



# Pulmonary Embolism - 2021

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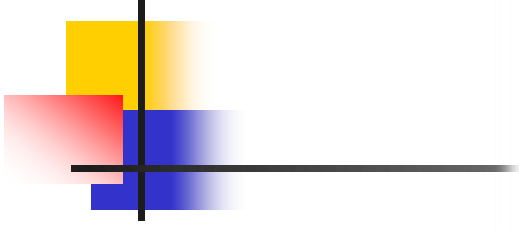
# Pulmonary Embolism (PE)

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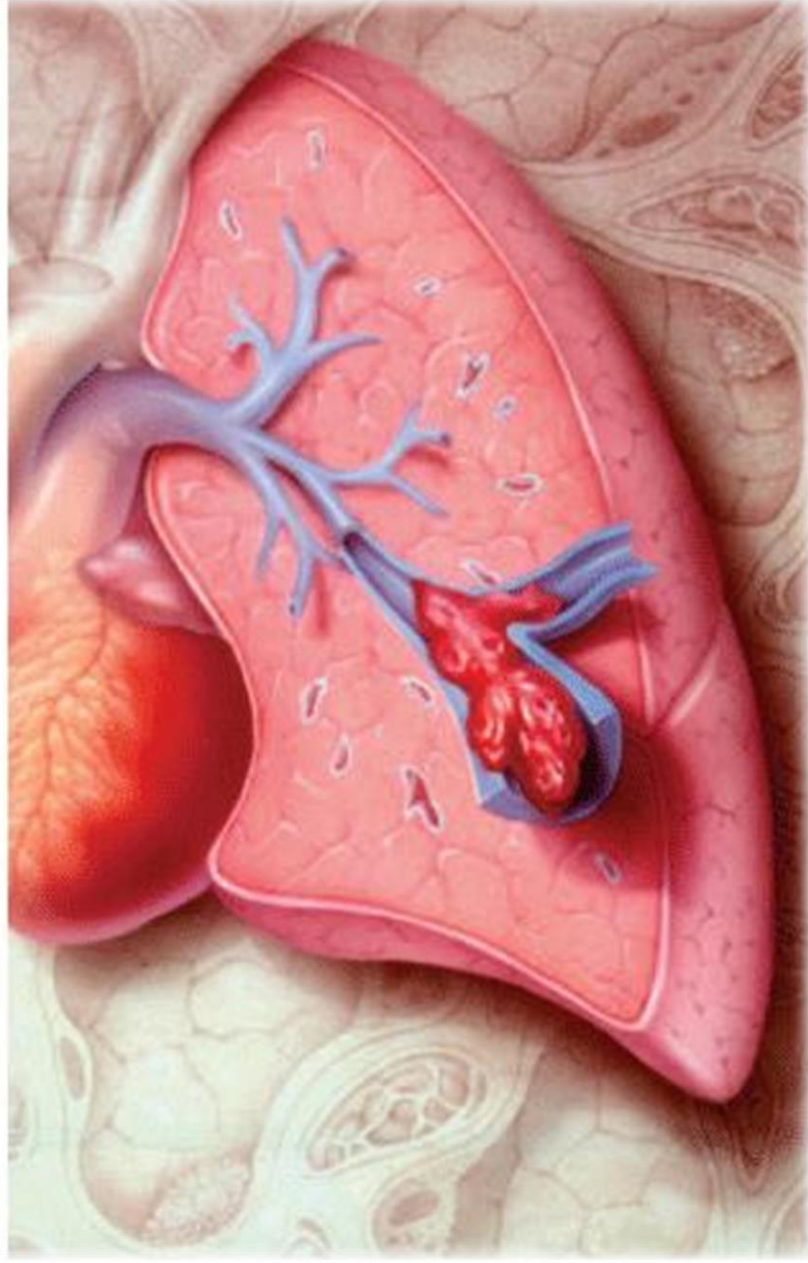
## **Lecture Objectives:**

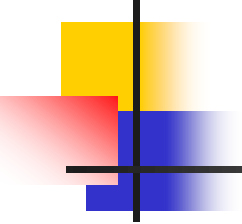
### **To understand the followings:**

- Prevalence of PE
- Risk factors
- Clinical features
- Pathophysiology
- Massive PE
- Diagnostic workup
- Treatment

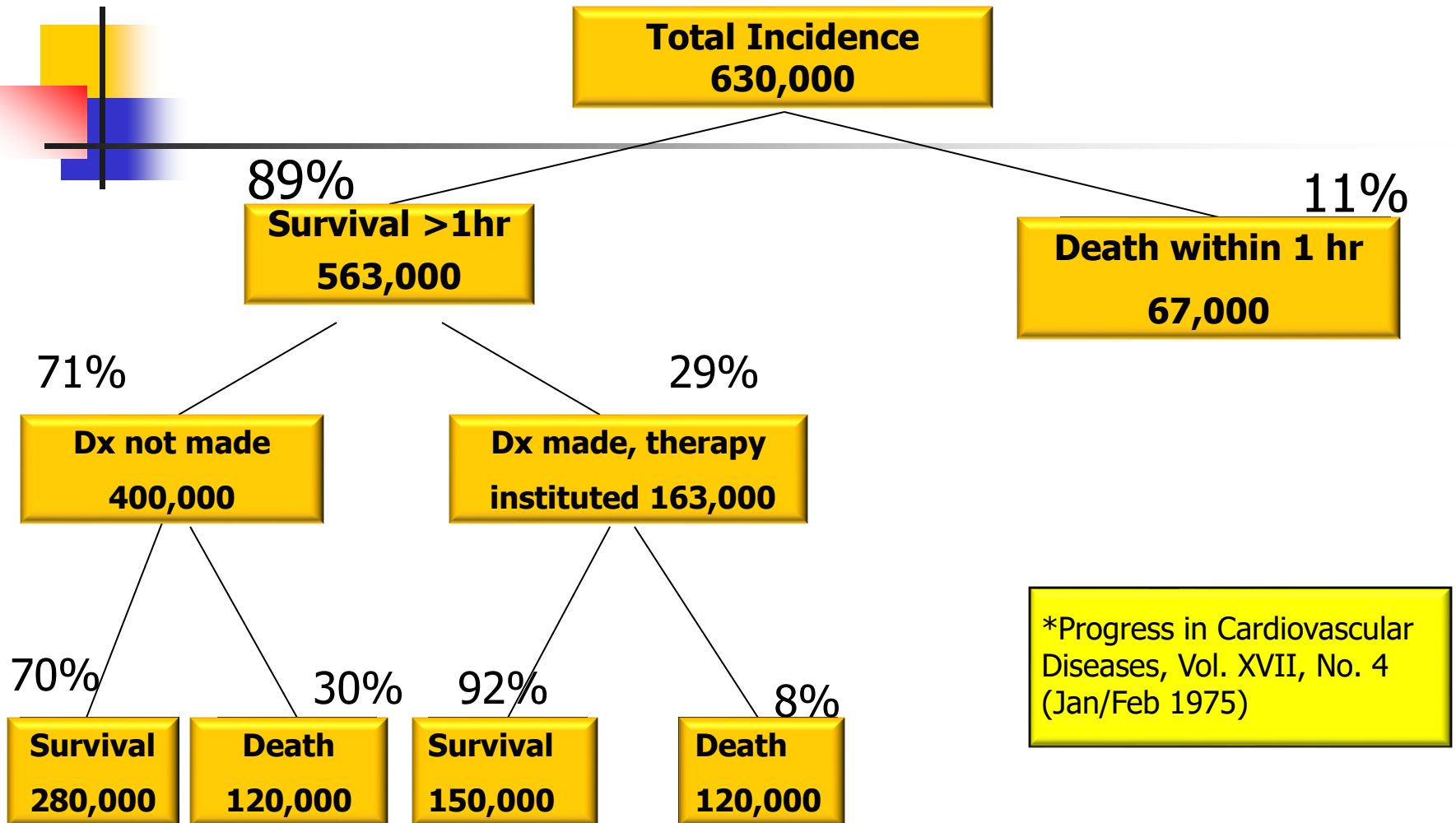


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- 50,000 individuals die from PE each year in USA
  - The incidence of PE in USA is 500,000 per year

# Incidence of Pulmonary Embolism Per Year in the United States\*





# Incidence

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- 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

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

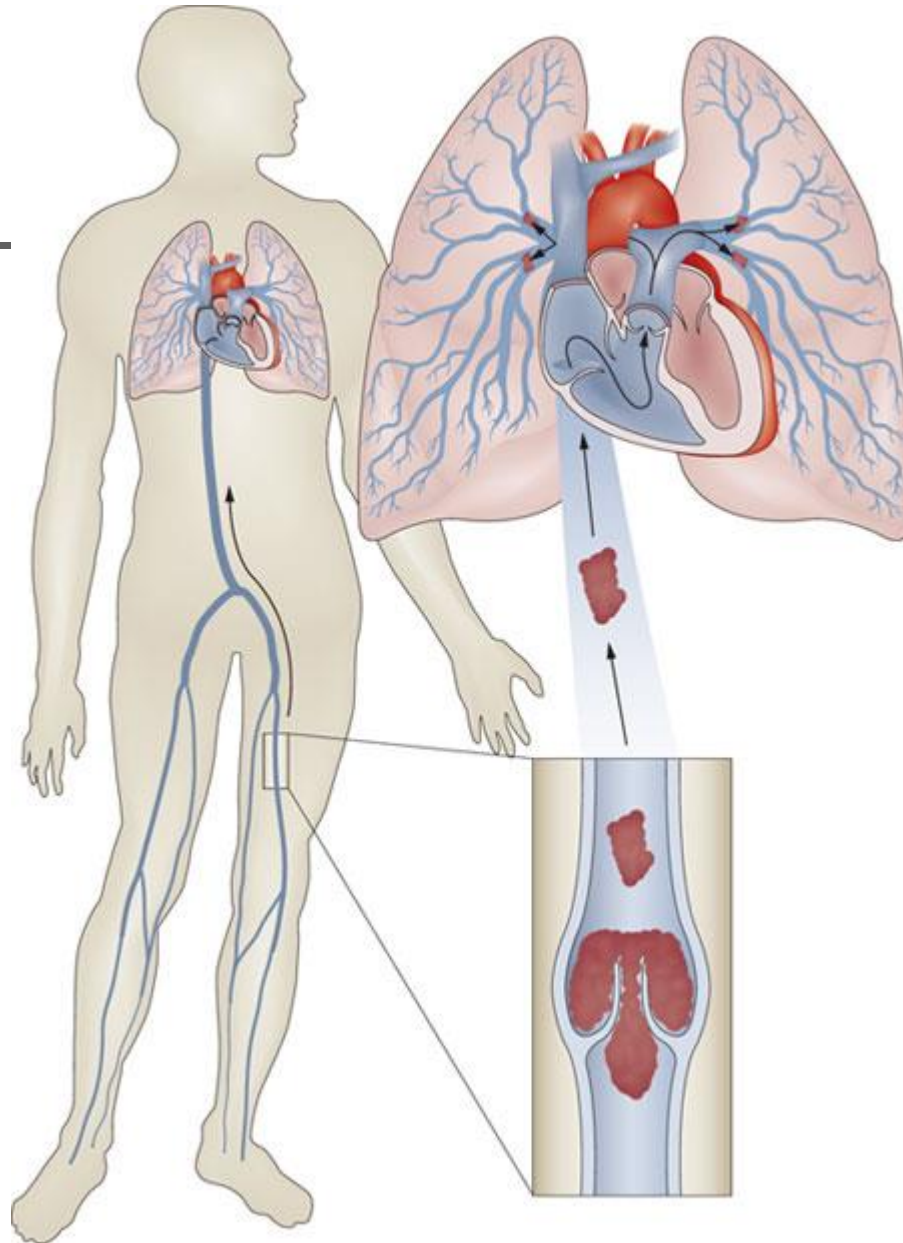
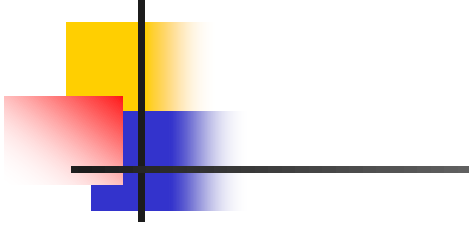


# Source of emboli

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







# Risk factors for DVT

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- 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<sup>16</sup>

### 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

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- 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

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- 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., %<br>(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., %<br>(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., %<br>(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\*<sup>33</sup>**

|   |   |
|---|---|
| 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†<sup>34</sup>**

|  |   |
|--|---|
| 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

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- Using modified score,  $<3$  points indicates low probability, 4-10 points indicates intermediate probability, and  $>10$  points indicates high probability.
- Using simplified score,  $\leq 2$  points indicates that PE is unlikely.



# Clinical probability scores

| Wells rule† <sup>35 36</sup>                 |     |
|--|-----|
| 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.

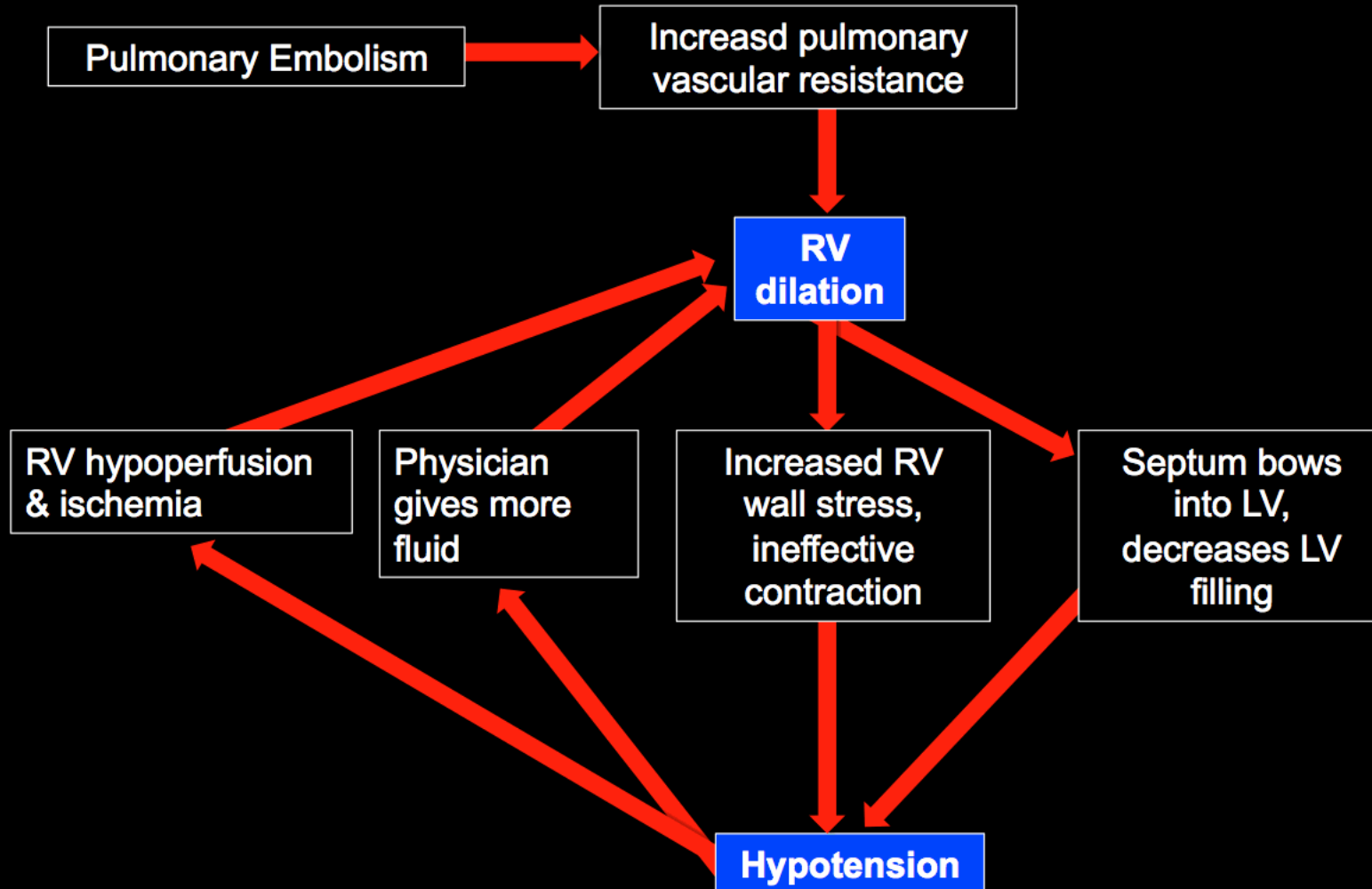


# Massive Pulmonary Embolism

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- 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





# Pathophysiology

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- Massive PE causes an increase in PVR → right ventricular outflow obstruction → decrease left ventricular preload → Decrease CO
- In patients without cardiopulmonary disease, occlusion of 25-30 % of the vascular bed → increase in Pulmonary artery pressure (PAP)
- Hypoxemia ensues → stimulating vasoconstriction → increase in PAP



# Pathophysiology

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- 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



# Diagnosis

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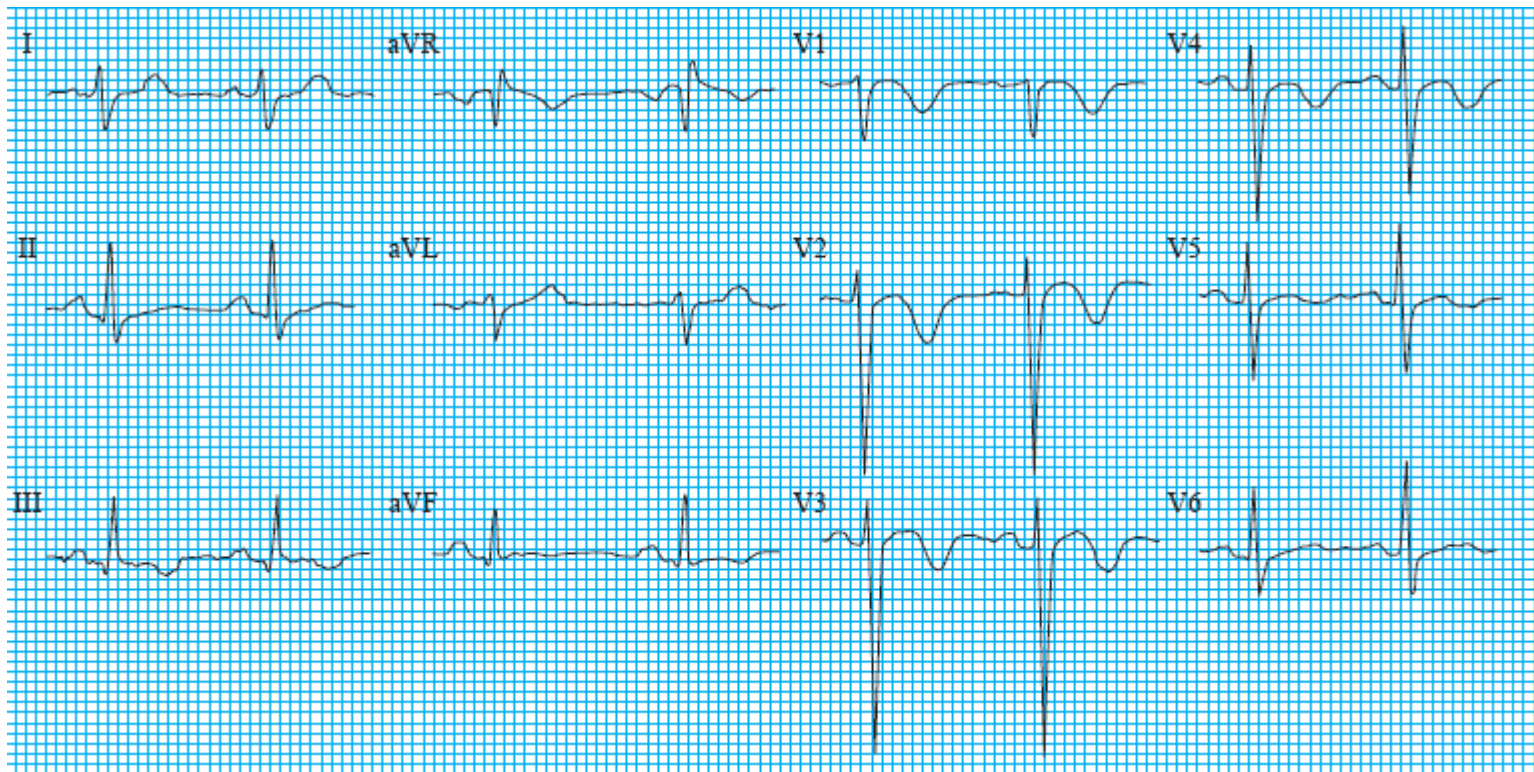
- CXR
- ABG:
- ECG
- V/Q
- Spiral CT
- Echo
- Angio
- D-dimer



# S1 Q3 T3 Pattern



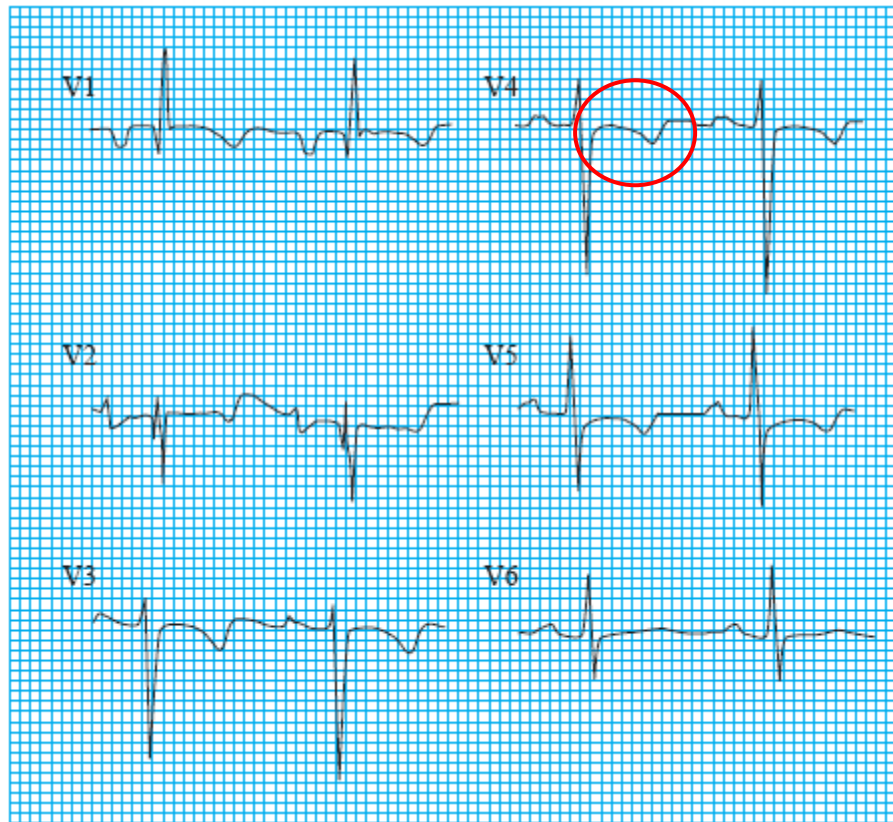
# T-wave inversion



# Rt. Bundle Branch Block



# Rt. Ventricular Strain





# D-Dimer

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- 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



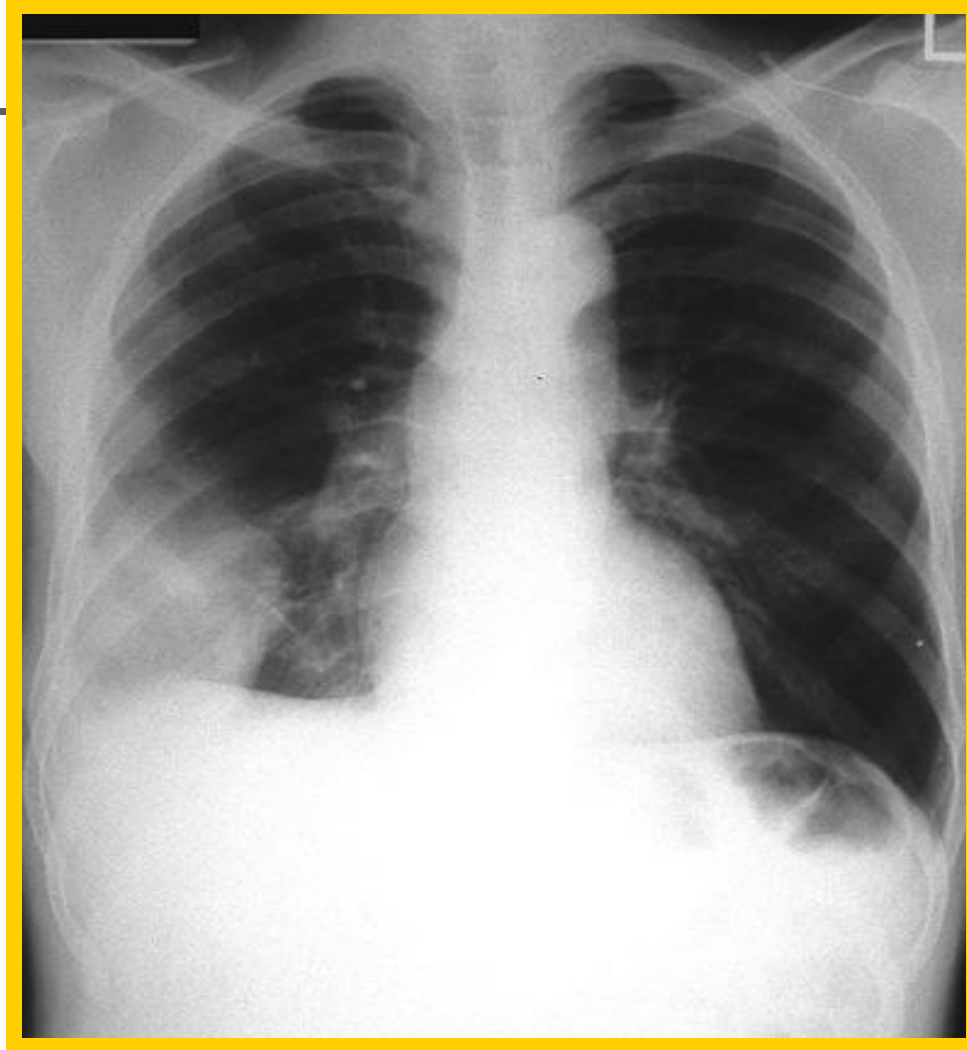
# Diagnosis

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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)

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



# The use of ventilation perfusion scan in diagnosing pulmonary embolism

## High probability

=2 large segmental (>75% of a segment) perfusion defects without corresponding ventilation or radiographic abnormalities or substantially larger than matching ventilation or radiologic abnormalities

OR

=2 moderate segmental (>25% and <75% of a segment) perfusion defects without matching ventilation or chest radiographic abnormalities plus one large unmatched segmental defect

OR

=4 moderate segmental perfusion defects without matching ventilation or chest radiologic abnormalities

# The use of ventilation perfusion scan in diagnosing pulmonary embolism

## Intermediate probability

Scans that do not fall into normal, very low, low, or high probability categories

# The use of ventilation perfusion scan in diagnosing pulmonary embolism

## Low probability

Nonsegmental perfusion defects

OR

Single moderate mismatched segmental perfusion defect with normal chest radiograph

OR

Any perfusion defect with a substantially larger abnormality on chest radiograph

OR

Large or moderate segmental perfusion defects involving no more than four segments in one lung and no more than three segments in one lung region with matching or larger ventilation/radiographic abnormalities

OR

More than three small segmental perfusion defects (<25% of a segment) with a normal chest radiograph

# The use of ventilation perfusion scan in diagnosing pulmonary embolism



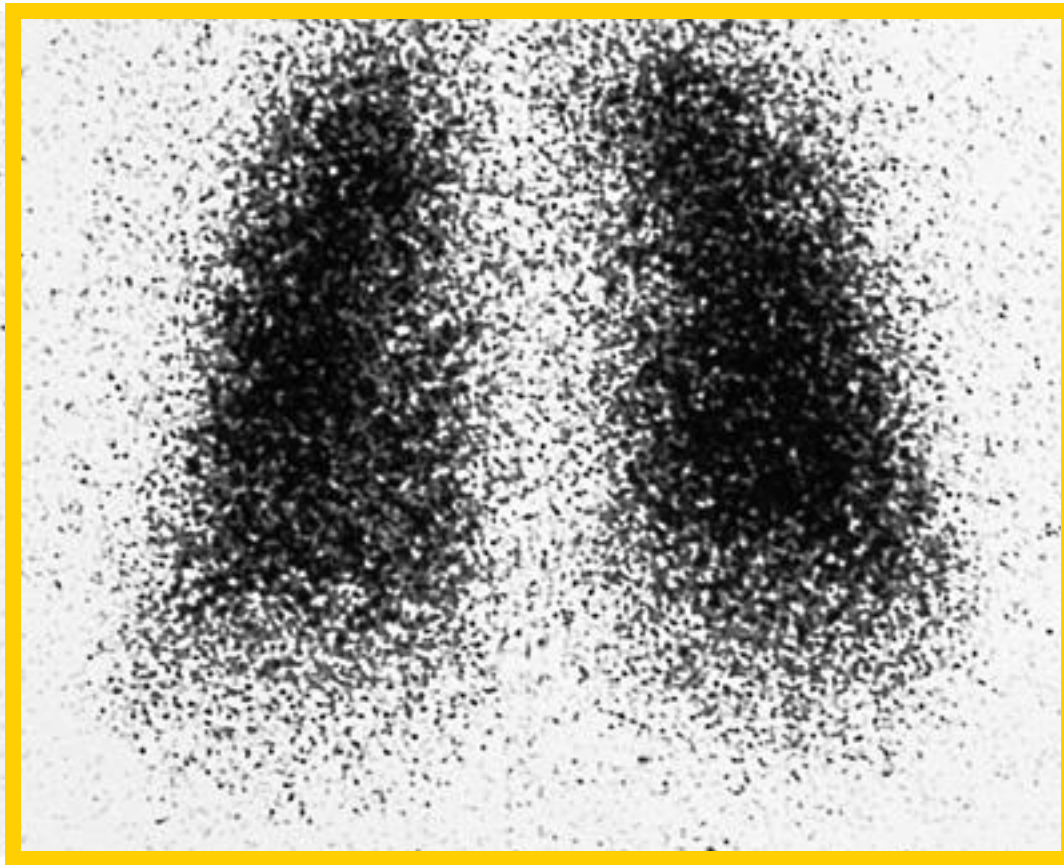
Very low probability

Three or fewer small segmental perfusion defects with a normal chest radiograph

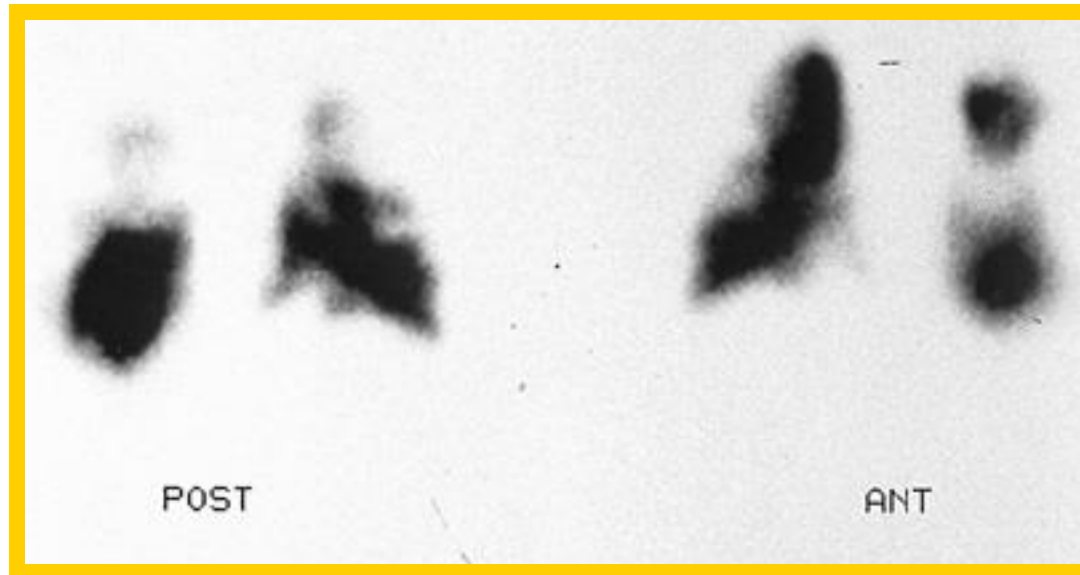
Normal

No perfusion defects present

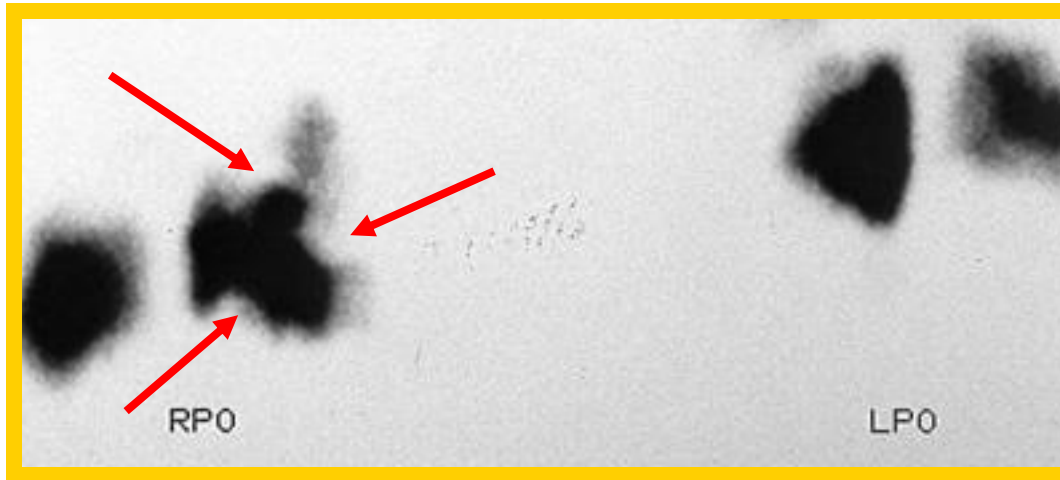
# High-probability ventilation-perfusion scan




## High-probability ventilation-perfusion scan



# High-probability ventilation-perfusion scan





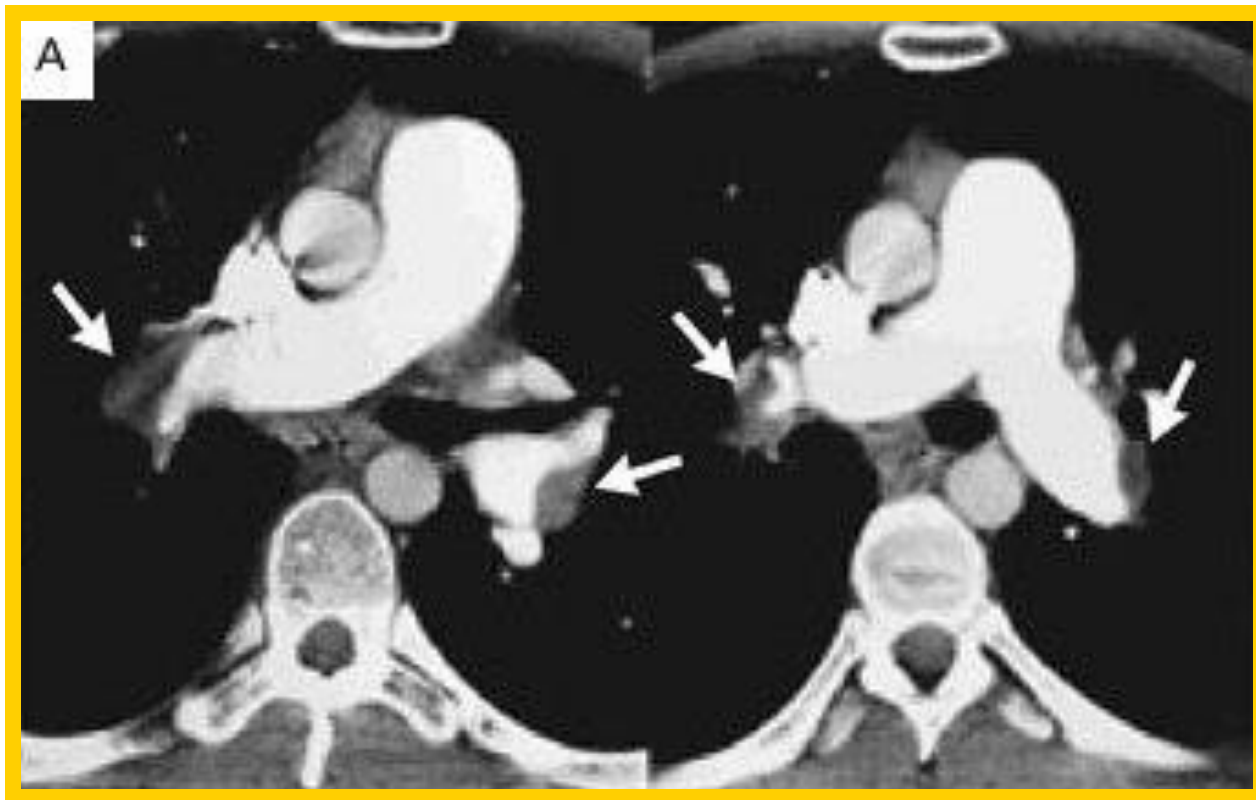
# Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) results

Prospective investigation of pulmonary embolism diagnosis results

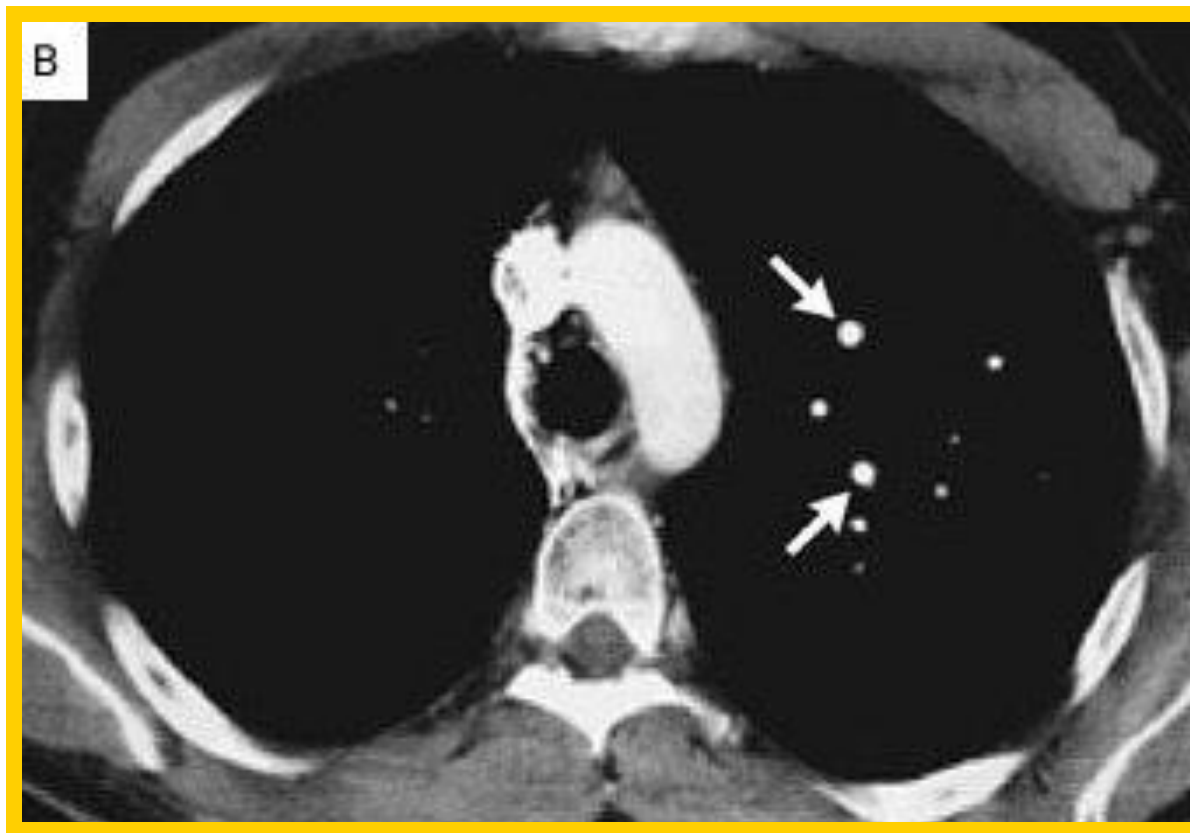
| Scan category            | PE present | PE absent | PE uncertain | No angiogram | Total |
|--------------------------|------------|-----------|--------------|--------------|-------|
| High probability         | 102        | 14        | 1            | 7            | 124   |
| Intermediate probability | 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   |



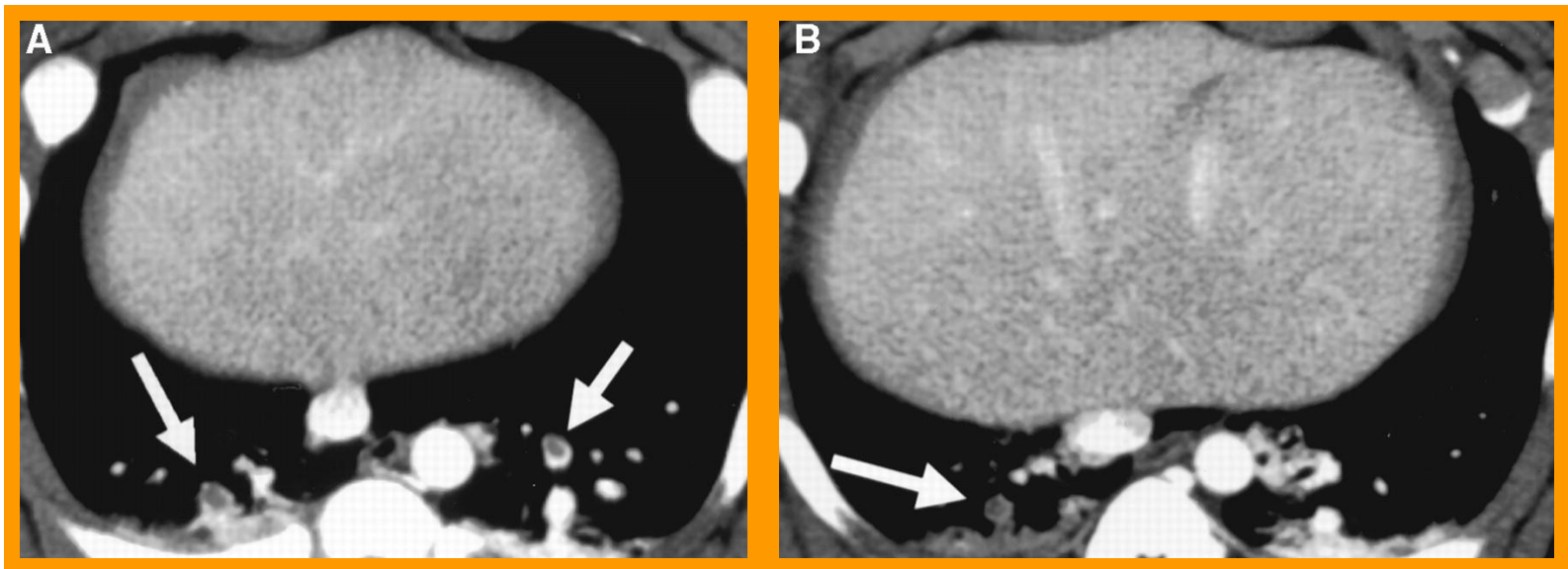
# Computed tomography pulmonary angiography (CTPA) (Spiral CT)

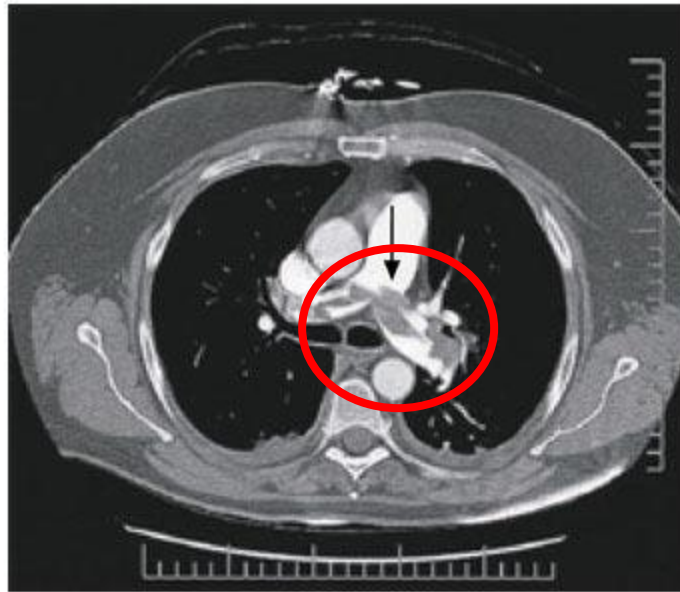
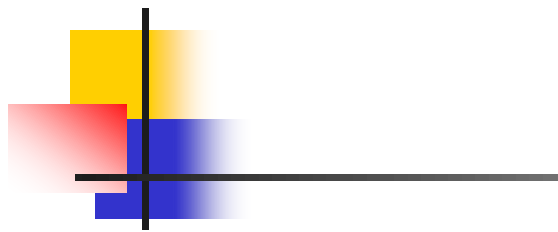


# Spiral CT



# Spiral CT





A

**Before**

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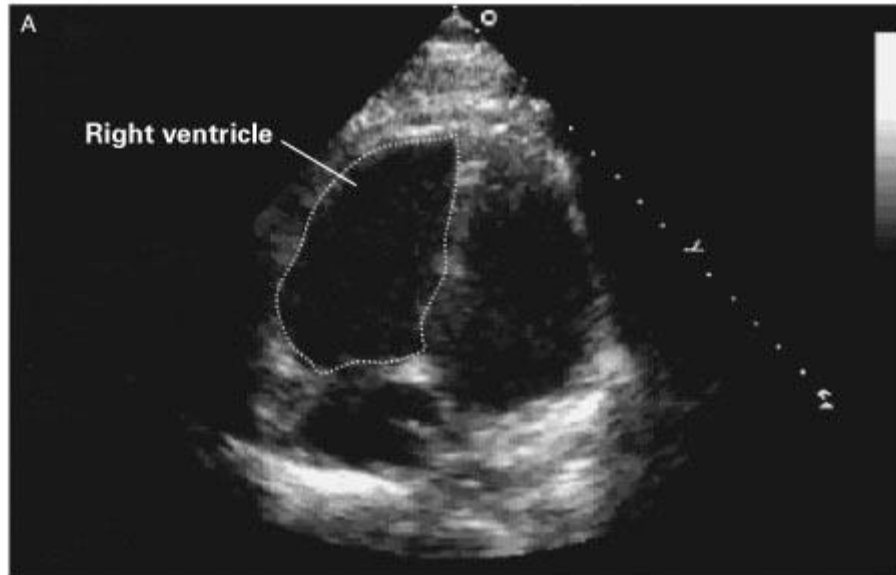
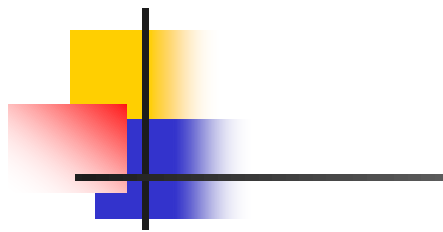


B

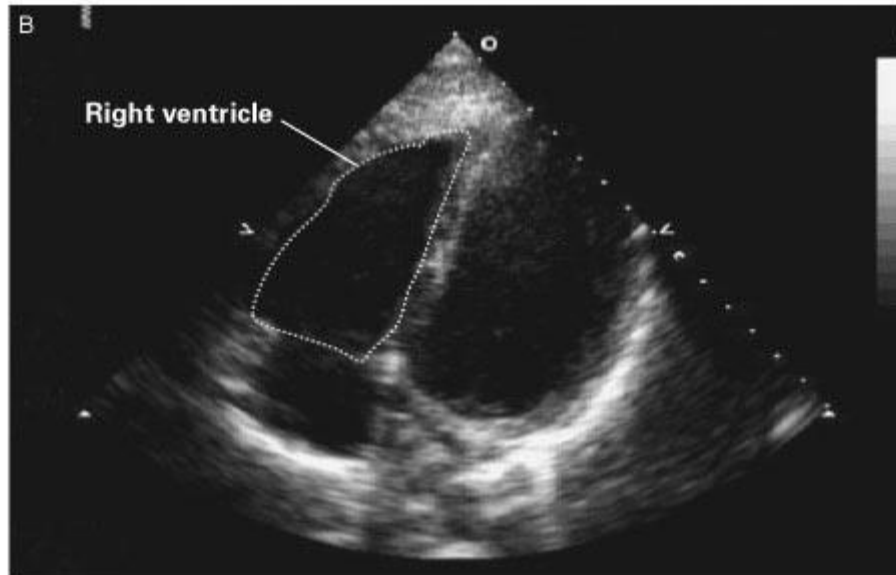
**After**

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



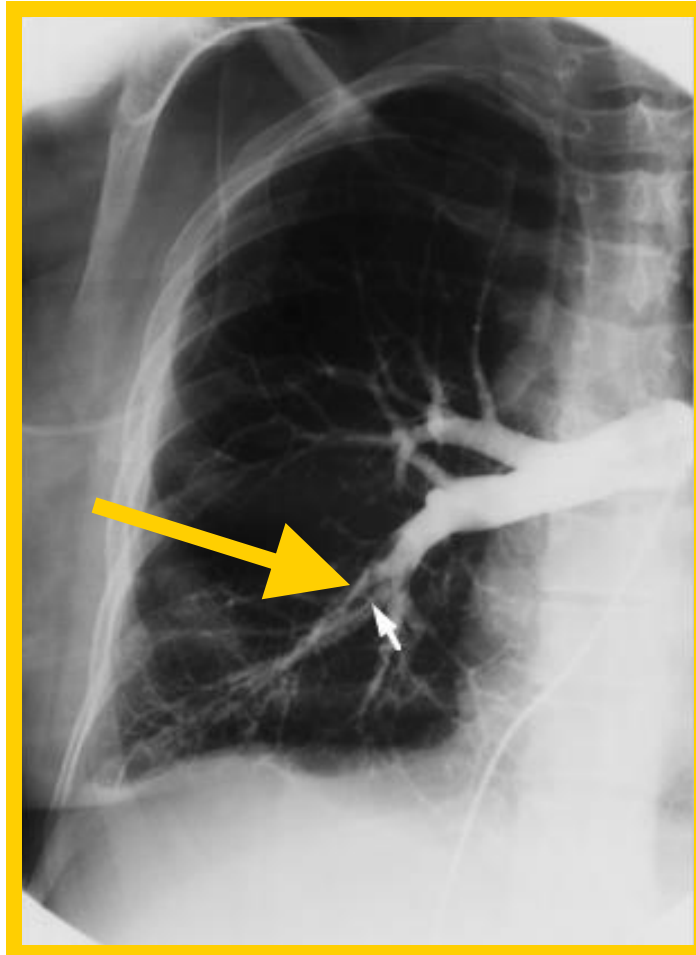


**Before**



**After**

# Pulmonary angiogram

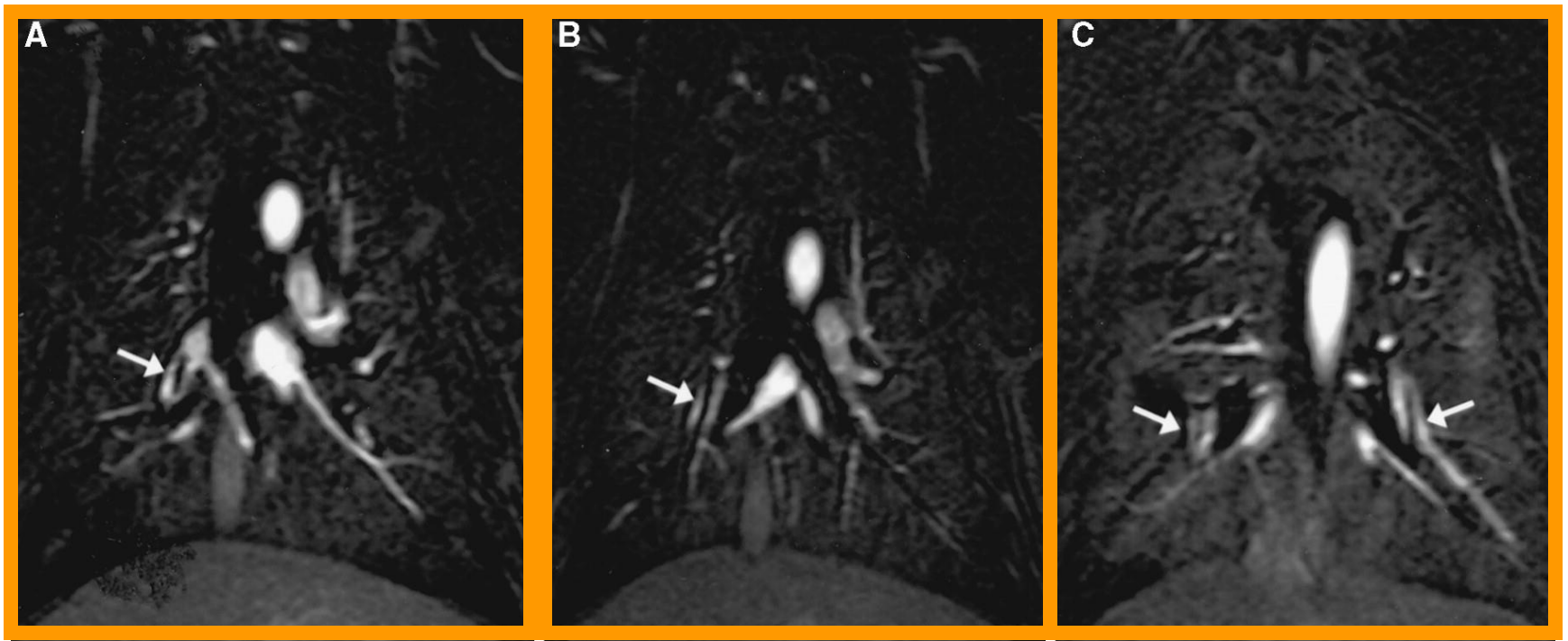


# Pulmonary Angiogram

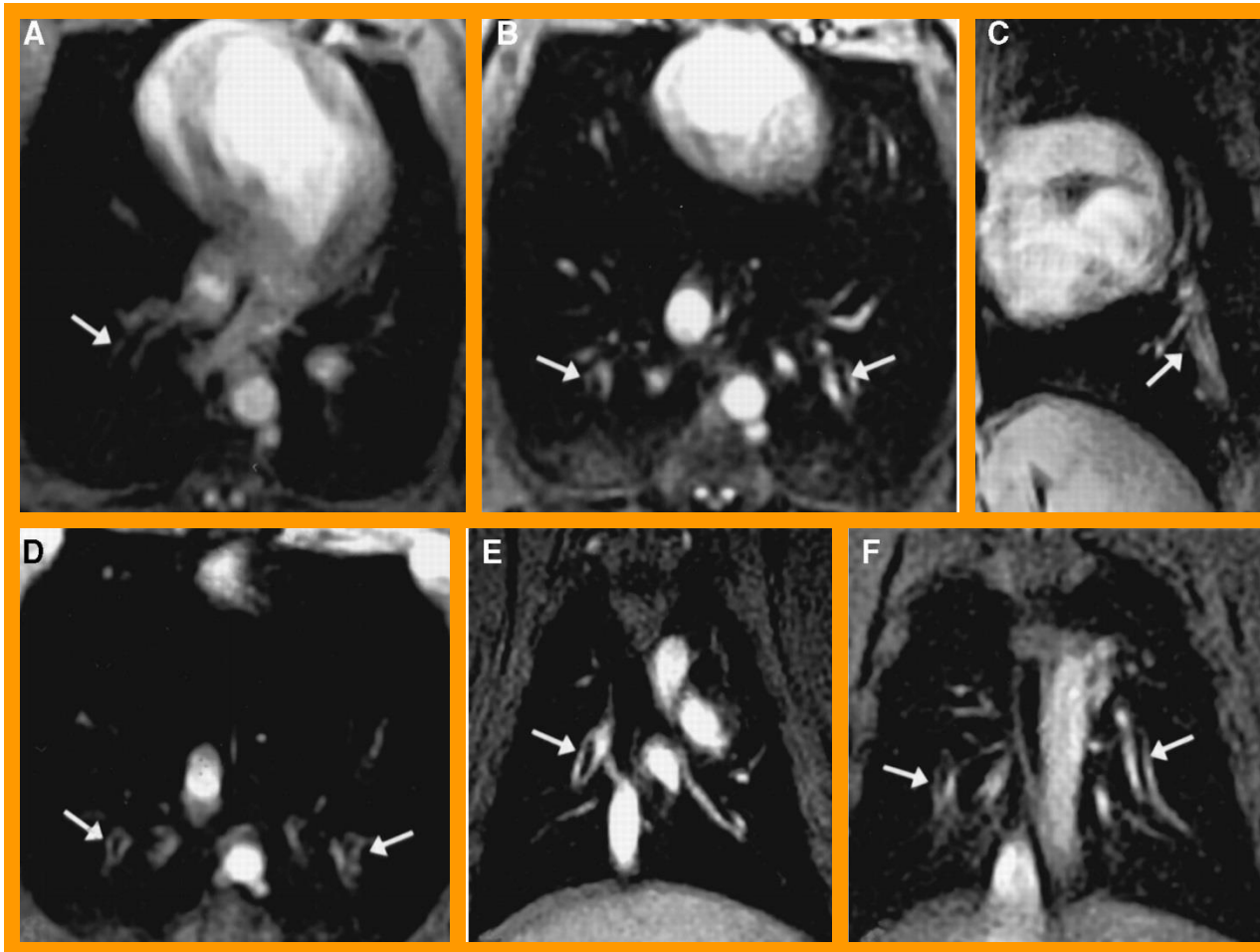




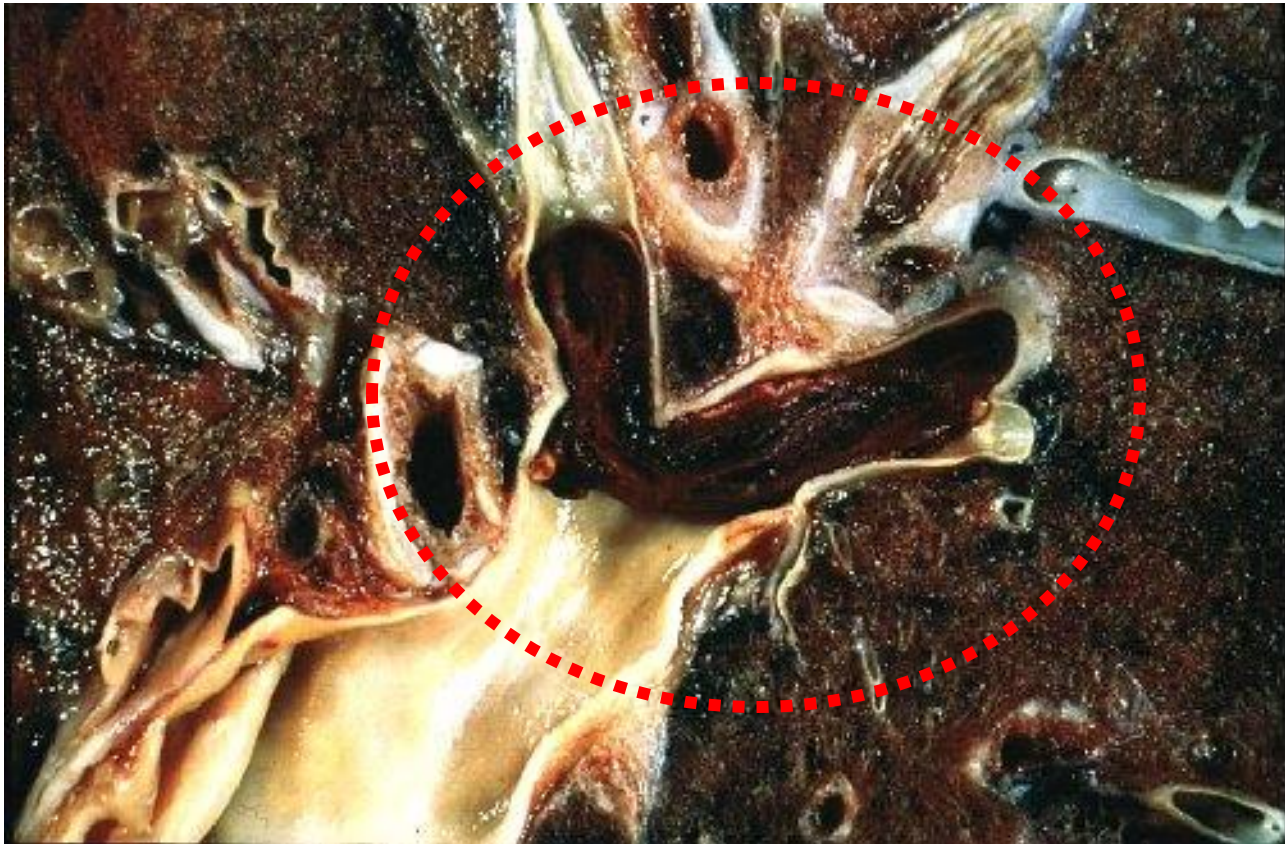
# MRA with contrast

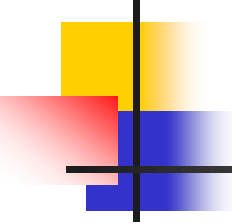


# MRA Real Time



# PULMONARY EMBOLISM





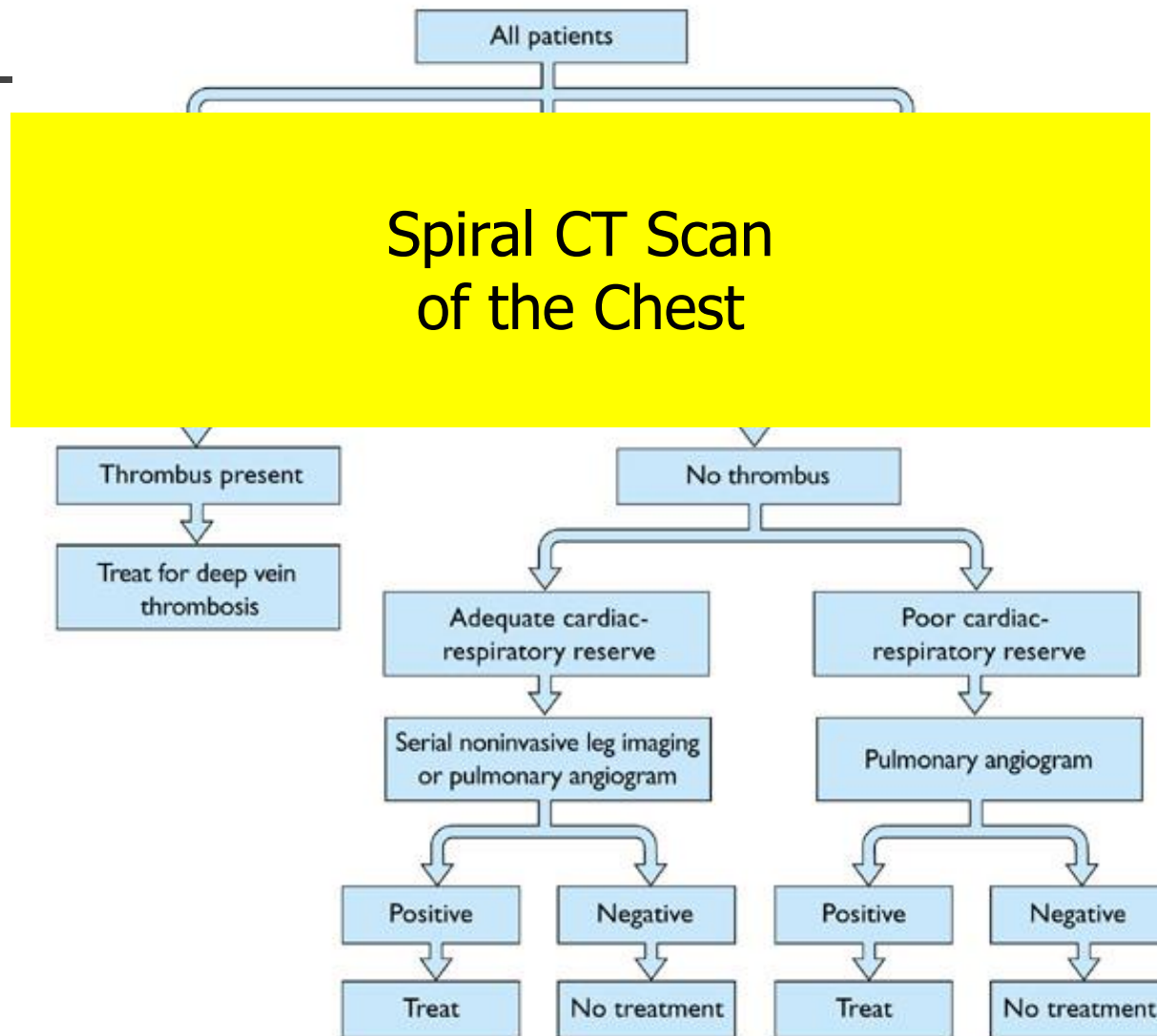
## Sensitivity of spiral computed tomography, magnetic resonance angiography, and real-time magnetic resonance angiography, for detecting pulmonary emboli

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| <b>Reader</b> | <b>CT</b> | <b>MRA</b> | <b>RT-MRA</b> |
|---------------|-----------|------------|---------------|
| 1             | 72.1      | 79.1       | 97.7          |
| 2             | 69.8      | 81.4       | 97.7          |
| Mean          | 71.0      | 80.3       | 97.7          |
| K             | 0.86      | 0.84       | 1             |

*Am J Respir Crit Care Med 2003*

# Suggested diagnostic strategy for venous thromboembolism





**Table 2 | Comparison of pulmonary embolism risk prediction scores**

| Variable  | Points        |
|---|---------------|
| <b>Pulmonary Embolism Severity Index (PESI)*<sup>87</sup></b>   |               |
| 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 $\geq 110$ /min  | +20           |
| Systolic blood pressure $< 100$ mm Hg   | +30           |
| Respiratory rate $\geq 30$ /min   | +20           |
| Temperature $< 36^\circ\text{C}$  | +20           |
| Altered mental status   | +60           |
| Arterial oxygen saturation $< 90\%$   | +20           |
| <b>Simplified Pulmonary Embolism Severity Index (sPESI)†<sup>88</sup></b>                                       |               |
| Age $> 80$ years  | 1             |
| History of cancer   | 1             |
| History of chronic lung disease   | 1             |
| Pulse rate $\geq 110$ beats/min   | 1             |
| Systolic blood pressure $< 100$ mm Hg   | 1             |
| Arterial oxygen saturation $< 90\%$   | 1             |
| <b>Hestia criteria‡<sup>89</sup></b>  |               |
| 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;  $\geq 1$  high risk.

‡Yes to any question. admission required.



# Treatment

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



# Types of anticoagulants

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## **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

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**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.



# 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

Phenylbutazone

Metronidazole

Trimethoprim-sulfamethoxazole

Amiodarone

Second- and third-generation cephalosporins

Clofibrate

Erythromycin

Anabolic steroids

Thyroxine

## Drugs that increase warfarin requirement

Barbiturates

Carbamazepine

Rifampin

Penicillin

Griseofulvin

Cholestyramine

# Complications of anticoagulation



## Complication

## Management

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-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-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

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

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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<sup>104</sup>

### 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  $\geq 2$  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

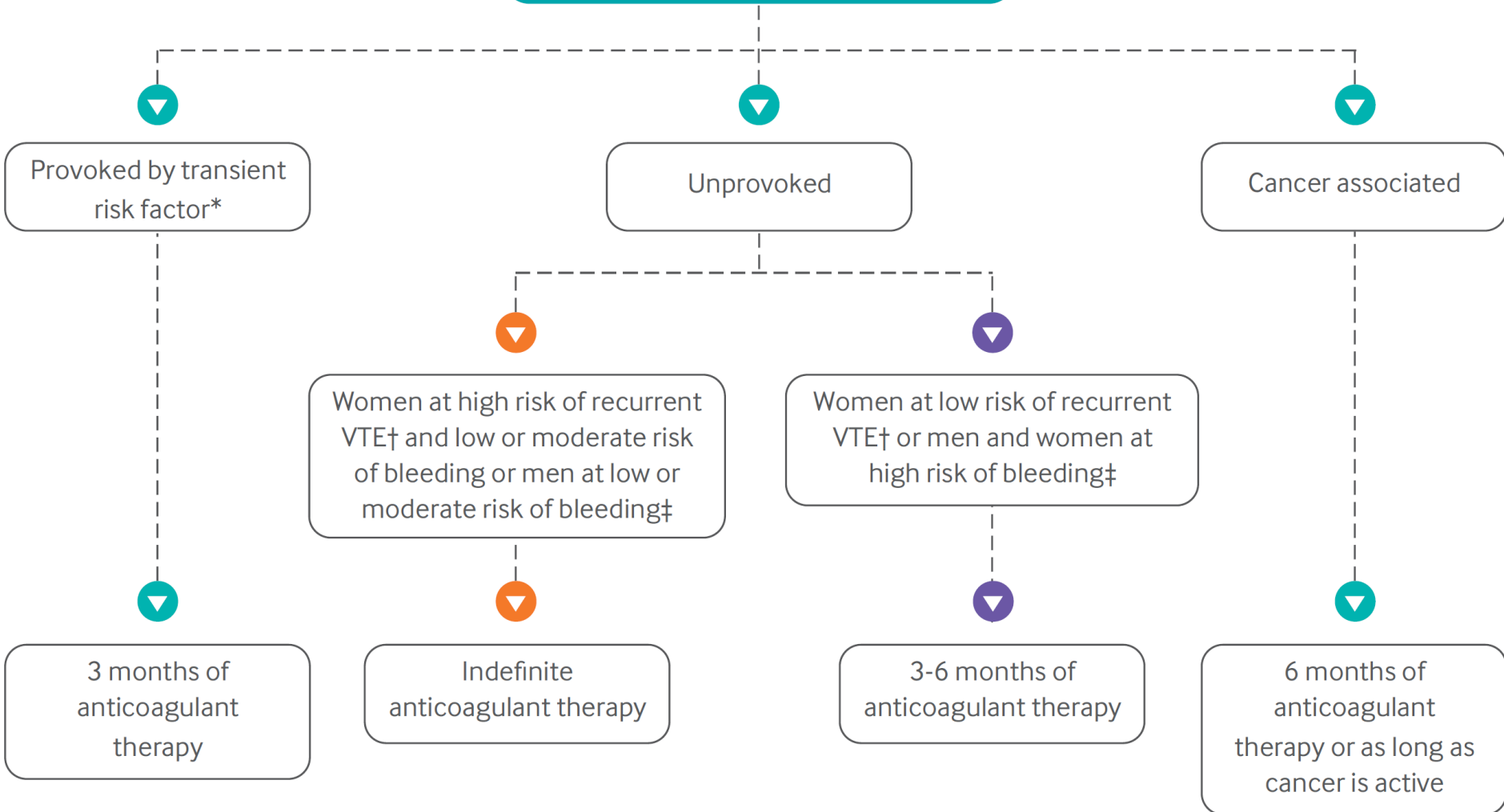
\*LMWH is needed for 5-10 days before starting dabigatran or edoxaban

†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

BMJ 2020;370:m2177 | doi:  
10.1136/bmj.m2177

## IDENTIFY CATEGORY OF VTE EVENT





# Outpatient vs. inpatient therapy

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



# Approved thrombolytics for pulmonary embolism

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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
- Neurosurgery within 6 mo
- Ophthalmologic surgery within 6 wk
- Hypertension >200 mm Hg systolic or 110 mm Hg diastolic
- Hypertensive retinopathy with hemorrhages or exudates
- Cardiopulmonary resuscitation within 2 wk
- Cerebrovascular disease
- Major internal bleeding within the last 6 mo
- Infectious endocarditis
- Pericarditis
- Previous arterial punctures within 10 d
- Bleeding disorder (thrombocytopenia, renal failure, liver failure)
- Placement of central venous catheter within 48 h
- Intracerebral aneurysm or malignancy
- Pregnancy and the 1st 10 d postpartum
- Severe trauma within 2 mo

## Absolute

- Active internal bleeding



# Conclusions

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- 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