



Διαγνωστικά προβλήματα & νεότερες οδηγίες για την πνευμονική εμβολή

Αναστασία Άνθη

Β' Κλινική Εντατικής Θεραπείας & Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης Π.Γ.Ν. «ΑΤΤΙΚΟΝ»

New ESC/ERS Guidelines on the diagnosis and management of pulmonary embolism:

- Many recommendations have been **retained** or their validity has been **reinforced**
- New data have **extended** or **modified** our knowledge

in respect of
the optimal diagnosis, assessment, and treatment of patients with PE

Epidemiology

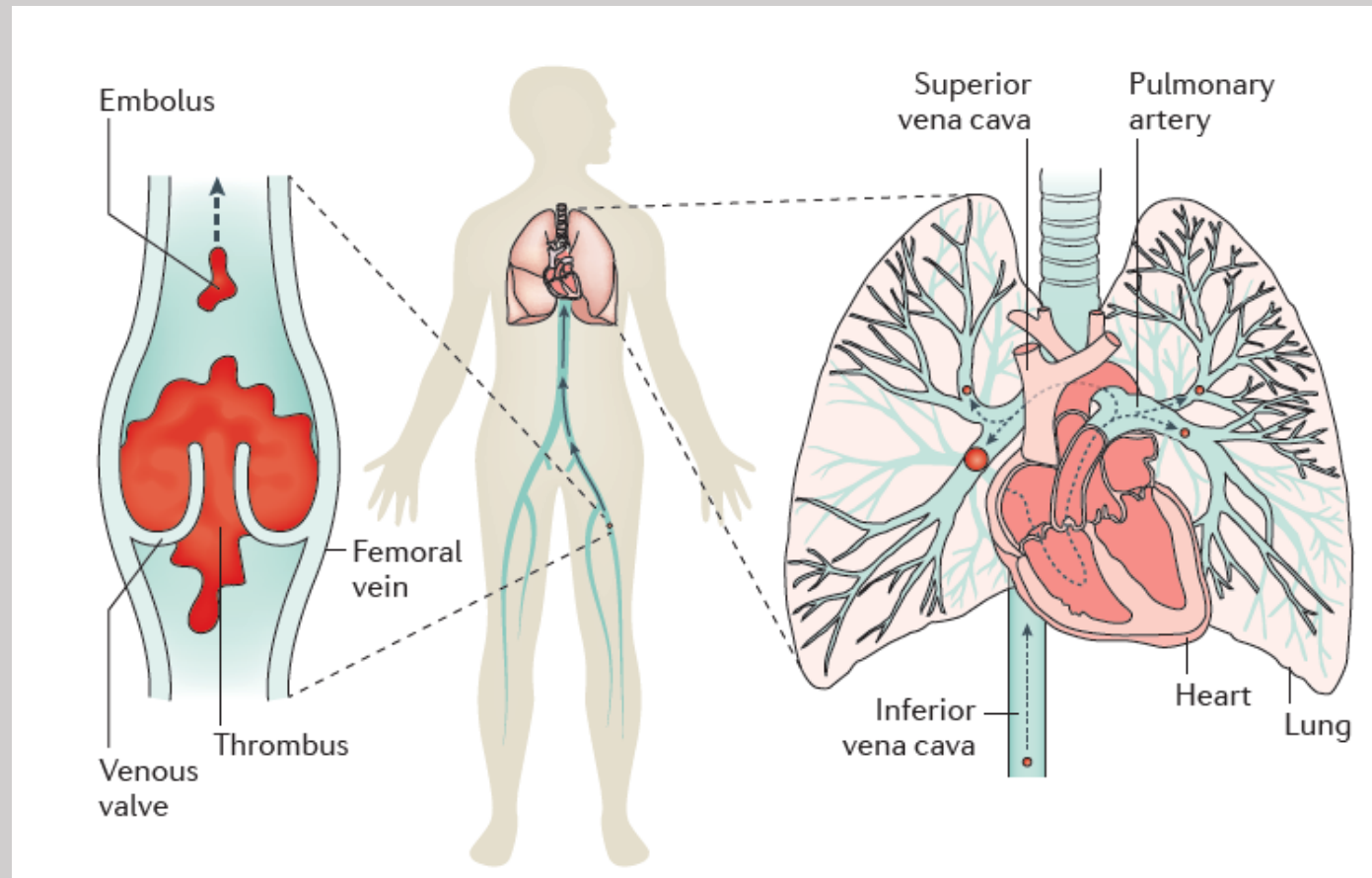
Venous thrombo-embolism (VTE)

includes deep-vein thrombosis (DVT)
& pulmonary embolism (PE)

Epidemiology

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- is the **third** most common cause
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after myocardial infarction and stroke

Epidemiology

Venous thrombo-embolism (VTE)

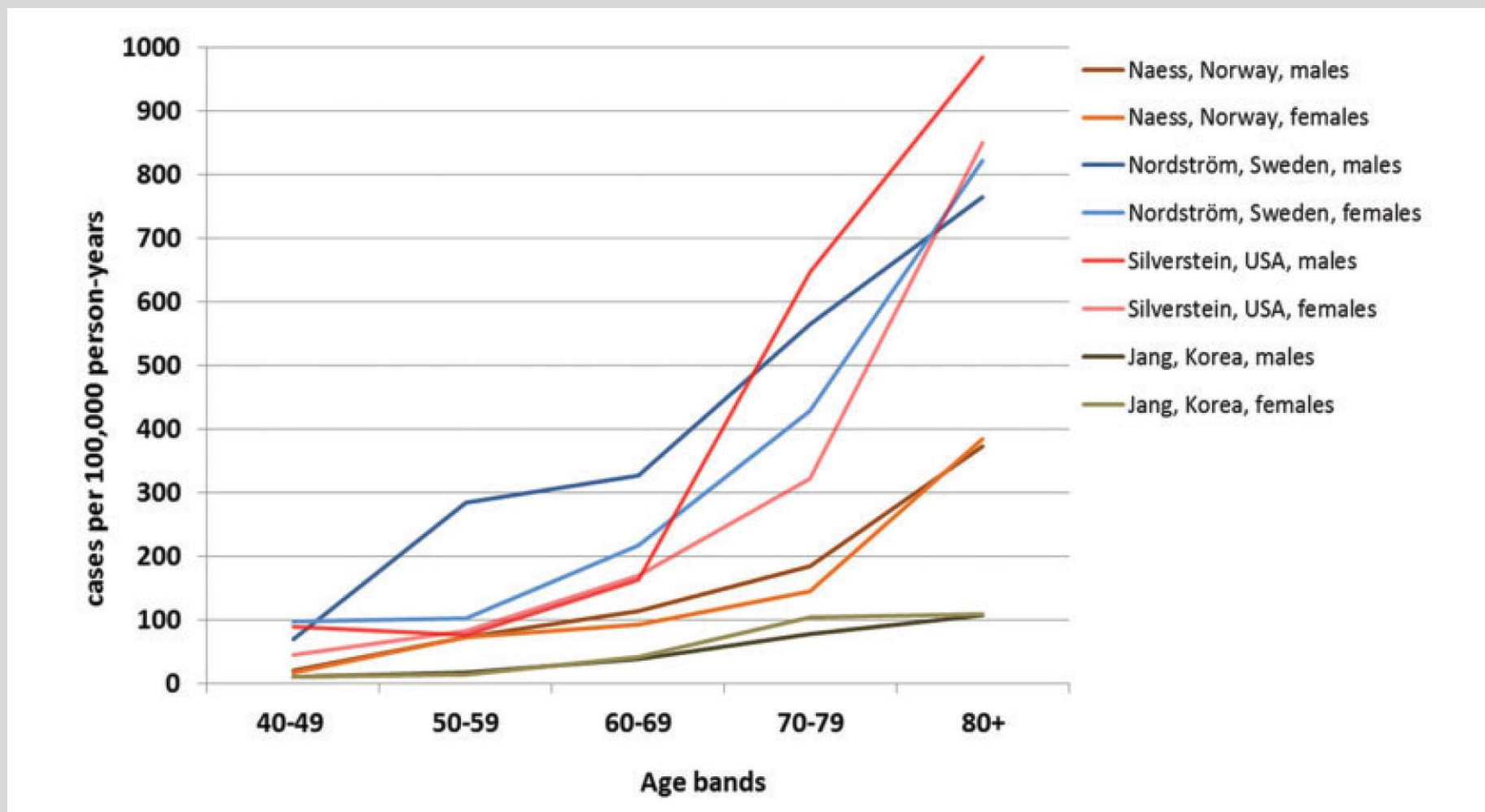
includes deep-vein thrombosis (DVT)
& pulmonary embolism (PE)

- is the **third** most common cause
of vascular disease–related deaths
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incidence

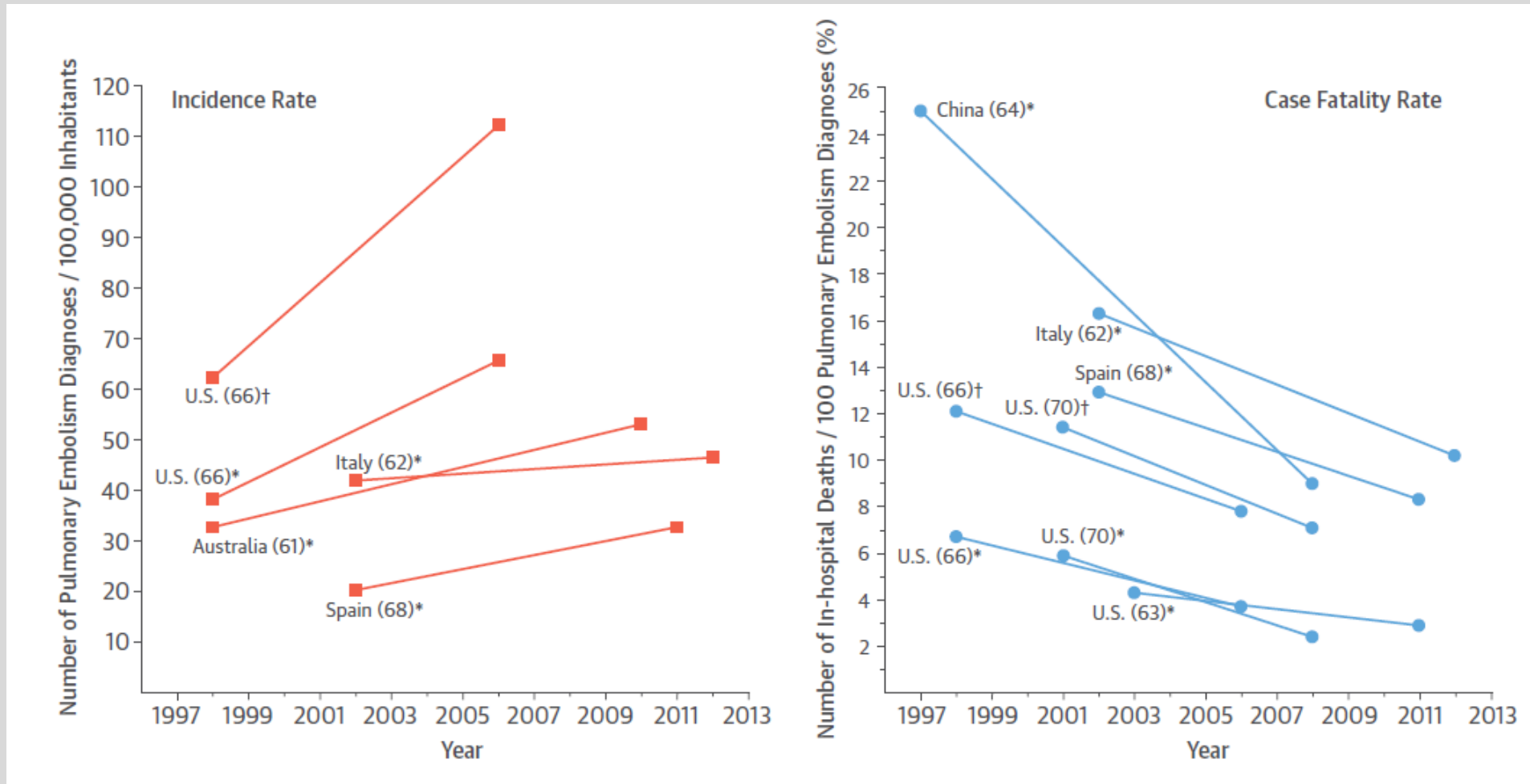
- **1 - 2 cases / 1000/ year** in the general population
- is steadily **increasing**

Venous thromboembolism incidence according to age group

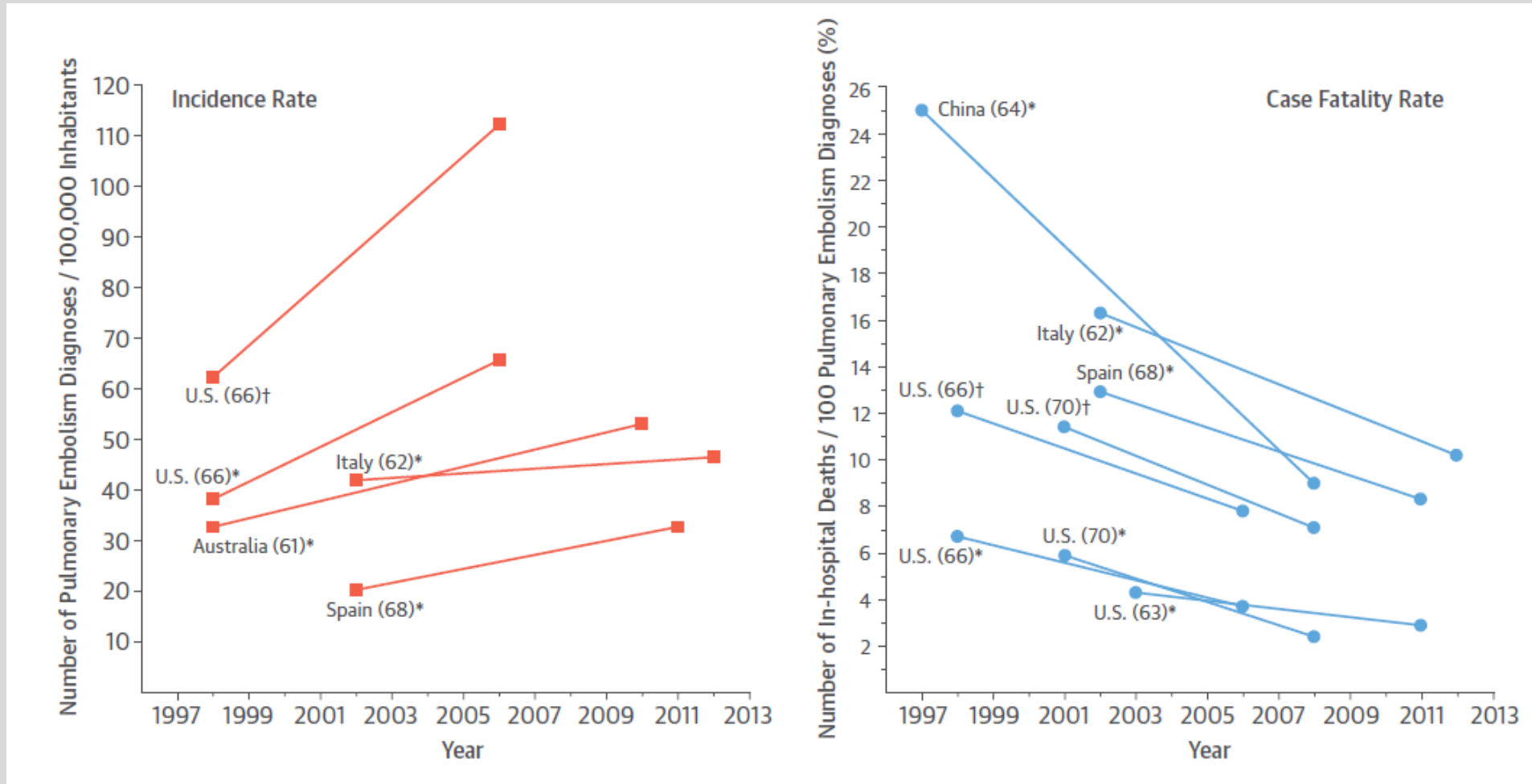


*ESC consensus document on diagnosis and management of acute DVT
European Heart Journal (2017)*

Global Trends in PE Incidence & Case Fatality Rates



Global Trends in PE Incidence & Case Fatality Rates



diagnosis and treatment of PE have both improved

VTE is considered to be a consequence of **the interaction** between
patient-related—*usually permanent*—risk factors &
setting-related—*usually temporary*—risk factors.

Predisposing factors for VTE

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)

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)

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

Predisposing factors for VTE

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

2019 ESC /ERS Guidelines for the diagnosis & management of acute pulmonary embolism

Symptoms and signs and initial prognostic triage in suspected PE

Cardiovascular s/s

including but not limited to:

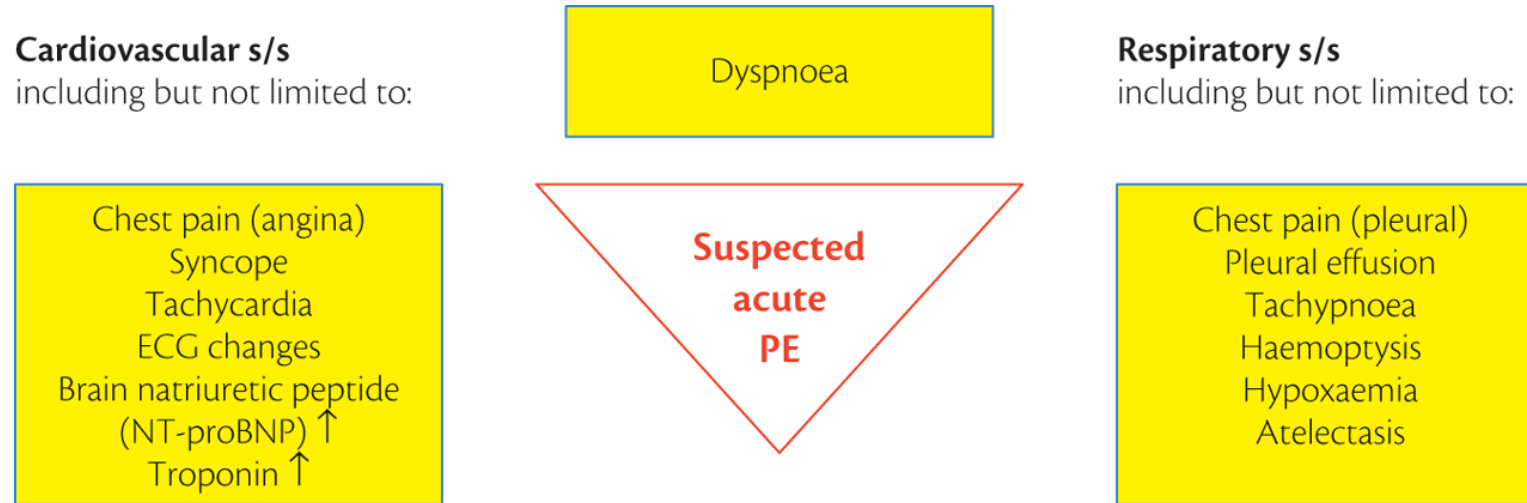
Chest pain (angina)
Syncope
Tachycardia
ECG changes
Brain natriuretic peptide
(NT-proBNP) ↑
Troponin ↑

Respiratory s/s

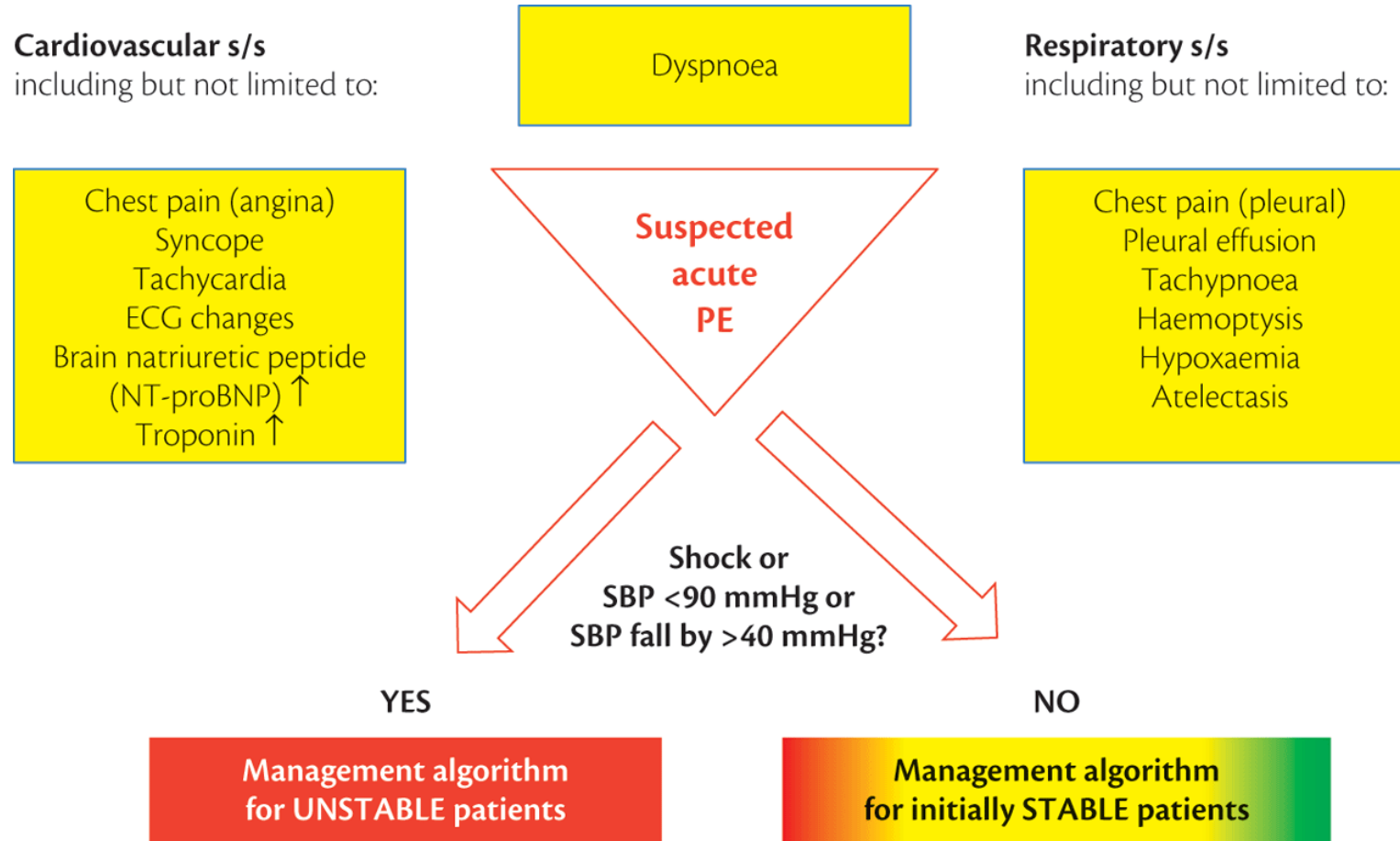
including but not limited to:

Chest pain (pleural)
Pleural effusion
Tachypnoea
Haemoptysis
Hypoxaemia
Atelectasis

Symptoms and signs and initial prognostic triage in suspected PE



Symptoms and signs and initial prognostic triage in suspected PE

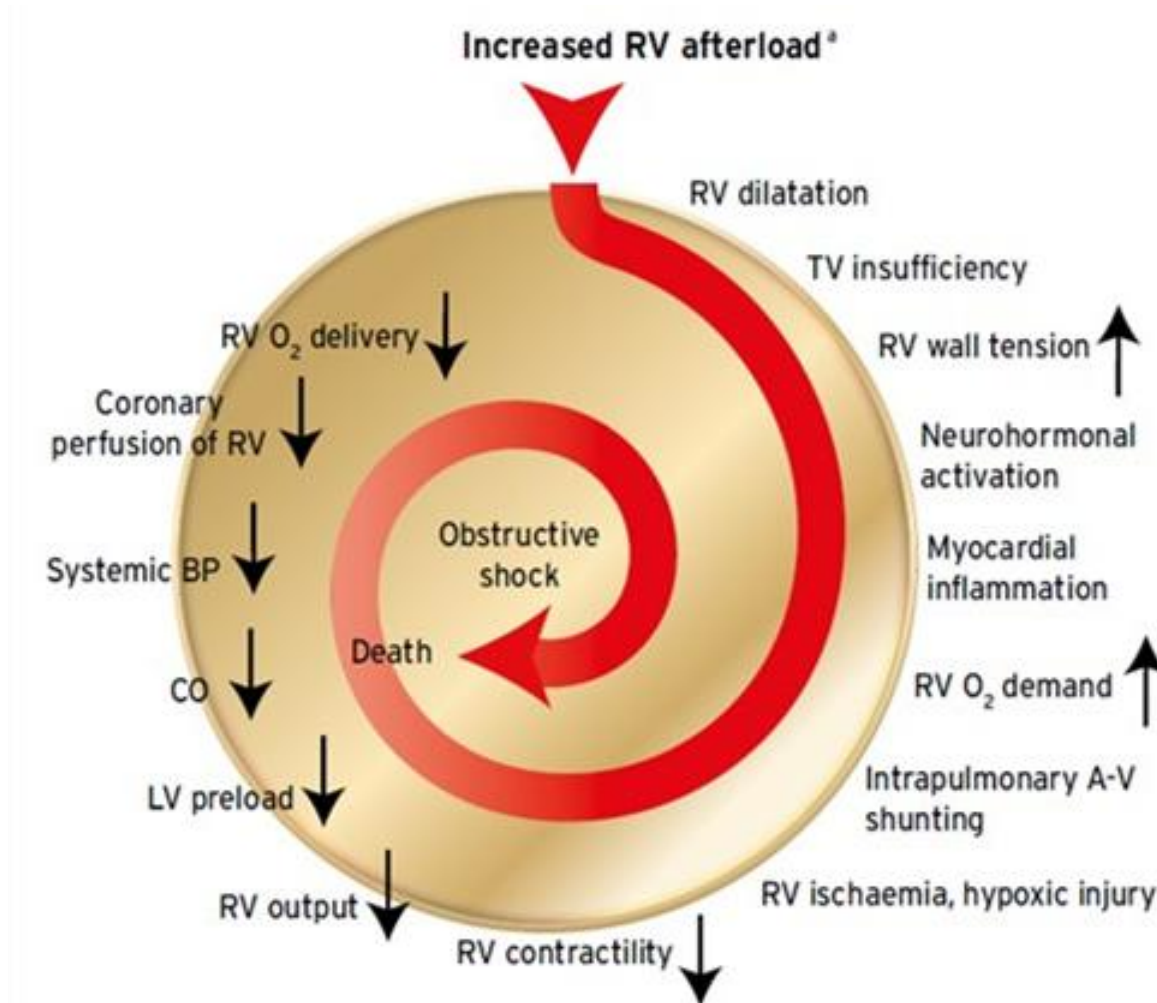


Acute PE interferes with both **circulation & **gas exchange****

Primary cause of death in severe PE: RV failure due to acute pressure overload

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2019 ESC /ERS Guidelines for the diagnosis & management of acute pulmonary embolism

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 \geq 90 mmHg despite adequate filling status	Systolic BP <90 mmHg, or systolic BP drop \geq 40 mmHg, either lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	<i>And</i>	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

2019 ESC /ERS Guidelines for the diagnosis & management of acute pulmonary embolism

Complications associated with overtesting and overdiagnosis of PE

Complication	Associated Risk
Bleeding	<ul style="list-style-type: none">• Major bleeding can occur in up to 12% of treated VTE patients^{69,70}• Anticoagulation complications increased from 3.1 to 5.3 per 100,000 from 1998 to 2006 ($P<.001$)⁶⁹• Bleeding risk may outweigh benefit in some populations, with a 5.3% major bleed rate in isolated subsegmental PE but only a 0.7% risk of recurrent VTE⁷¹
Cost	<ul style="list-style-type: none">• Total charges for PE admission increased from \$25,293 to \$43,740 from 1998 to 2006⁷²• Newer anticoagulants can cost \$3000 annually and, although the warfarin drug itself is cheaper, the associated bridge and monitoring increase its cost^{69,73,74}
Nephrotoxin exposure	<ul style="list-style-type: none">• CTPA contrast nephropathy occurs in 14%–24% of patients, with higher rates in those with critical illness or renal comorbidities^{75–77}• There are no protective effects from <i>N</i>-acetylcysteine, normal saline, or sodium bicarbonate⁷⁶
Contrast dye allergy	<ul style="list-style-type: none">• Although not studied specifically in CTPAs, it is recognized that mild contrast reactions occur in 15% of patients receiving iodinated contrast, moderate in 1%–2%, and severe in 0.2%⁷⁷
Radiation	<ul style="list-style-type: none">• Females have a significantly higher CTPA-related lifetime attributable risk of cancer death (vs males, 48.7 vs 42.1 per 100,000 for age group 20–29; $P<.0001$)⁷⁸• Estimates suggest that 3 out of every 1000 20-year-old women who undergo CTPA will develop cancer^{69,79}

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In recent studies <20% (in some studies only 5%) of pts investigated for a suspected PE actually have the disease

allergy	<ul style="list-style-type: none">• Reactions occur in 15% of patients receiving iodinated contrast; moderate in 1%–2%, and severe in 0.2%⁷⁷
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Generally, the use of clinical decision rules and D-dimer testing

- standardizes the diagnostic work-up for VTE
- reduces the use of invasive tests &
- is cost-effective

The revised Geneva clinical **prediction rule** for PE

Items	Clinical decision rule points	
	Original version ⁹¹	Simplified version ⁸⁷
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥ 95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Pain on lower-limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
<i>Three-level score</i>		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥ 11	≥ 5
<i>Two-level score</i>		
PE-unlikely	0–5	0–2
PE-likely	≥ 6	≥ 3

2019 ESC /ERS Guidelines for the diagnosis & management of acute pulmonary embolism

The revised Geneva clinical **prediction rule** for PE

PE confirmation

10%

30%

65%

12%

35%

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2019 ESC /ERS Guidelines for the diagnosis & management of acute pulmonary embolism

Pulmonary embolism rule-out criteria (**PERC**)

- age <50 years
- pulse rate <100/min
- SpO2 >94%
- no unilateral leg swelling
- no haemoptysis
- no surgery or trauma within 4 weeks
- no prior DVT or PE
- no oral hormone use

*Patients meeting PERC criteria (PERC (–)) should **not** require any **further testing***

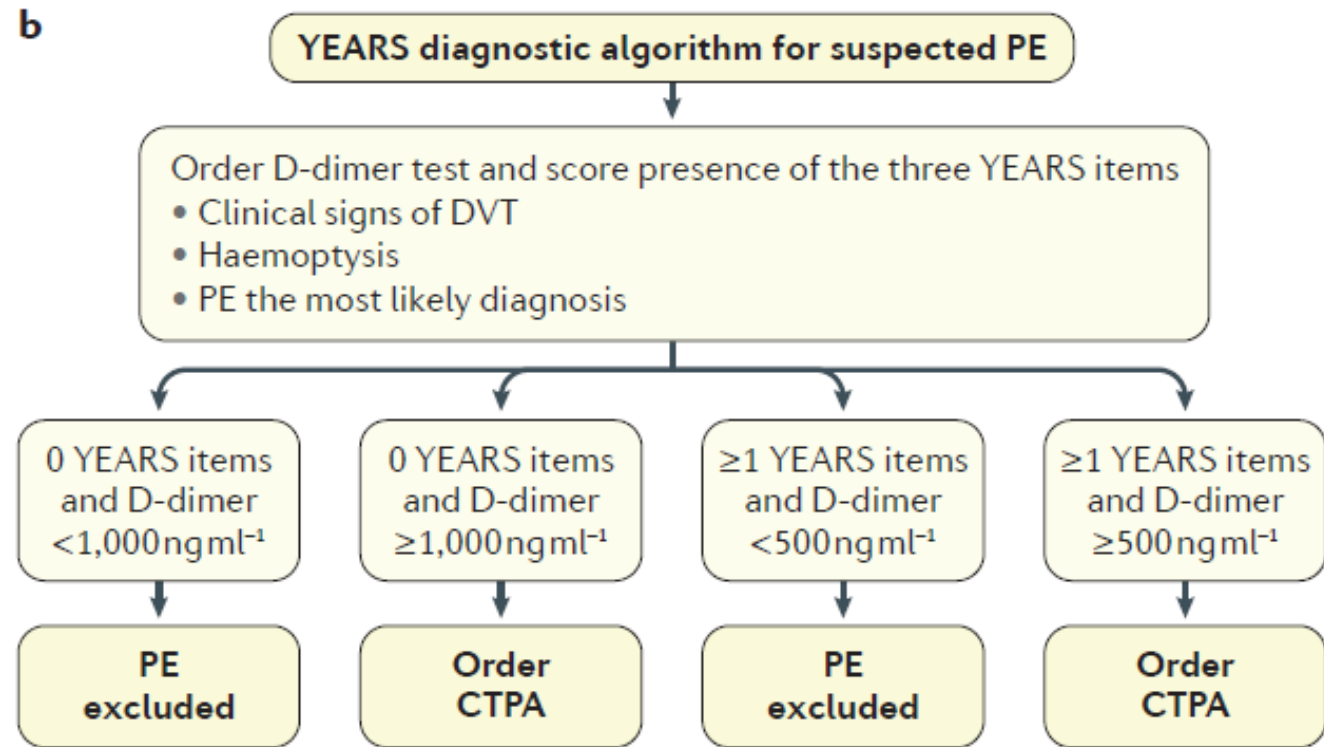
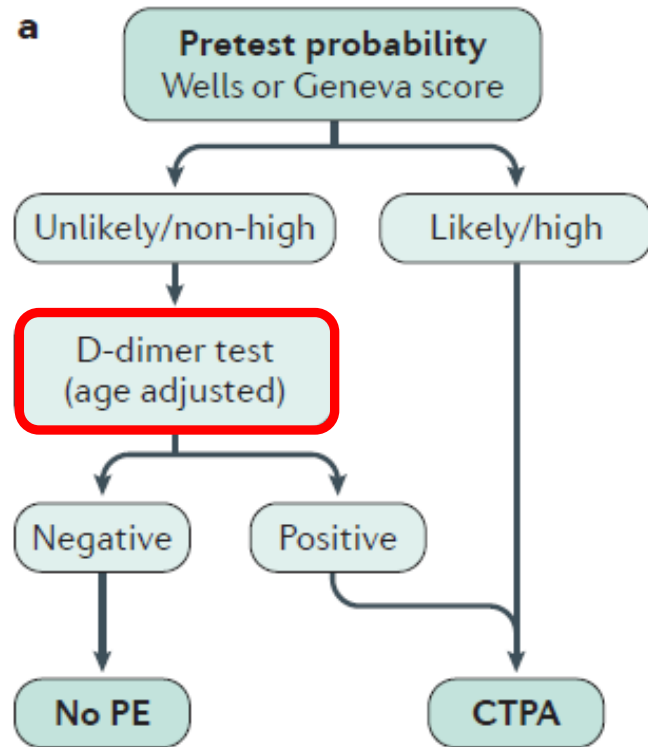
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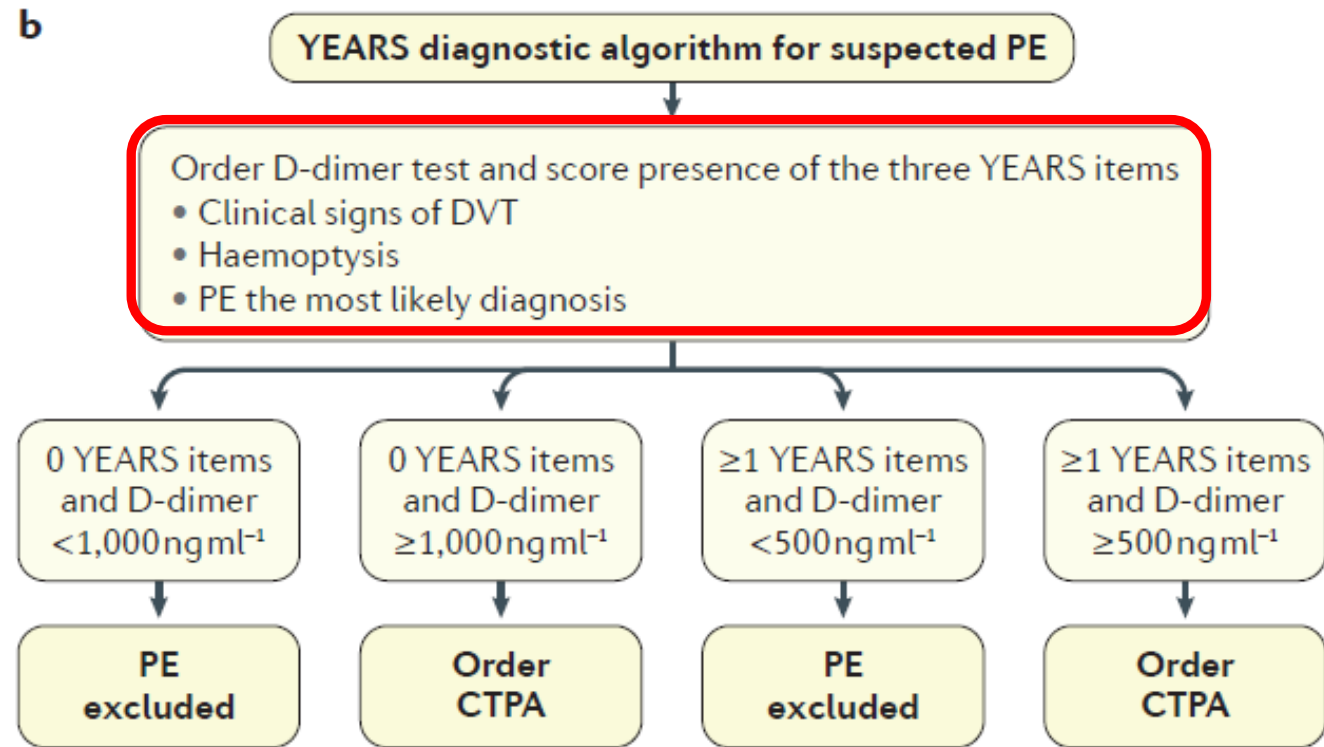
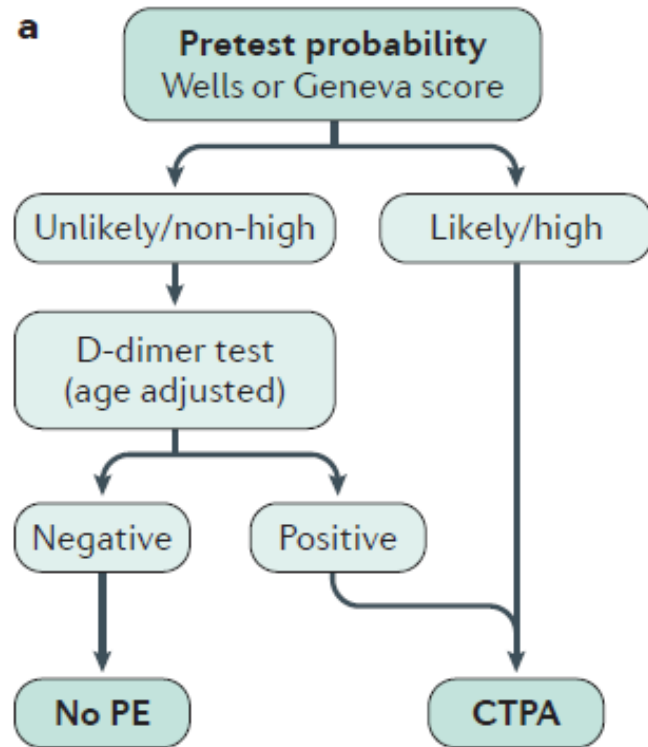
*PERC rule should be used **only** in **low-prevalence** settings or
for pts considered to have a **low probability of PE***

Recommendations for diagnosis

Recommendations	Class	Level
D-dimer		
Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or PE-unlikely, to reduce the need for unnecessary imaging and irradiation.	I	A
As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an <u>age-adjusted</u> cut-off (age x 10 µg/L, in patients >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or PE-unlikely.	IIa	B
As an alternative to the fixed or age-adjusted D-dimer cut-off, D-dimer levels <u>adapted to clinical probability</u> should be considered for excluding PE.	IIa	B
D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay.	III	A



the **YEARS** study: Lancet, 390: 289-297, 2017

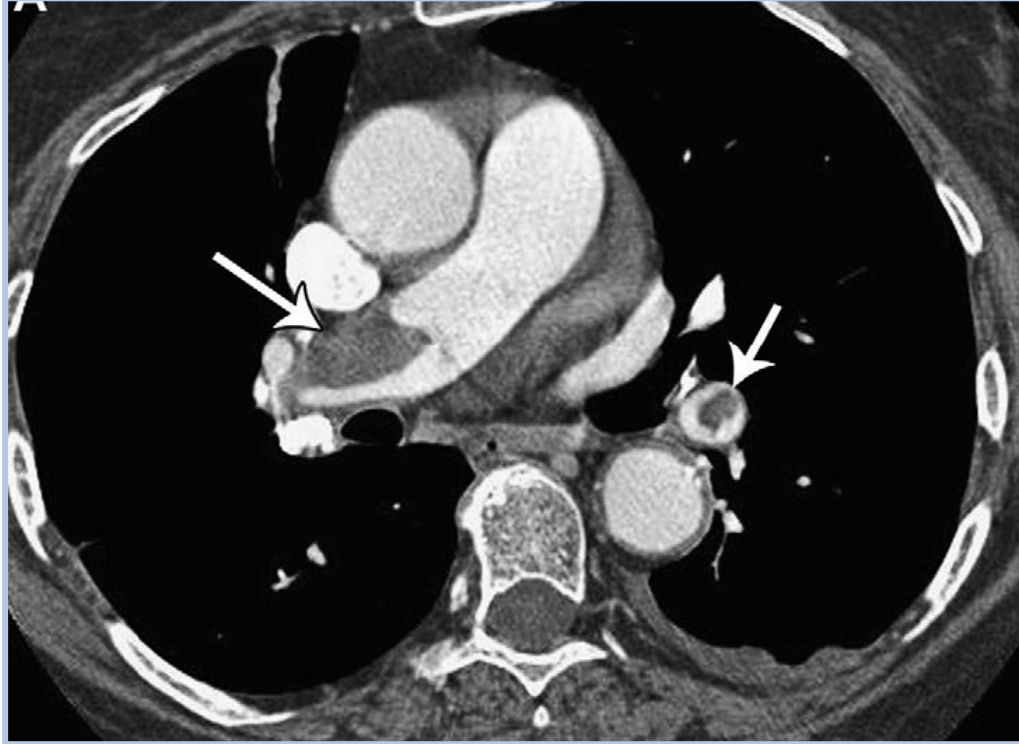


*Compared with the conventional algorithm, the YEARS algorithm spares the need for CTPA in an additional **14%** of patients with suspected PE*

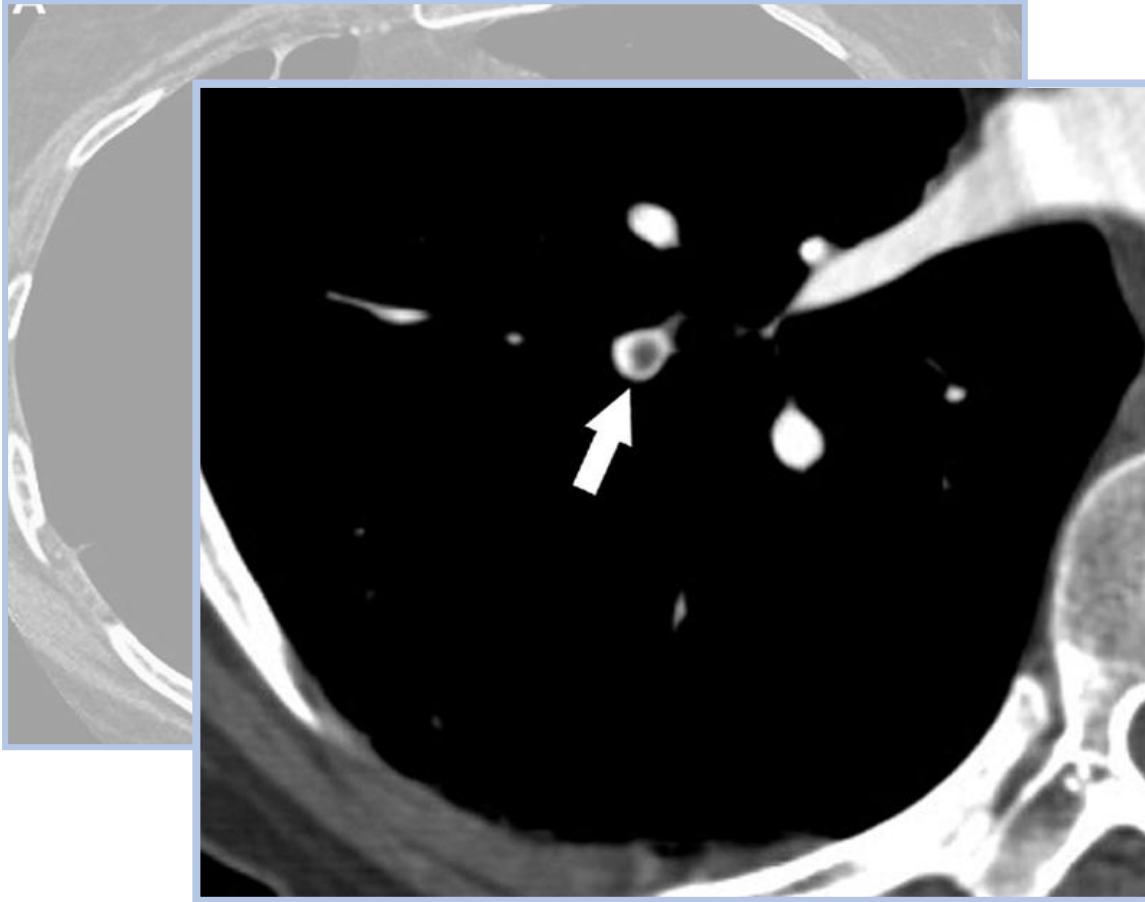
Imaging tests for diagnosis of pulmonary embolism

	Strengths	Weaknesses/limitations	Radiation issues ^a
CTPA	<ul style="list-style-type: none"> ● Readily available around the clock in most centres ● Excellent accuracy ● Strong validation in prospective management outcome studies ● Low rate of inconclusive results (3–5%) ● May provide alternative diagnosis if PE excluded ● Short acquisition time 	<ul style="list-style-type: none"> ● Radiation exposure ● Exposure to iodine contrast: <ul style="list-style-type: none"> ○ limited use in iodine allergy and hyperthyroidism ○ risks in pregnant and breastfeeding women ○ contraindicated in severe renal failure ● Tendency to overuse because of easy accessibility ● Clinical relevance of CTPA diagnosis of subsegmental PE unknown 	<ul style="list-style-type: none"> ● Radiation effective dose 3–10 mSv^b ● Significant radiation exposure to young female breast tissue

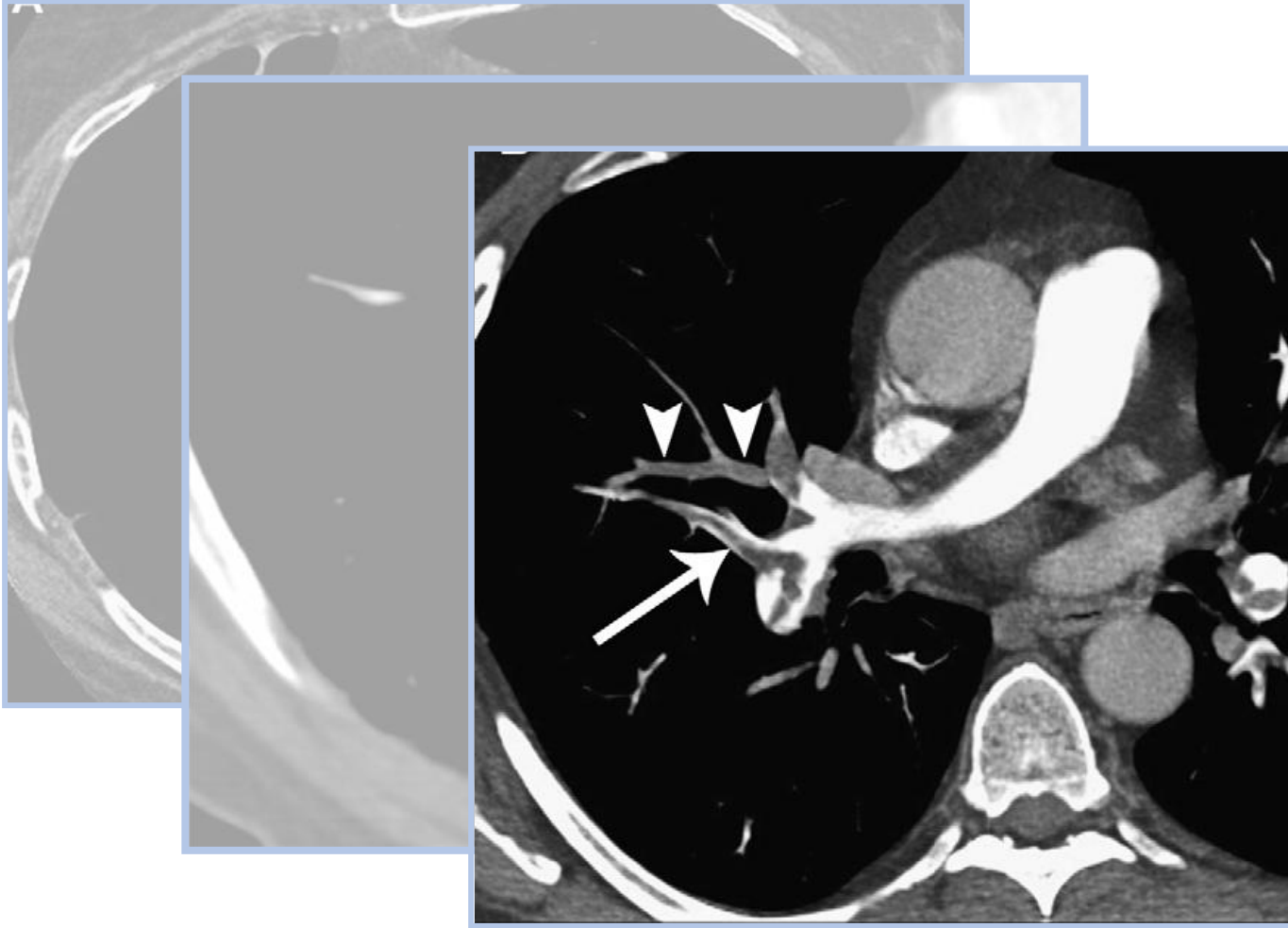
CTPA



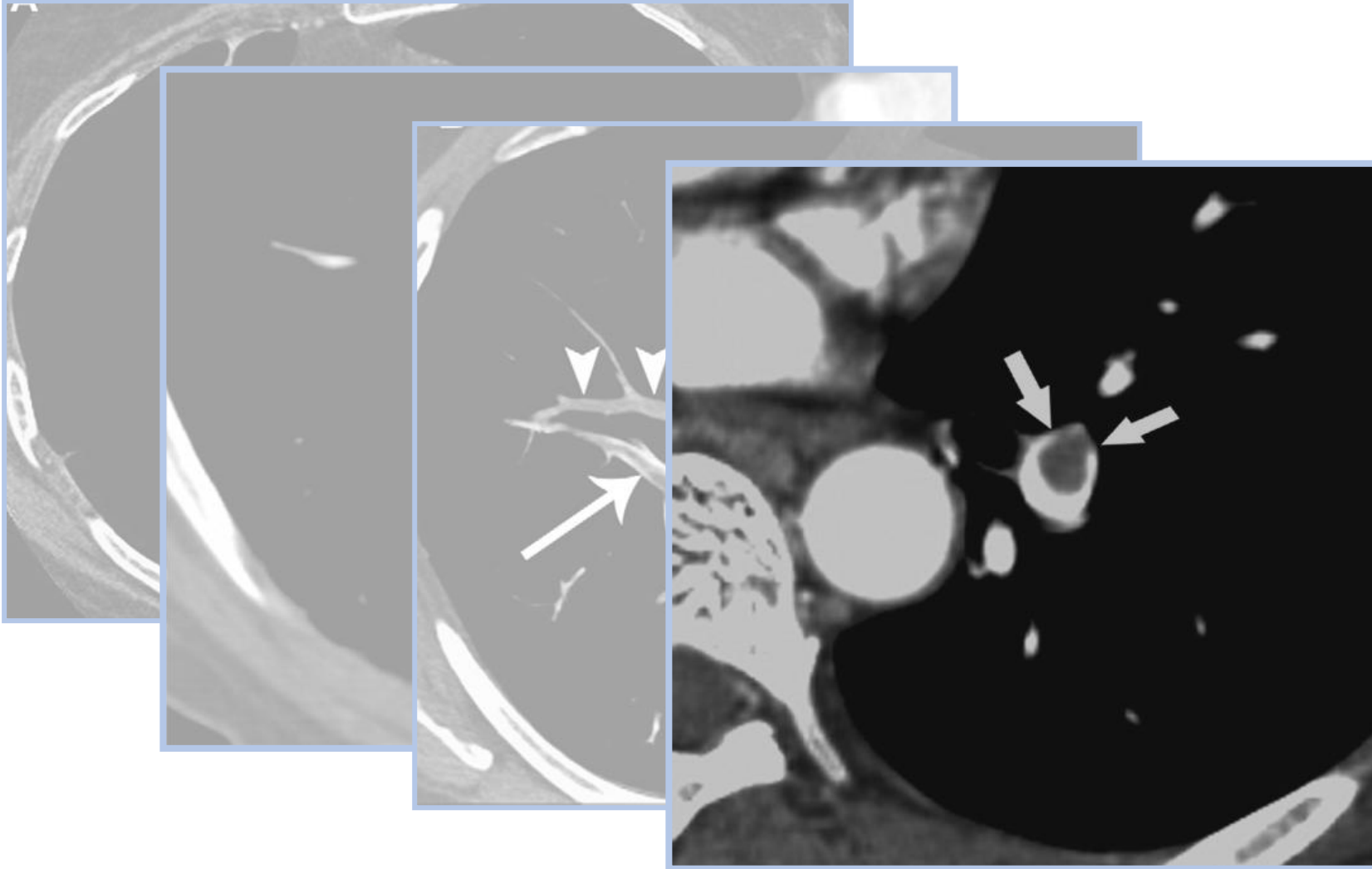
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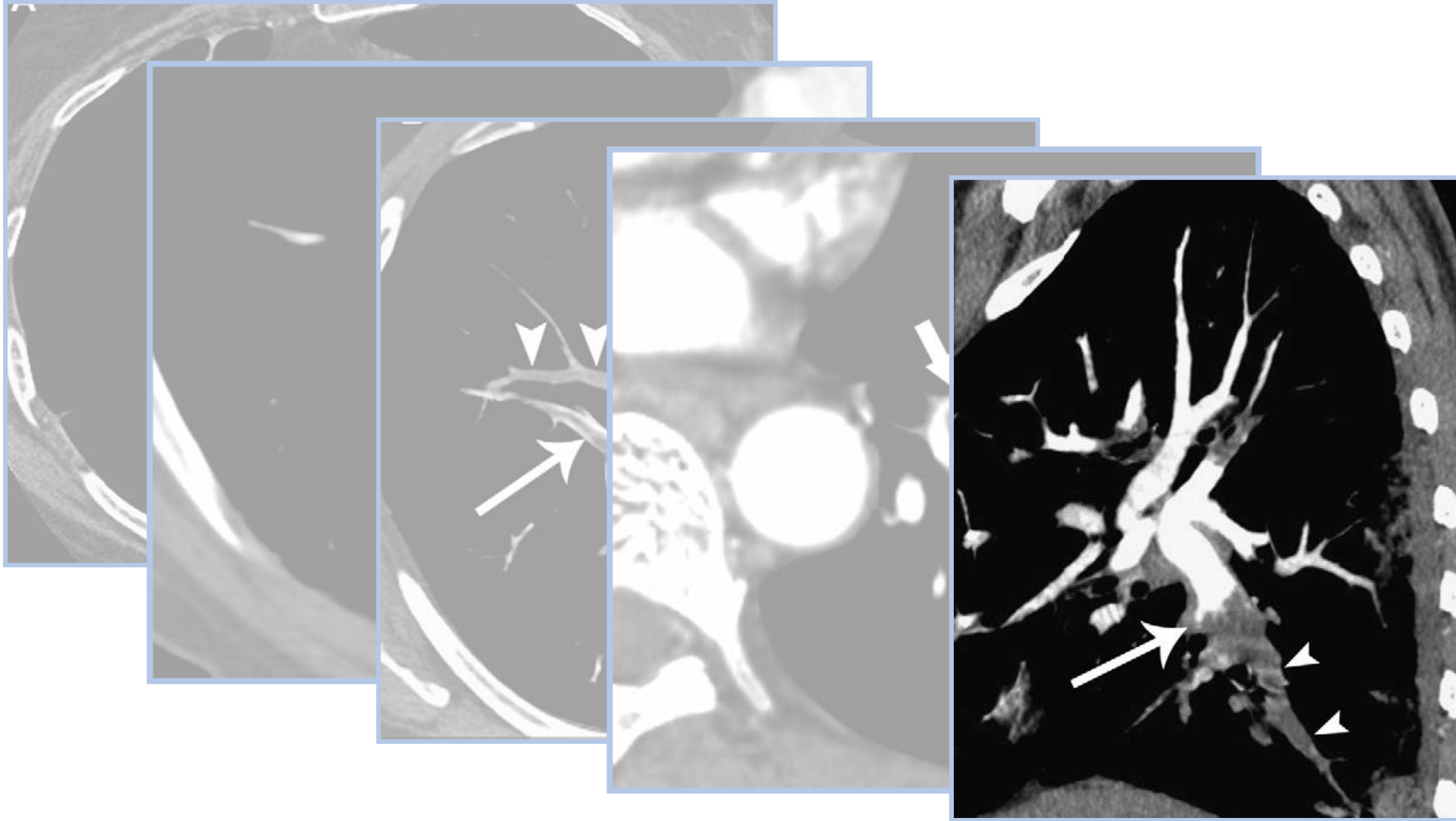
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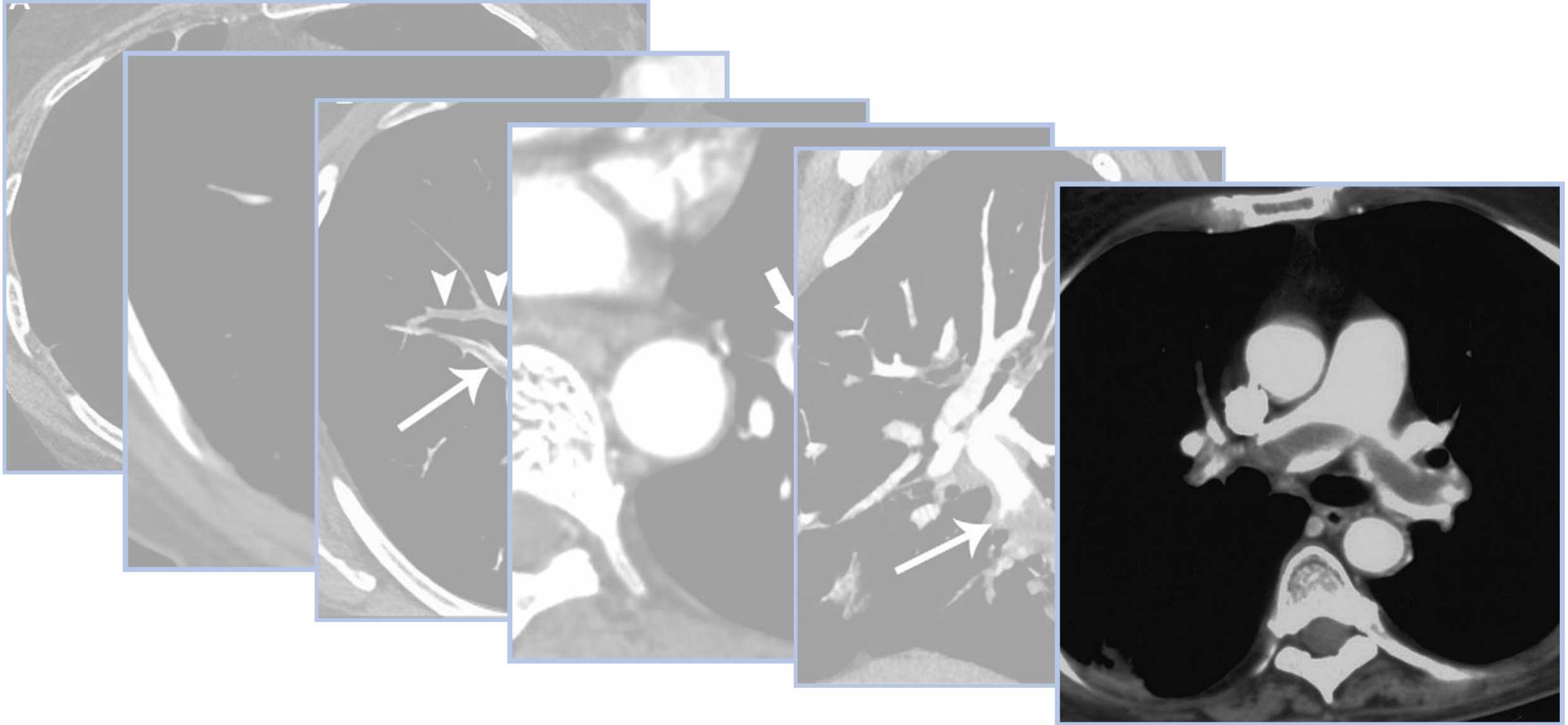
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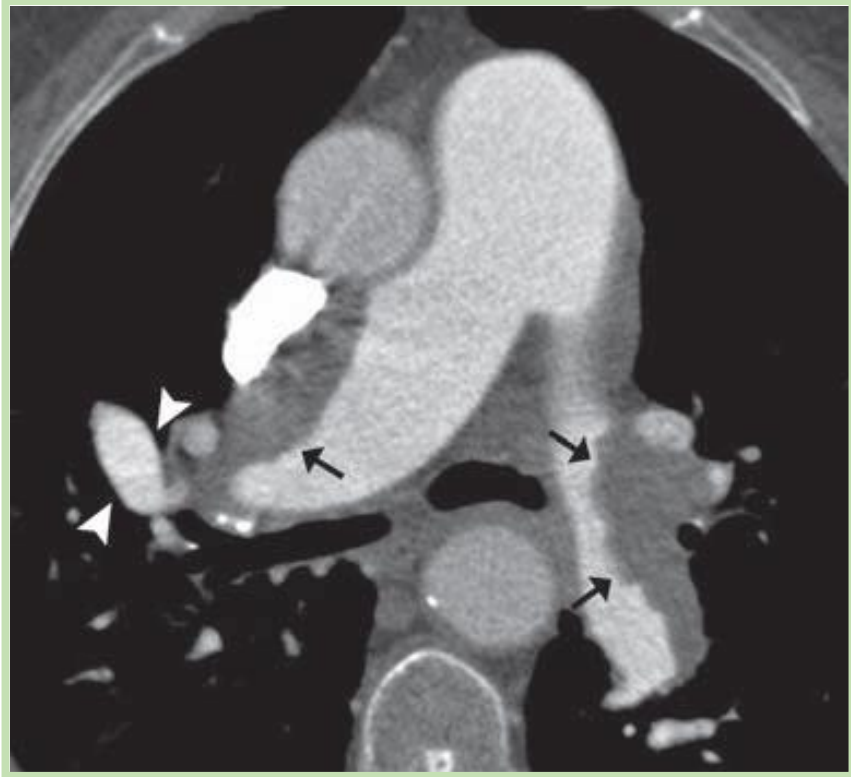


CTPA



Findings of pre-existing CTEPH on CTPA

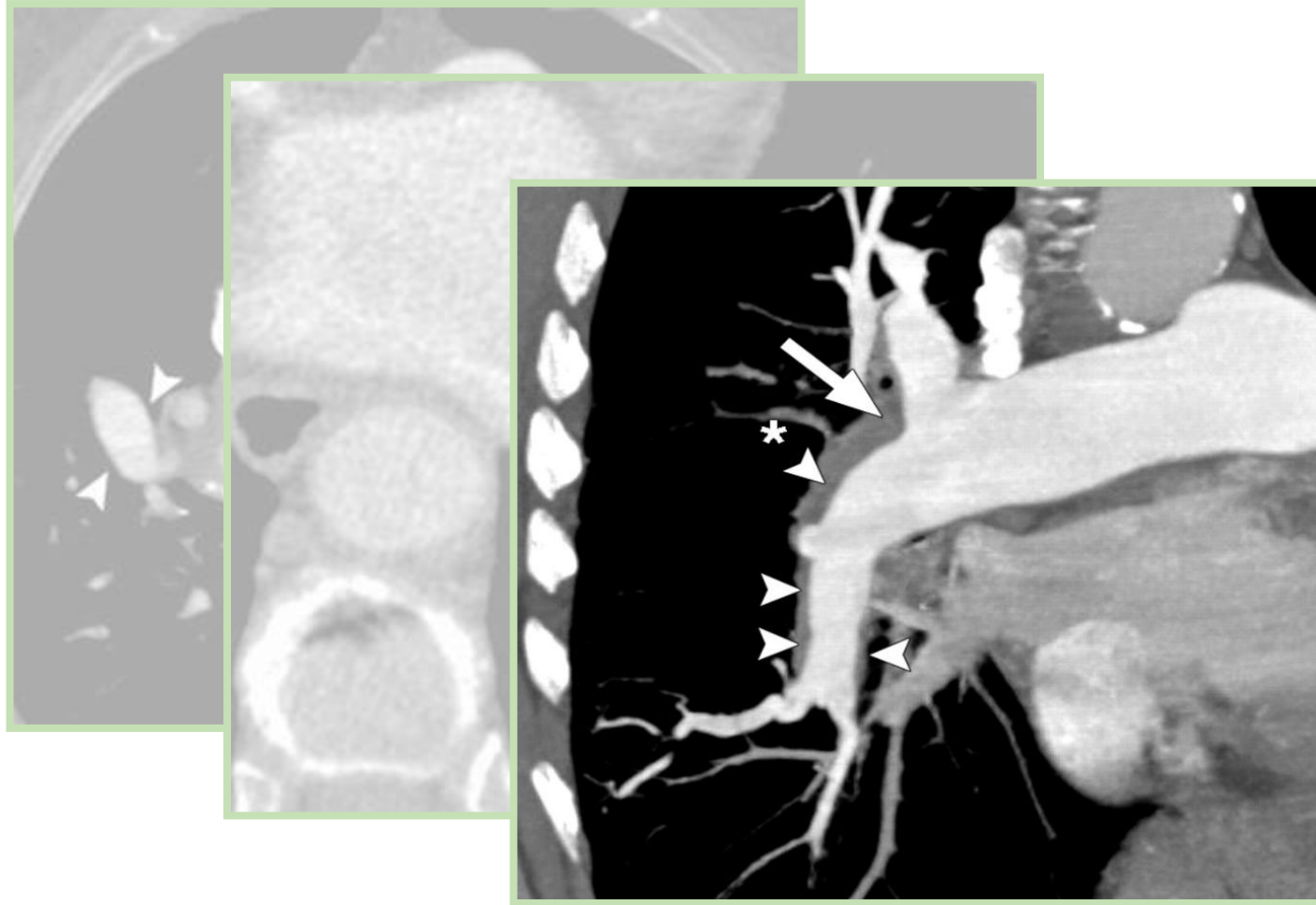
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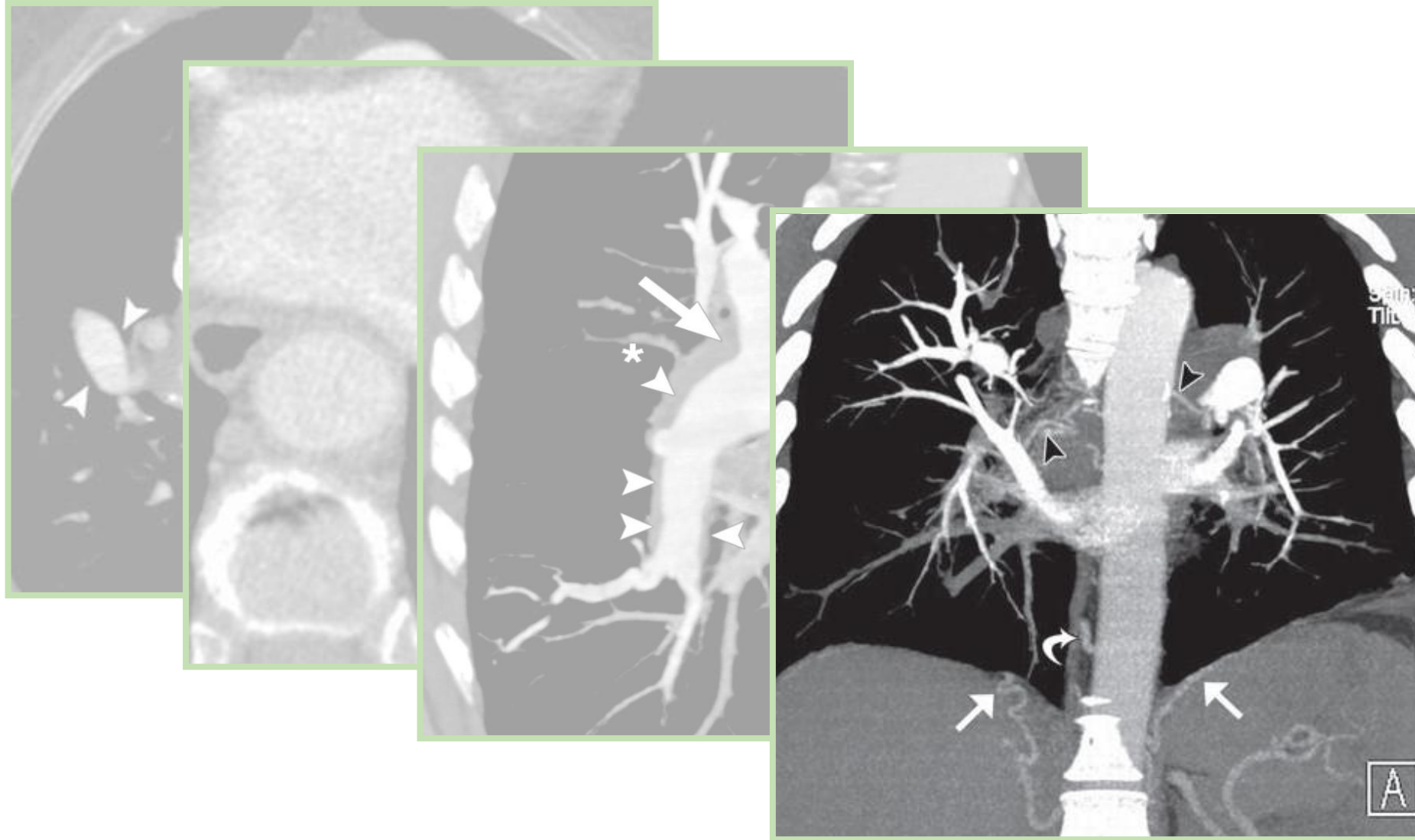
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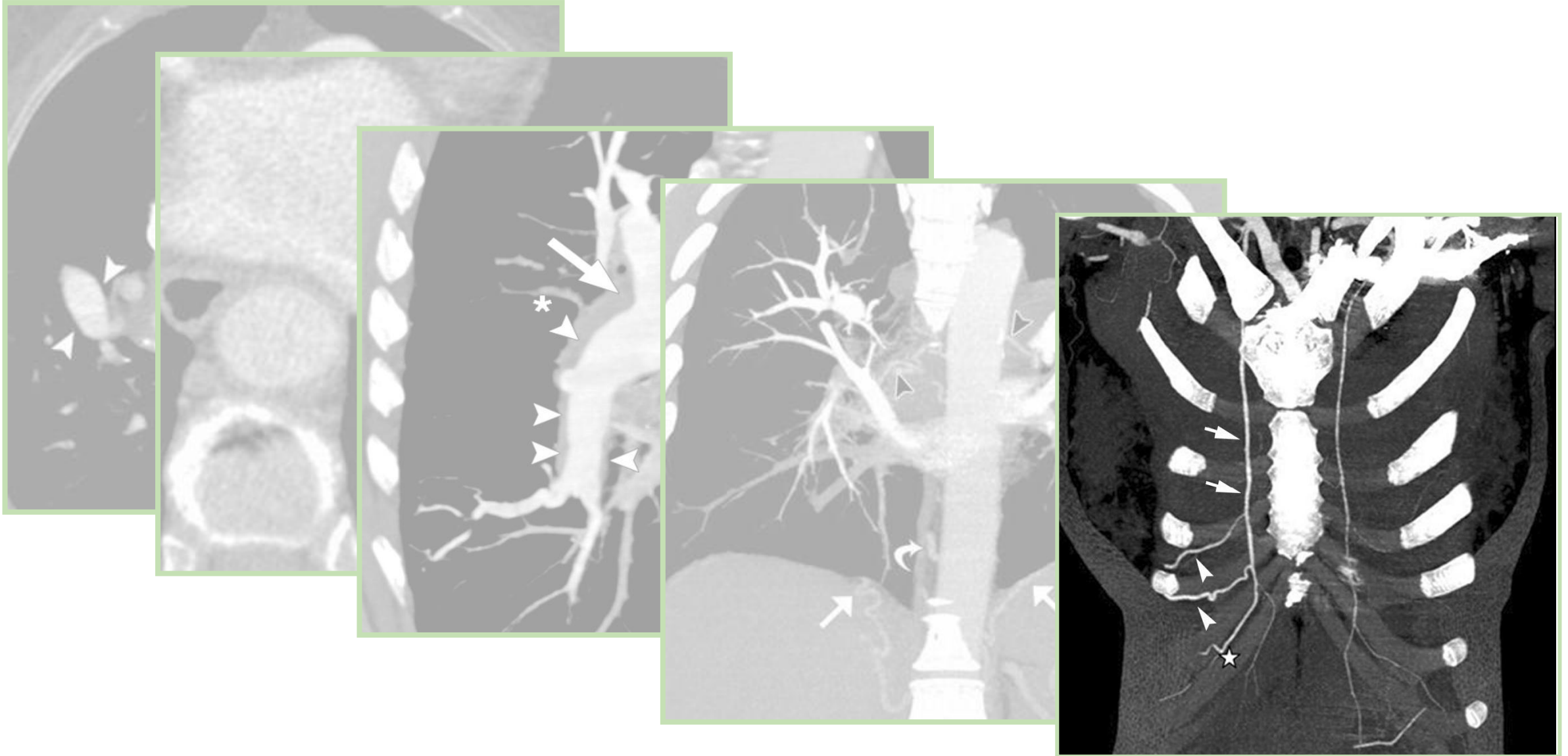
Findings of pre-existing CTEPH on CTPA



Findings of pre-existing CTEPH on CTPA



Findings of pre-existing CTEPH on CTPA



Imaging tests for diagnosis of pulmonary embolism

Planar V/Q scan	<ul style="list-style-type: none"> ● Almost no contraindications ● Relatively inexpensive ● Strong validation in prospective management outcome studies 	<ul style="list-style-type: none"> ● Not readily available in all centres ● Interobserver variability in interpretation ● Results reported as likelihood ratios ● Inconclusive in 50% of cases ● Cannot provide alternative diagnosis if PE excluded 	<ul style="list-style-type: none"> ● Lower radiation than CTPA, effective dose ~ 2 mSv^b
V/Q SPECT	<ul style="list-style-type: none"> ● Almost no contraindications ● Lowest rate of non-diagnostic tests (<3%) ● High accuracy according to available data ● Binary interpretation ('PE' vs. 'no PE') 	<ul style="list-style-type: none"> ● Variability of techniques ● Variability of diagnostic criteria ● Cannot provide alternative diagnosis if PE excluded ● No validation in prospective management outcome studies 	<ul style="list-style-type: none"> ● Lower radiation than CTPA, effective dose ~ 2 mSv^b
Pulmonary angiography	<ul style="list-style-type: none"> ● Historical gold standard 	<ul style="list-style-type: none"> ● Invasive procedure ● Not readily available in all centres 	<ul style="list-style-type: none"> ● Highest radiation, effective dose 10–20 mSv^b

Recommendations for diagnosis

Recommendations	Class	Level
Lower-limb compression ultrasonography (CUS)		
It is recommended to accept the diagnosis of VTE (and PE) if a CUS shows a proximal DVT in a patient with clinical suspicion of PE.	I	A
If CUS shows only a distal DVT, further testing should be considered to confirm PE.	IIa	A
If a positive proximal CUS is used to confirm PE, assessment of PE severity should be considered to permit risk-adjusted management.	IIa	C

Main new recommendations 2019

Diagnosis	
D-dimer test using an age-adjusted cut-off, or adapted to clinical probability, should be considered as an alternative to the fixed cut-off level.	IIa
If a positive proximal CUS is used to confirm PE, risk assessment should be considered to guide management.	IIa
V/Q SPECT may be considered for PE diagnosis.	IIb

Main new recommendations 2019

Diagnosis	
D-dimer test using an age-adjusted cut-off, or adapted to clinical probability, should be considered as an alternative to the fixed cut-off level.	IIa
If a positive proximal CUS is used to confirm PE, risk assessment should be considered to guide management.	IIa
V/Q SPECT may be considered for PE diagnosis.	IIb
Risk assessment	
Assessing the RV by imaging or laboratory biomarkers should be considered even in the presence of a low PESI or a sPESI of 0.	IIa
Validated scores combining clinical, imaging and laboratory prognostic factors may be considered to further stratify PE severity.	IIb

Original and simplified Pulmonary Embolism Severity Index

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 ≥ 110 b.p.m.	+20 points	1point
Systolic BP <100 mmHg	+30 points	1point
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

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Chronic pulmonary disease	<table><tr><th colspan="2">Risk strata</th></tr><tr><td>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%)</td><td>0 points = 30-day mortality risk 1.0% (95% CI 0.0–2.1%)</td></tr><tr><td>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%)</td><td>≥1point(s) = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)</td></tr></table>		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%)	≥1point(s) = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)
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Original and simplified Pulmonary Embolism Severity Index

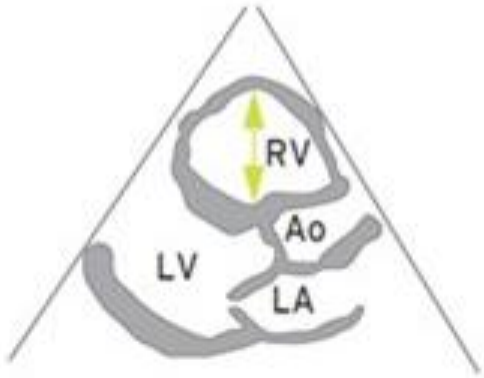
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The principal strength of the PESI lies in the **reliable identification** of pts at **low risk for 30-day mortality** (PESI classes I and II)

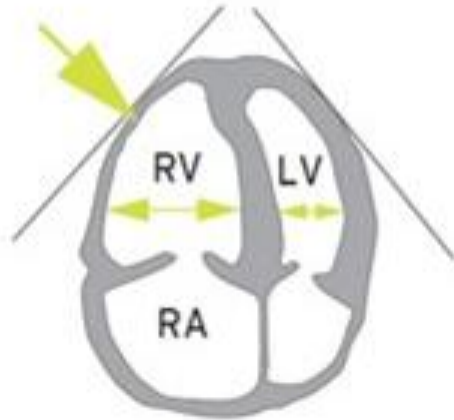
Systolic BP <100mmHg	+30 points	1point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1point

- the **diagnosis** of PE is based on identifying **clots** in the pulmonary arteries
- the short-term **prognosis** of PE is mainly determined by **RV function**

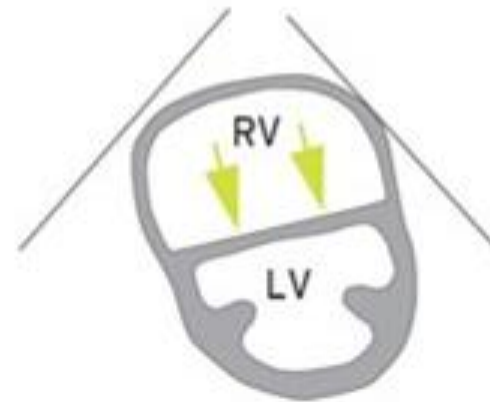
TEE parameters for RV pressure overload



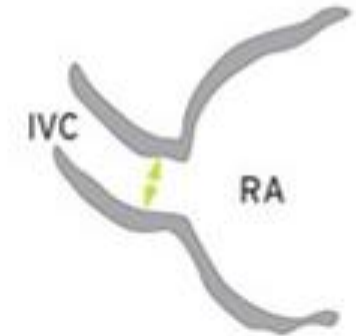
A. Enlarged right ventricle, parasternal long axis view



B. Dilated RV with basal RV/LV ratio >1.0 , and McConnell sign (arrow), four chamber view



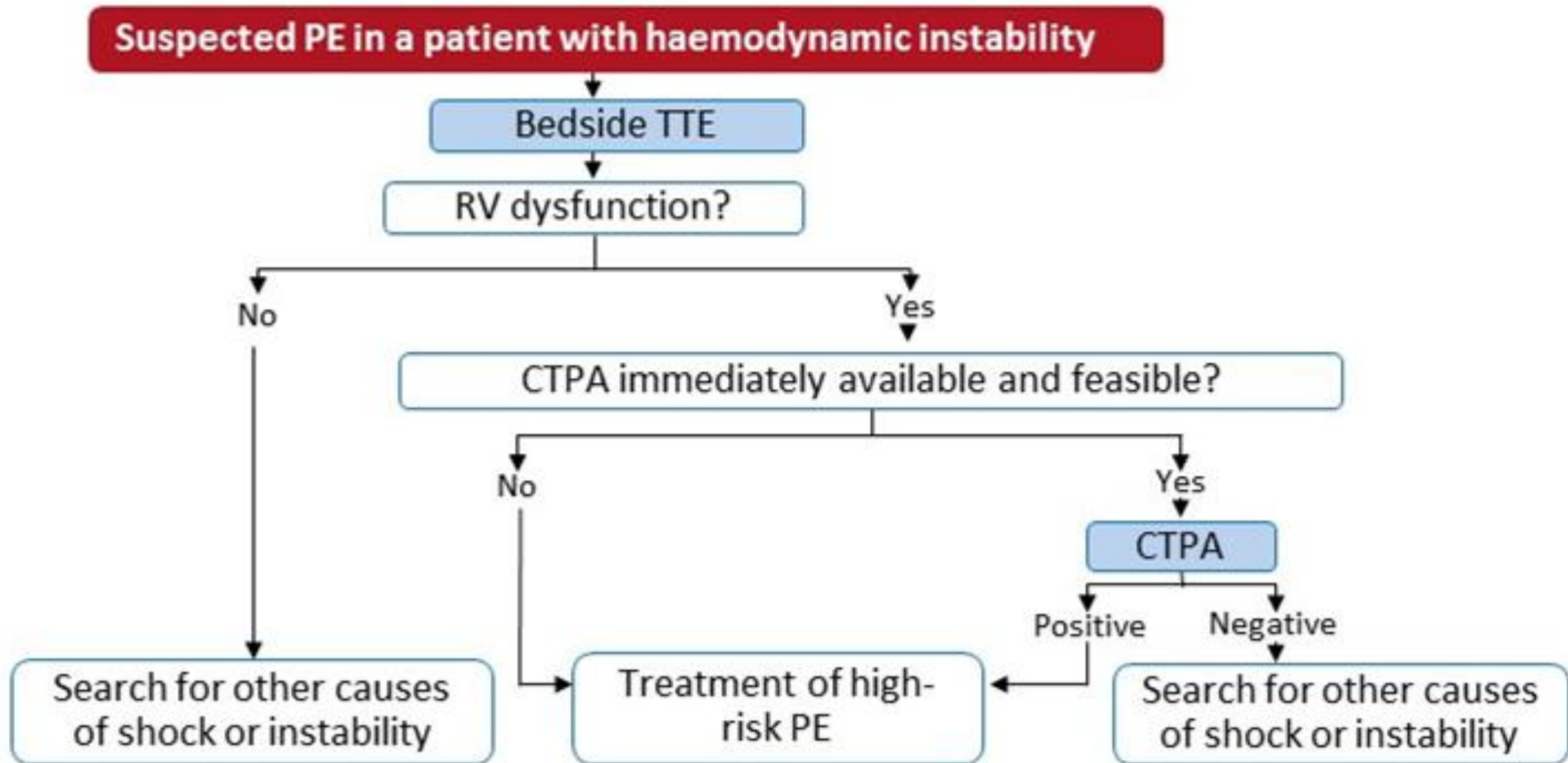
C. Flattened interventricular septum (arrows) parasternal short axis view



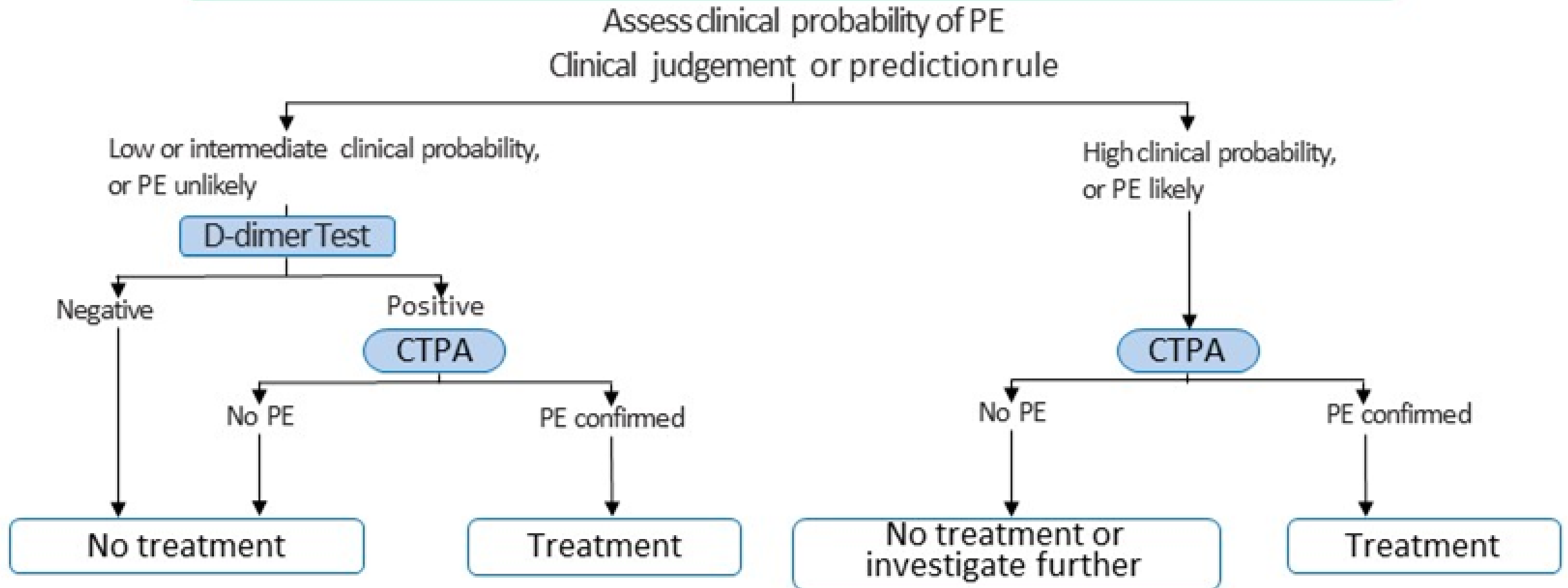
D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view

Classification of PE based on early mortality risk

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



Suspected PE in a patient without haemodynamic instability



HESTIA clinical decision rule

If at least **one** of the following questions is answered with **yes**, the patient cannot be treated at home:

Hemodynamically unstable?*

Thrombolysis or embolectomy necessary?

High risk for bleeding?[†]

Oxygen supply to maintain oxygen saturation >90%?

Pulmonary embolism diagnosed during anticoagulant treatment?

Severe pain needing intravenous pain medication >24 h?

Medical or social reason for treatment in the hospital >24 h?

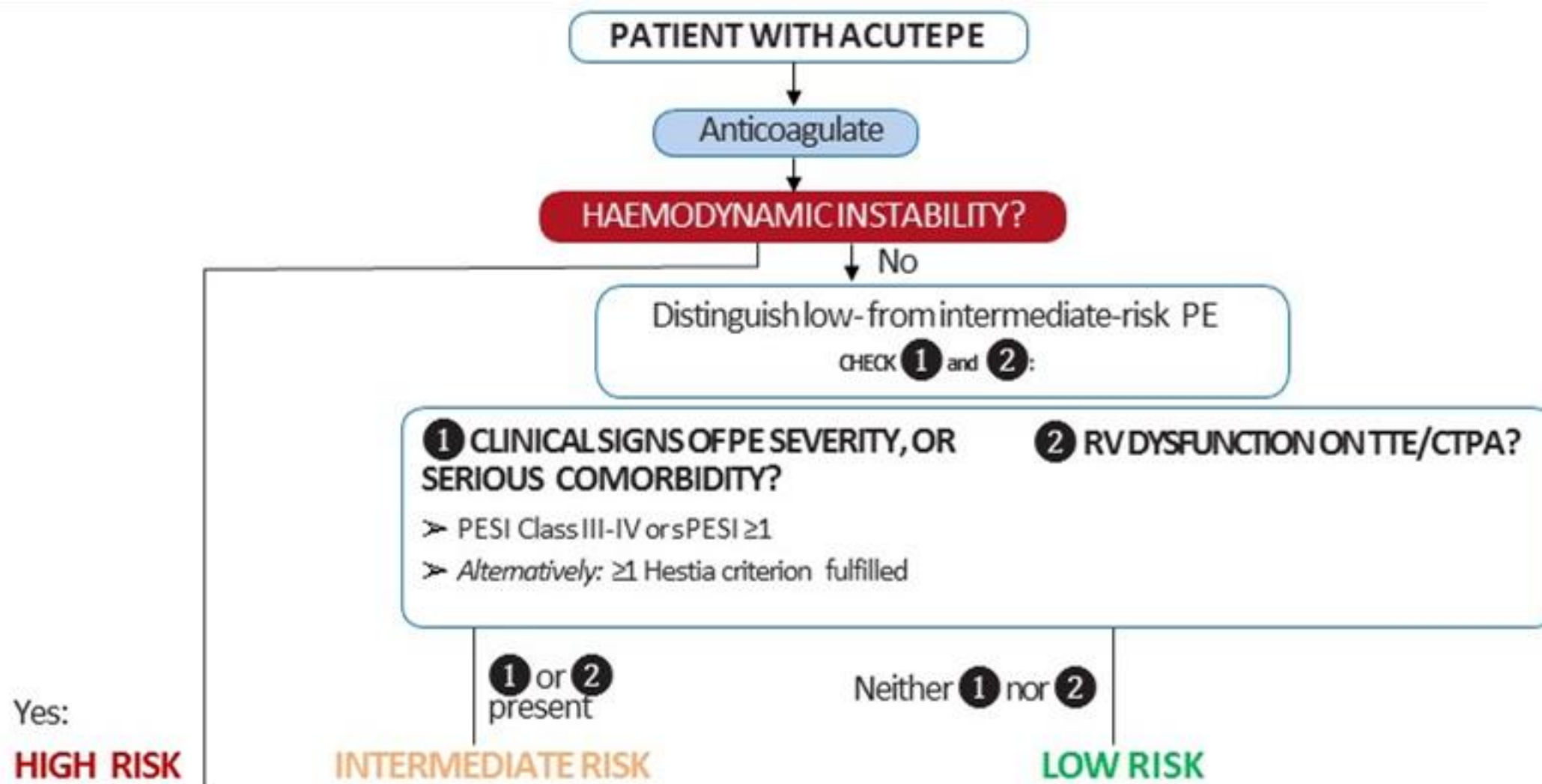
Creatinine clearance < 30 ml/min?[‡]

Severe liver impairment?[§]

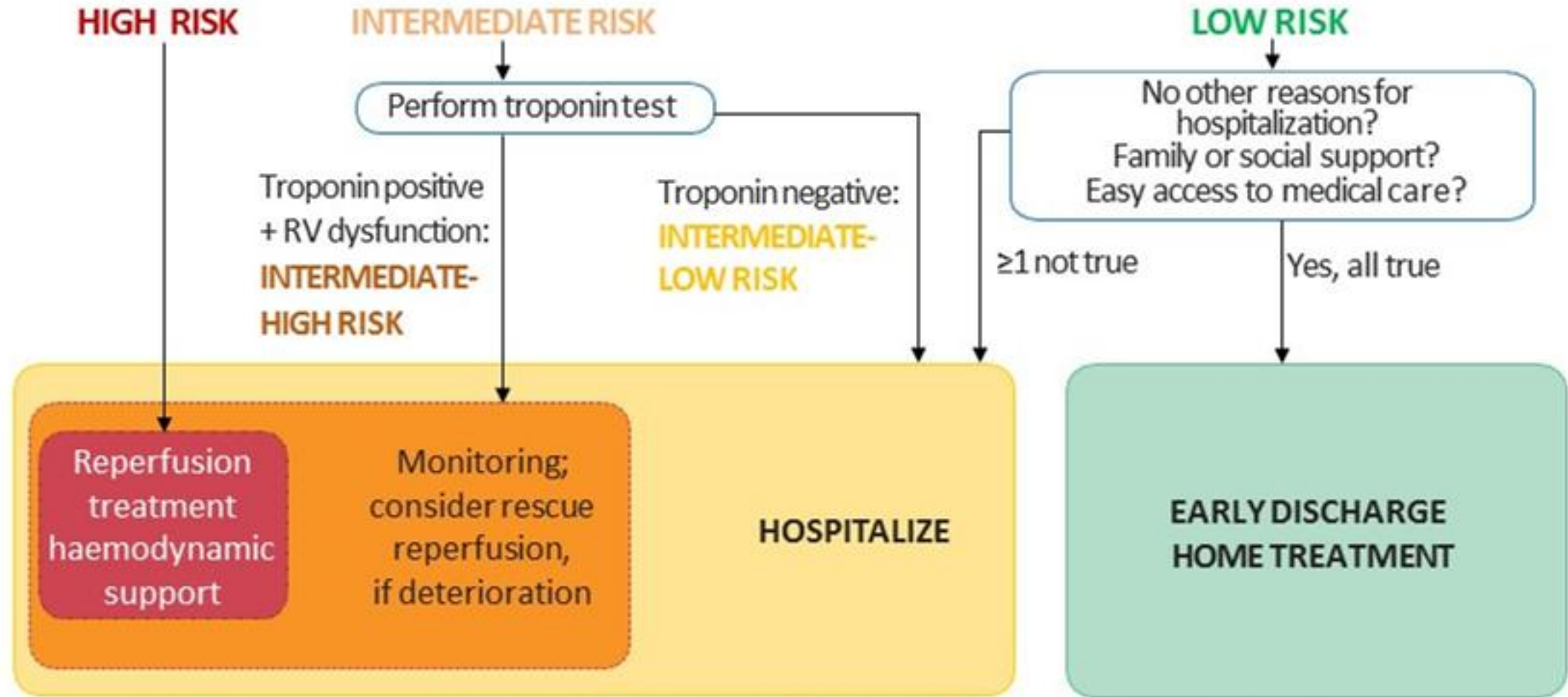
Pregnant?

Documented history of heparin-induced thrombocytopenia?

Risk –adjusted management of pts with acute pulmonary embolism



Risk –adjusted management of pts with acute pulmonary embolism



Three key steps are vital in the management of PE:

1. rapid, simple and accessible **diagnosis**
2. accurate **triaging** of PE (Risk Stratification) -
appropriate **treatment**
3. optimal **duration of treatment**
(assessment of recurrent VTE &/or
anticoagulation associated bleeding)

The mainstay of treatment for VTE is anticoagulation

Treatment consists of three phases:

- an **acute phase** comprising the first 5–10 days
after presentation of PE
- an **intermediate phase** between 10 days & 3 months
after presentation
- an **extended long-term phase** beyond this period

Thrombolytic regimens, doses, and contraindications

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	Absolute History of haemorrhagic stroke or stroke of unknown origin Ischaemic stroke in previous 6 months Central nervous system neoplasm Major trauma, surgery, or head injury in previous 3 weeks Bleeding diathesis Active bleeding
	0.6 mg/kg over 15 min (maximum dose 50 mg) ^a	
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Relative Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first post-partum week Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic BP >180 mmHg) Advanced liver disease Infective endocarditis Active peptic ulcer
	Accelerated regimen: 1.5 million IU over 2 h	
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	
	Accelerated regimen: 3 million IU over 2 h	

Changes in recommendations 2014 -19

Recommendations	2014	2019
Rescue thrombolytic therapy is recommended for patients who deteriorate haemodynamically.	IIa	I
Surgical embolectomy or catheter-directed treatment should be considered as alternatives to rescue thrombolytic therapy for patients who deteriorate haemodynamically.	IIb	IIa
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period.	IIb	IIa
Further evaluation may be considered for asymptomatic PE survivors at increased risk for CTEPH.	III	IIb

Duration of anticoagulant treatment

beyond the initial 3-month treatment

- the risk of **recurrent VTE**

versus

- the risk of **major bleeding**

should be assessed

Extended Anticoagulation for VTE

DOAC

→ ≈ 5 (95% CI, 1 to 9) fewer deaths

→ ≈ 4 (95% CI, 1 to 6) fewer VTE-related deaths

→ ≈ 70 (95% CI, 41 to 99) fewer VTE recurrence

→ ≈ 3 (95% CI, -2 to 8) more major bleeding^b

→ ≈ 67 (95% CI, 39 to 94) net clinical benefit
(absence of VTE recurrence or major bleeding)

VKA

→ ≈ 78 (95% CI, 40 to 117) fewer VTE recurrence

→ ≈ 14 (95% CI, 02 to 29) more major bleeding

→ ≈ 63 (95% CI, 20 to 107) net clinical benefit
(absence of VTE recurrence or major bleeding)

Main new recommendations 2019

Treatment in the acute phase	
When oral anticoagulation is initiated in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is the recommended form of anticoagulant treatment.	I
Set-up of multidisciplinary teams for management of high-risk and selected cases of intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in refractory circulatory collapse or cardiac arrest.	IIb

Main new recommendations 2019

Chronic treatment and prevention of recurrence	
Indefinite treatment with a VKA is recommended for patients with antiphospholipid antibody syndrome.	I
Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event.	IIa
Extended anticoagulation should be considered for patients with a persistent risk factor other than anti-phospholipid antibody syndrome.	IIa
Extended anticoagulation should be considered for patients with a minor transient/reversible risk factor for the index PE event.	IIa
A reduced dose of apixaban or rivaroxaban should be considered after the first 6 months.	IIa

2019 ESC /ERS
Guidelines for
the diagnosis &
management of
acute PE

- Anticoagulants reduce the risk of recurrent VTE by 80% - 90% at the cost of a 1% - 3% annual risk of major bleeding
- *The continuation is justified when the annual risk of recurrence is higher than 3% - 5%*

- Anticoagulants reduce the risk of recurrent VTE by **80% - 90%** at the cost of a **1% - 3%** annual risk of **major bleeding**
- *The continuation is justified when the annual risk of **recurrence** is higher than **3% - 5%***
- After withdrawal of anticoagulant treatment the **risk of recurrence** - if anticoagulants are stopped after 6 or 12 months - is **similar** to that after 3 months
- Anticoagulants are discontinued when
the risk of anticoagulation-related **bleeding**
outweighs
the risk of **recurrent** VTE

‘What **to do**’ and ‘what **not to do**’ messages from the Guidelines

Diagnosis
In suspected high-risk PE, perform bedside echocardiography or emergency CTPA (depending on availability and clinical circumstances) for diagnosis.
In suspected high-risk PE, initiate intravenous anticoagulation with UFH without delay, including a weight-adjusted bolus injection.
In suspected PE without haemodynamic instability, use validated diagnostic criteria.
In suspected PE without haemodynamic instability, initiate anticoagulation in case of high or intermediate clinical probability, while diagnostic workup is in progress.
Base the diagnostic strategy on clinical probability, using either clinical judgement or a validated prediction rule.
Measure D-dimers in plasma, preferably with a highly sensitive assay, in outpatients/emergency department patients with low or intermediate clinical probability, or who are PE-unlikely.
Reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or if the patient is PE-unlikely.
Reject the diagnosis of PE (without further testing) if the perfusion lung scan is normal.
Accept the diagnosis of PE if CTPA shows a segmental or more proximal filling defect in a patient with intermediate or high clinical probability.
Accept the diagnosis of VTE if CUS shows a proximal DVT in a patient with clinical suspicion of PE.
Do not measure D-dimers in patients with high clinical probability, as a normal result does not safely exclude PE.
Do not perform CT venography as an adjunct to CTPA.
Do not perform MRA to rule out PE.

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