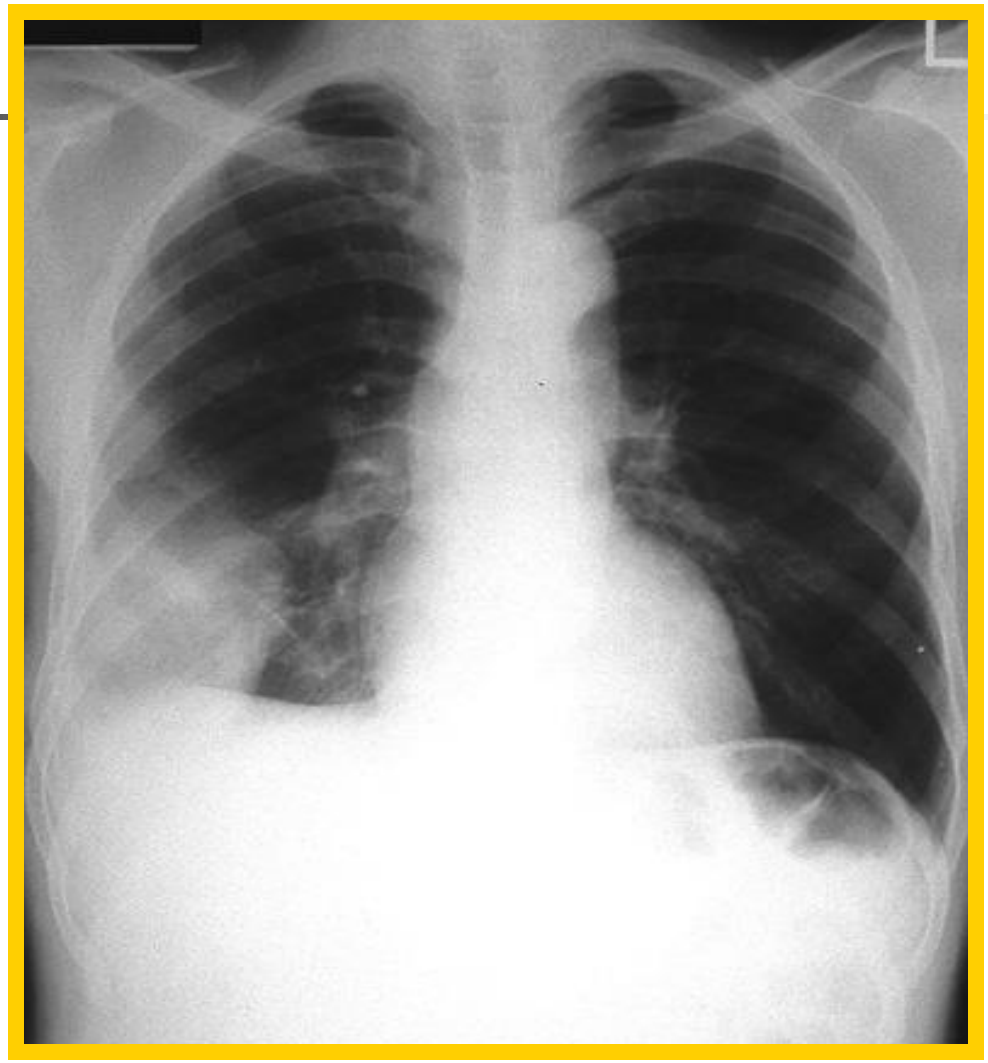
- A low clinical probability score is useful for excluding a diagnosis of venous thromboembolism

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

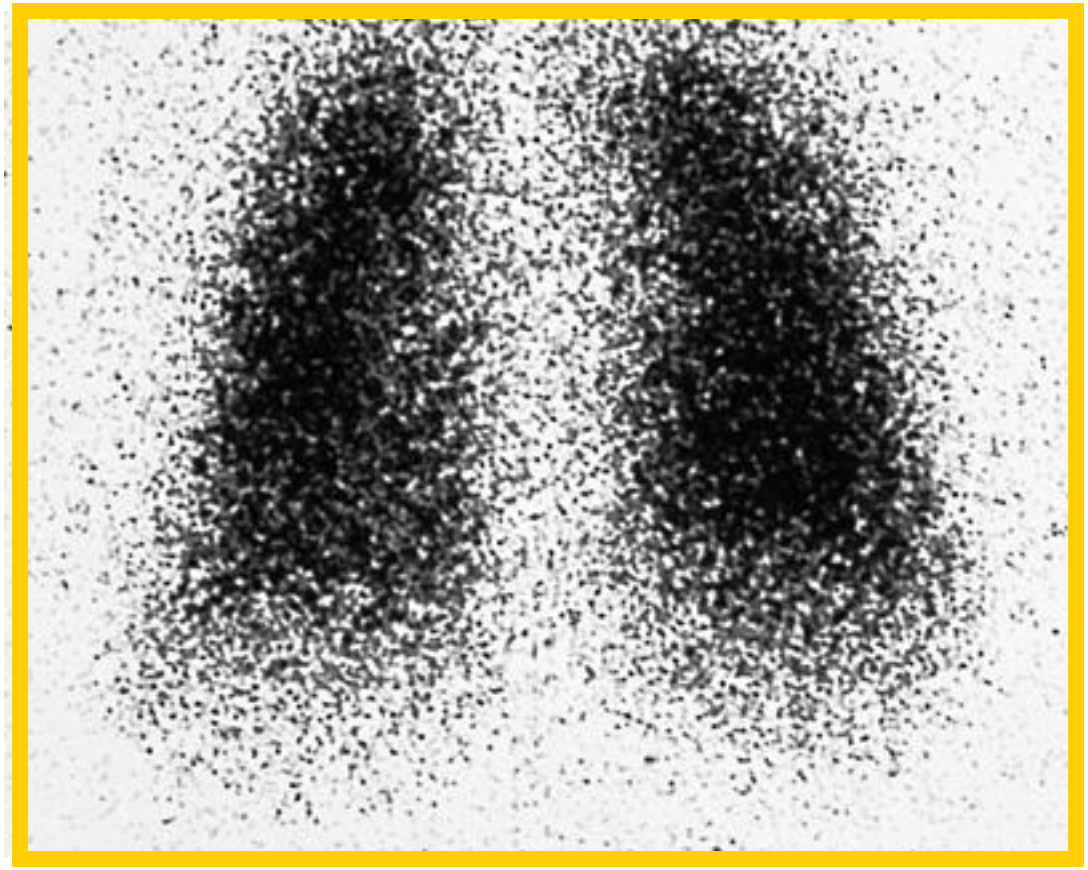
Chest radiograph showing pulmonary infarct in right lower lobe



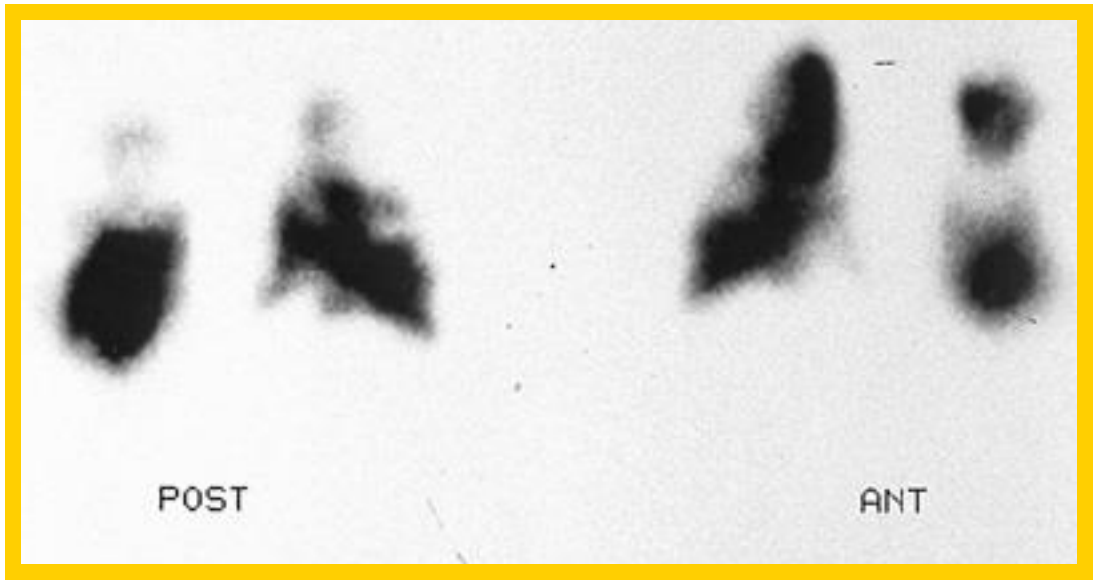
Chest radiographic findings in patients with pulmonary embolism

	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

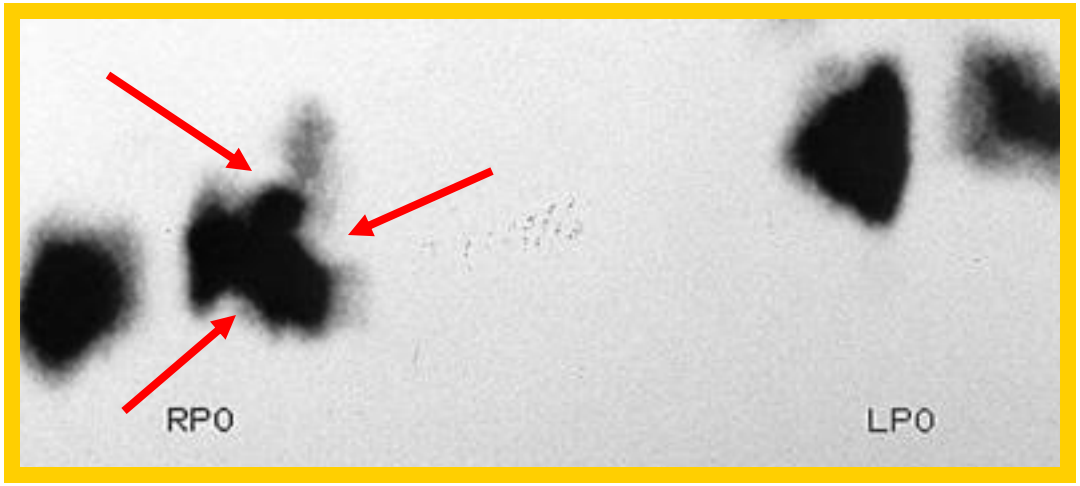
High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan

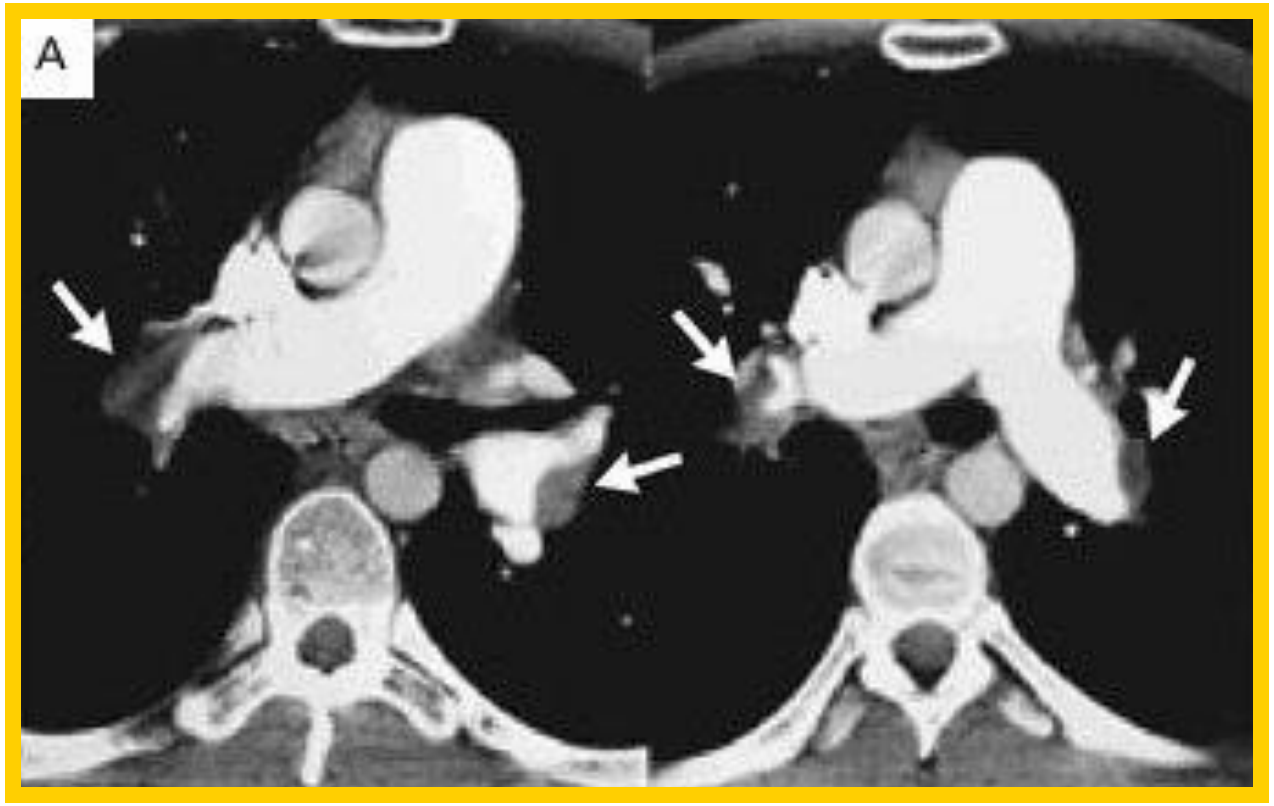


Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) results

Prospective investigation of pulmonary embolism diagnosis results

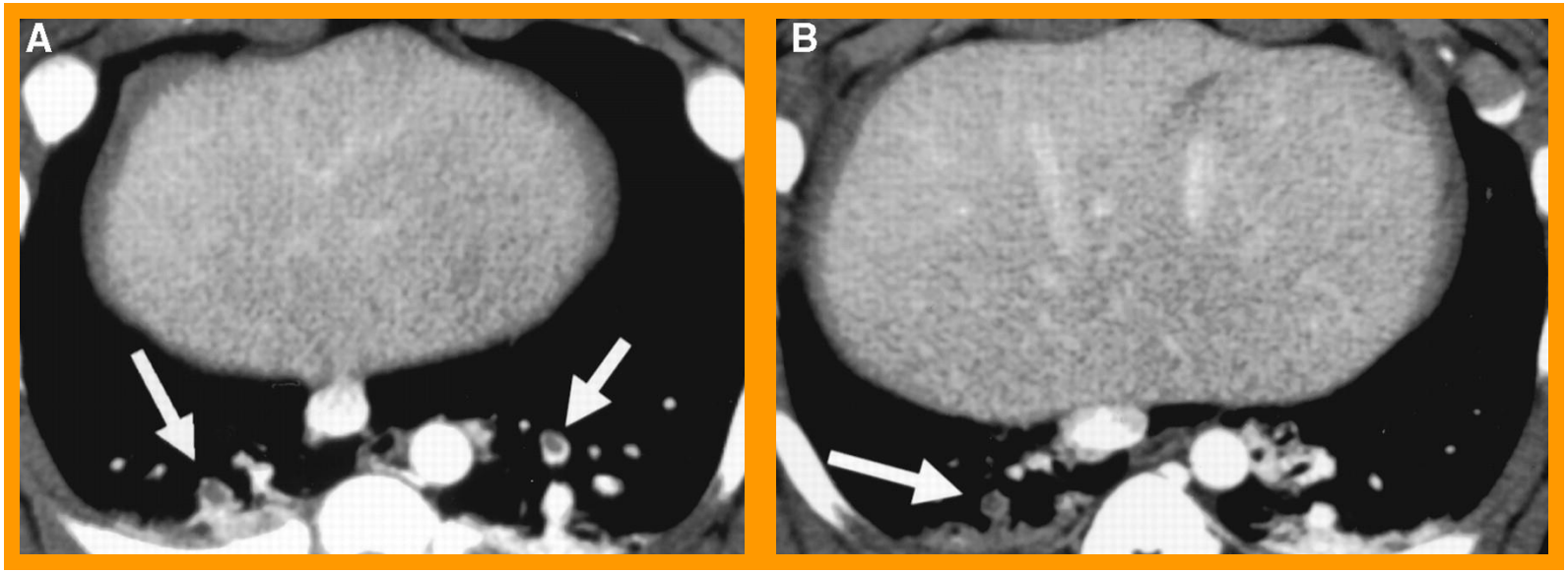
Scan category	PE present	PE absent	PE uncertain	No angiogram	Total
High probability	102	14	1	7	124
Intermediate probability	105	217	9	33	364
Low probability	39	199	12	62	312
Near normal or normal	5	50	2	74	131
Total	251	480	24	176	931

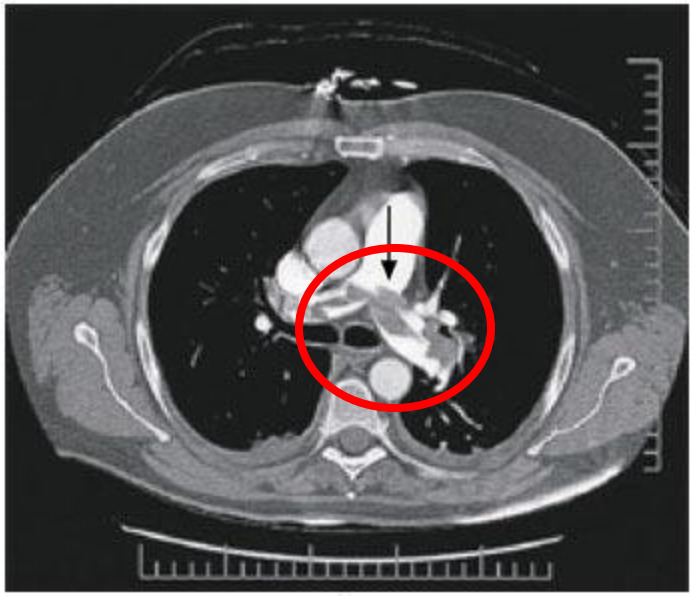
Computed tomography pulmonary angiography (CTPA) (Spiral CT)



Spiral CT

Spiral CT





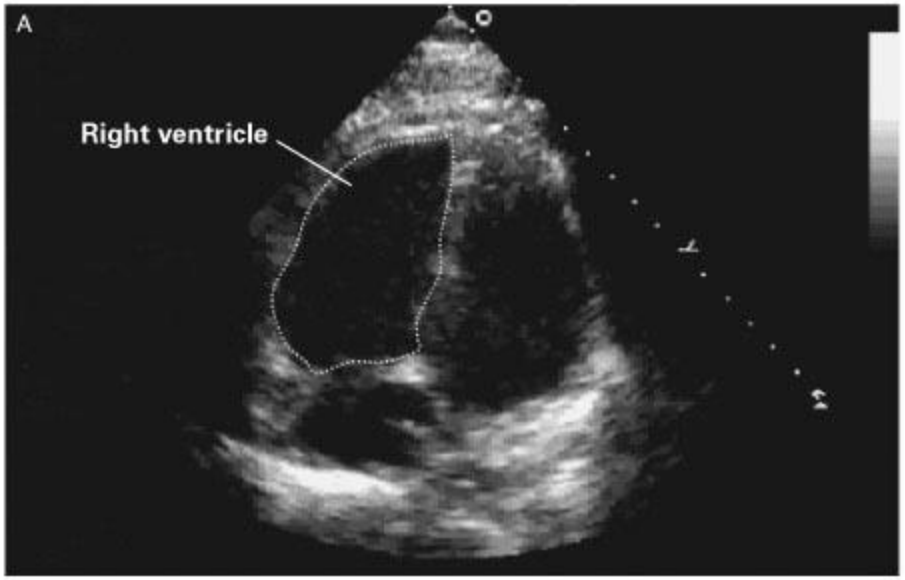
A

B

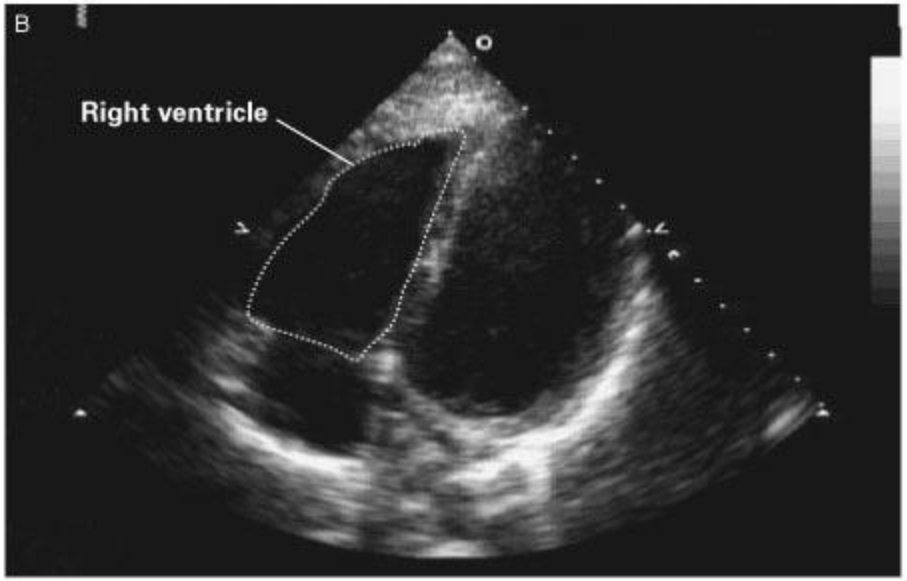
Before

After

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

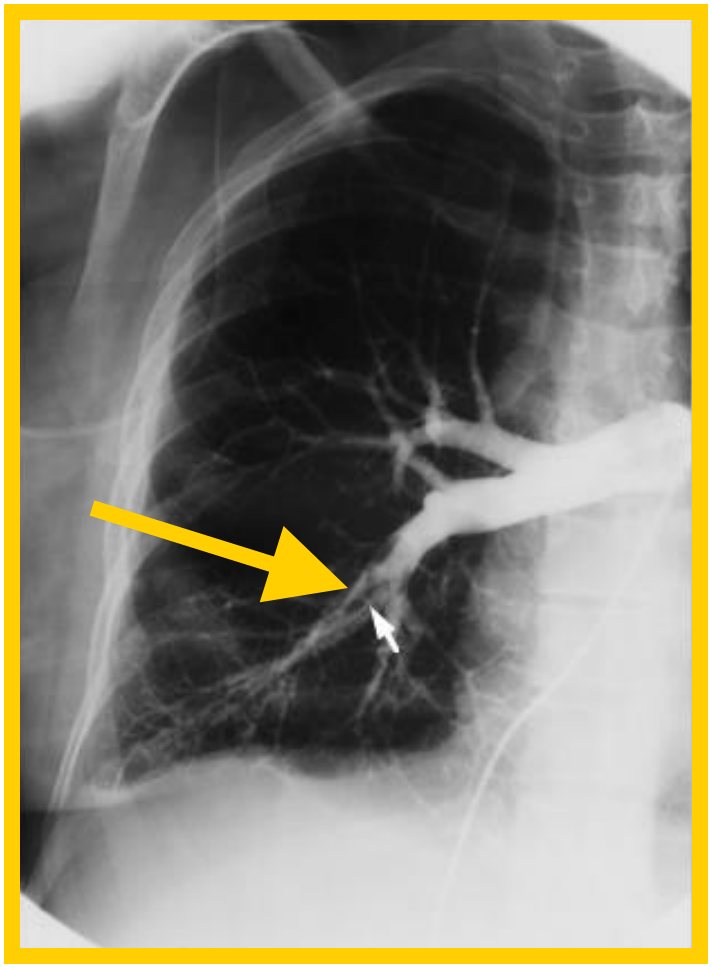


Before



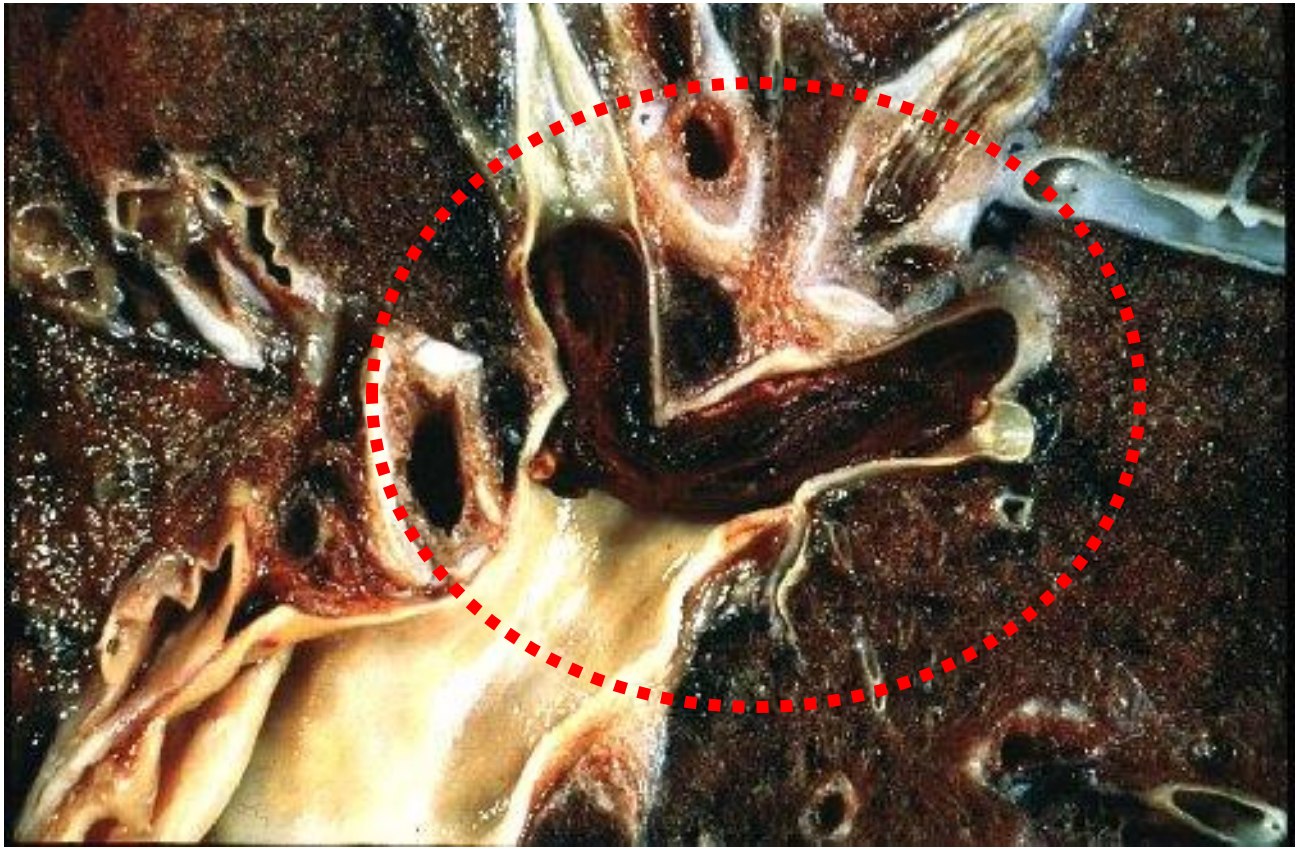
After

Pulmonary angiogram



Pulmonary Angiogram

PULMONARY EMBOLISM



Suggested diagnostic strategy for venous thromboembolism

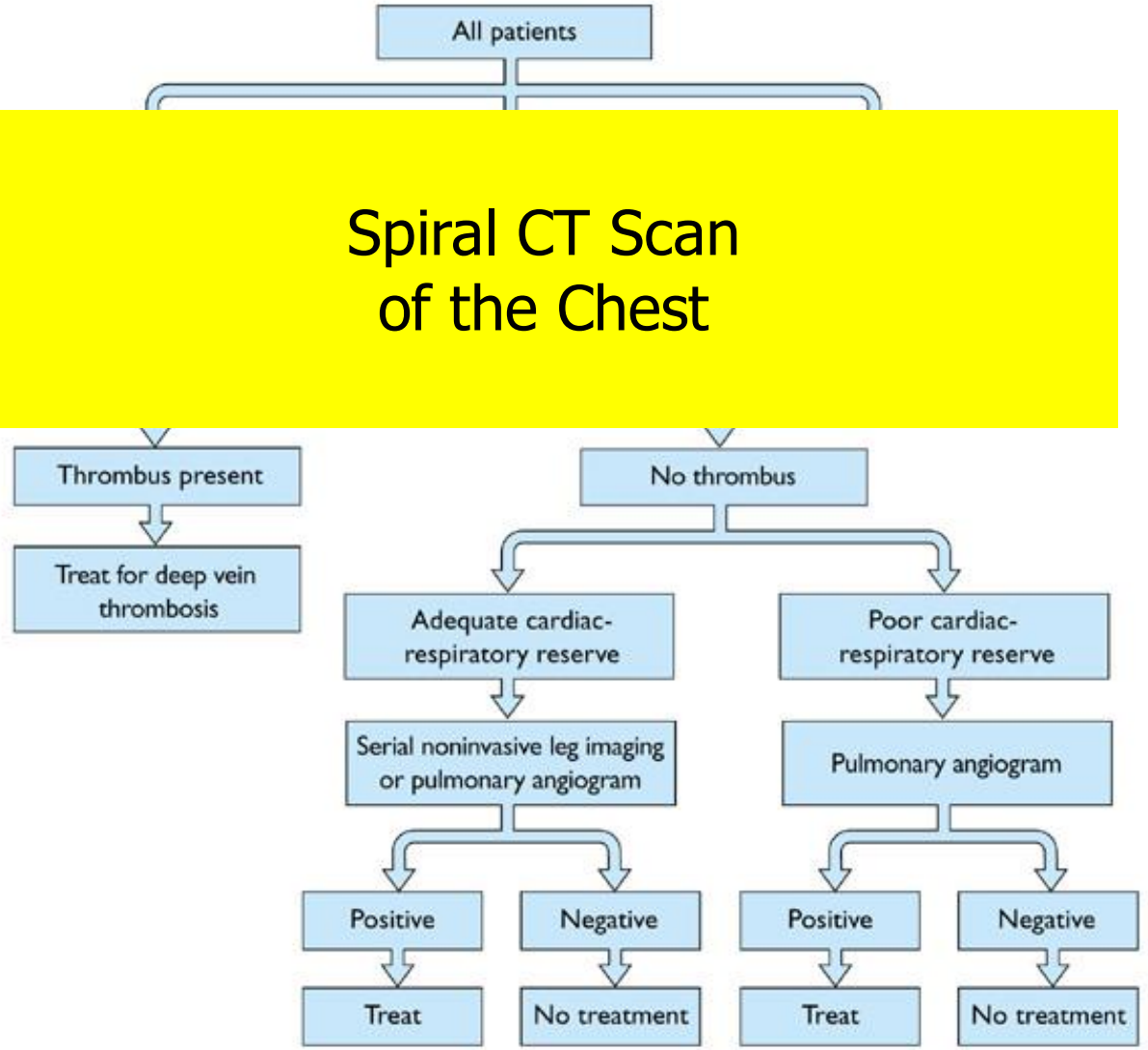


Table 2 | Comparison of pulmonary embolism risk prediction scores

Variable	Points
Pulmonary Embolism Severity Index (PESI)*[87]	
Age, per year	Age, in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse rate ≥110/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified Pulmonary Embolism Severity Index (sPESI)†[88]	
Age >80 years	1
History of cancer	1
History of chronic lung disease	1
Pulse rate ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxygen saturation <90%	1
Hestia criteria‡[89]	
Is the patient hemodynamically unstable?	–
Is thrombolysis or embolectomy necessary?	–
Active bleeding or high risk of bleeding?	–
>24 h of oxygen supply to maintain oxygen saturation >90%?	–
Is pulmonary embolism diagnosed during anticoagulant treatment?	–
Severe pain needing intravenous pain medication for >24 h?	–
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?	–
Does the patient have a creatinine clearance of <30 mL/min?	–
Does the patient have severe liver impairment?	–
Is the patient pregnant?	–
Does the patient have a documented history of heparin induced thrombocytopenia?	–

*66-85 class I; 86-105 class II; 106-125 class III; >125 class IV; class V. Class I and II defined as low risk.
†0 low risk; ≥1 high risk.
‡Yes to any question, admission required.

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Treatment

- Prompt initiation of anticoagulation while awaiting investigations is prudent because of the high risk of early mortality with untreated pulmonary embolism

Types of anticoagulants

Direct anticoagulants (DOACs)

- **DOACs are given at fixed doses and do not necessitate routine laboratory monitoring**

- **Each DOAC has been deemed non-inferior to the VKA/LMWH combination for the prevention of symptomatic recurrent venous thromboembolism in patients with an acute venous thromboembolism).**

- **DOACs have significantly fewer major bleeding events compared with VKAs**

DOACs

Table 3 | Characteristics of direct oral anticoagulant drugs

Drug	Target	Peak effect (hours)	Half life (hours)	Renal clearance (%)	Protein binding (%)
Dabigatran	Factor IIa (thrombin)	1.5	14-17	>80	35
Apixaban	Factor Xa	3	8-14	25	85
Edoxaban	Factor Xa	4	8-11	35	55
Rivaroxaban*	Factor Xa	2-3	7-11	33	90

*Rivaroxaban 15 mg and 20 mg tablets should be taken with food for maximum absorption and efficacy.

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Dosage and monitoring of anticoagulant therapy

- **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
  - Therapeutic APTT should correspond to plasma heparin level of 0.2–0.4 IU/mL
- **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
- **Low molecular weight heparin**

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

	Complication	Management
Warfarin	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.

Treatment phases

Treatment phases:

1. Initial phase from 0-7days,
2. Long term therapy 1 wk – 3 months
3. Extended therapy 3 months - indefinite.

Box 2: Phases of pulmonary embolism treatment[104]

Initial (0-7 days)

- Apixaban 10 mg BID for 7 days
- Rivaroxaban 15 mg BID for 21 days
- LMWH/fondaparinux for minimum 5 days* and INR ≥2 for 2 days

Long term (1 week to 3 months)

- Apixaban 5 mg BID
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily
- Warfarin for INR 2-3

Extended (3 months to indefinite)

- Apixaban 5 mg BID or 2.5 mg BID‡
- Acetylsalicylic acid 81-100 mg daily, if anticoagulation not possible
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily or 10 mg daily‡
- Warfarin for INR 2-3

BID=twice daily; INR=international normalized ratio; LMWH=low molecular weight heparin
*LMWH is needed for 5-10 days before starting dabigatran or edoxaban
†30 mg daily if creatinine clearance is 30-50 mL/min or weight ‹60 kg
‡Dose reduction may be considered after 6 months of therapy

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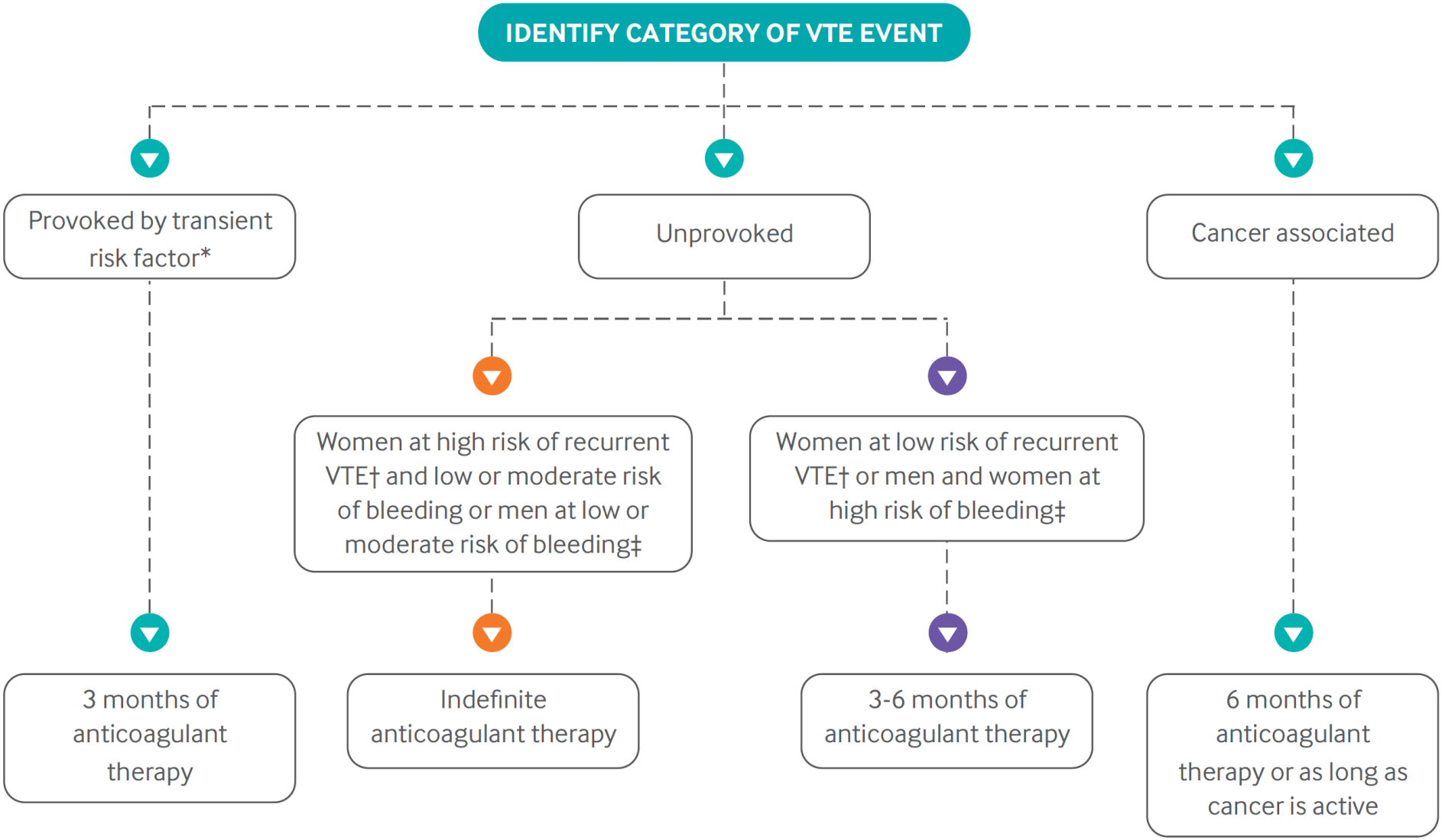
IDENTIFY CATEGORY OF VTE EVENT
Provoked by transient risk factor*
Unprovoked
Cancer associated
Women at high risk of recurrent VTE† and low or moderate risk of bleeding or men at low or moderate risk of bleeding‡
Women at low risk of recurrent VTE† or men and women at high risk of bleeding‡
3 months of anticoagulant therapy
Indefinite anticoagulant therapy
3-6 months of anticoagulant therapy
6 months of anticoagulant therapy or as long as cancer is active

Outpatient vs. inpatient therapy

- RCTs have compared outpatient versus inpatient management of pulmonary embolism and found no difference in outcomes in selected patients.

Approved thrombolytics for pulmonary embolism

Approved thrombolytics for pulmonary embolism

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

Recombinant tissue-plasminogen activator

100 mg as a continuous peripheral intravenous infusion administered over 2 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

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