Venous thromboembolism

Sergio Caravita, MD, PhD

Dyspnea and Pulmonary Hypertension Center, Dept of Cardiology, IRCCS Istituto Auxologico Italiano San Luca Hospital, Milano

Department of Management, Information and Production Engineering, University of Bergamo

sergio.caravita@unibg.it

ESC European Society of Cardiology

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ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

https://www.escardio.org/Guidelines

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Dipartimento di Ingegneria Gestionale, dell'Informazione e della Produzione

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Introduction

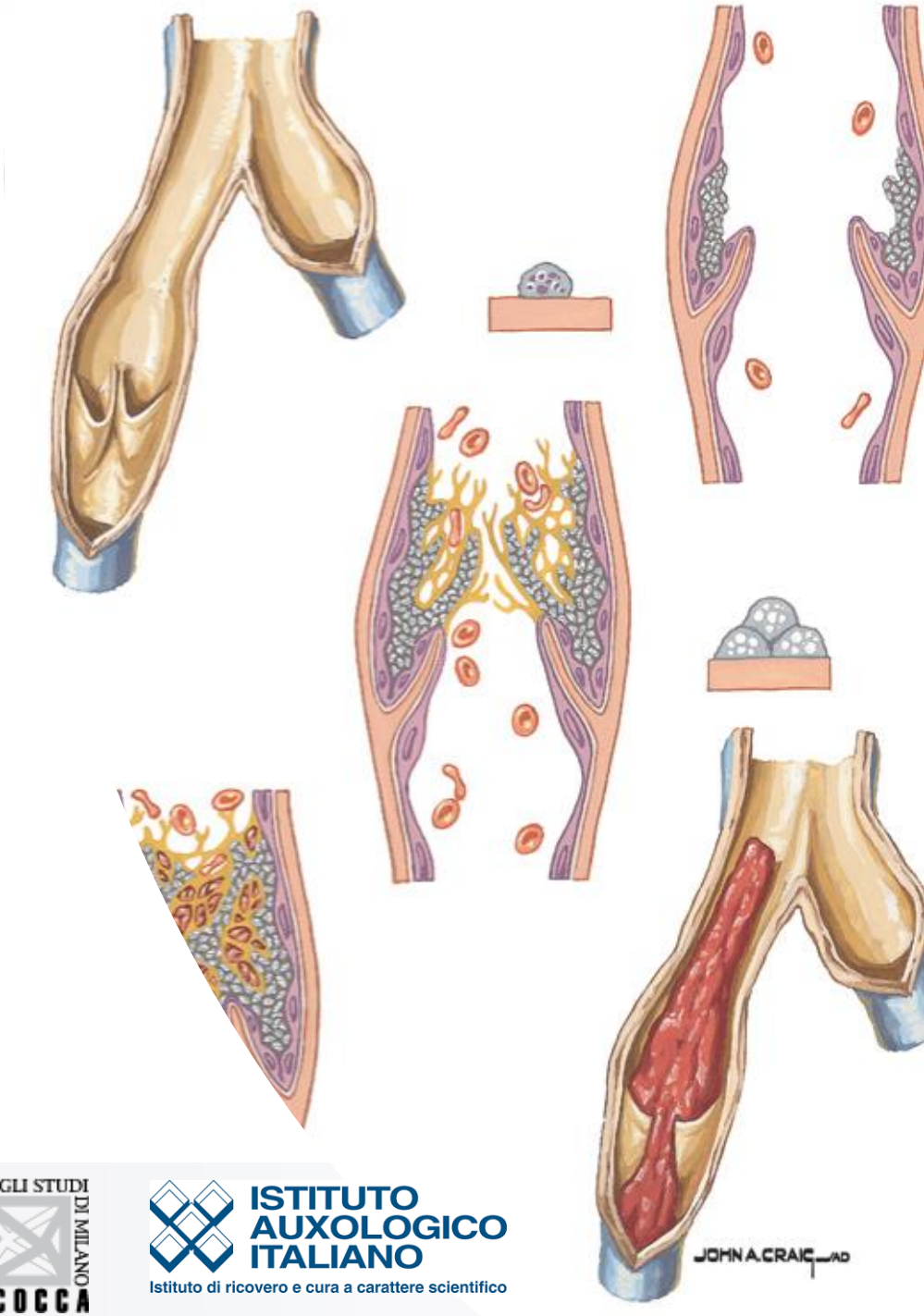
Venous thromboembolism (VTE) encompasses

- deep vein thrombosis (DVT) and
- pulmonary embolism (PE).

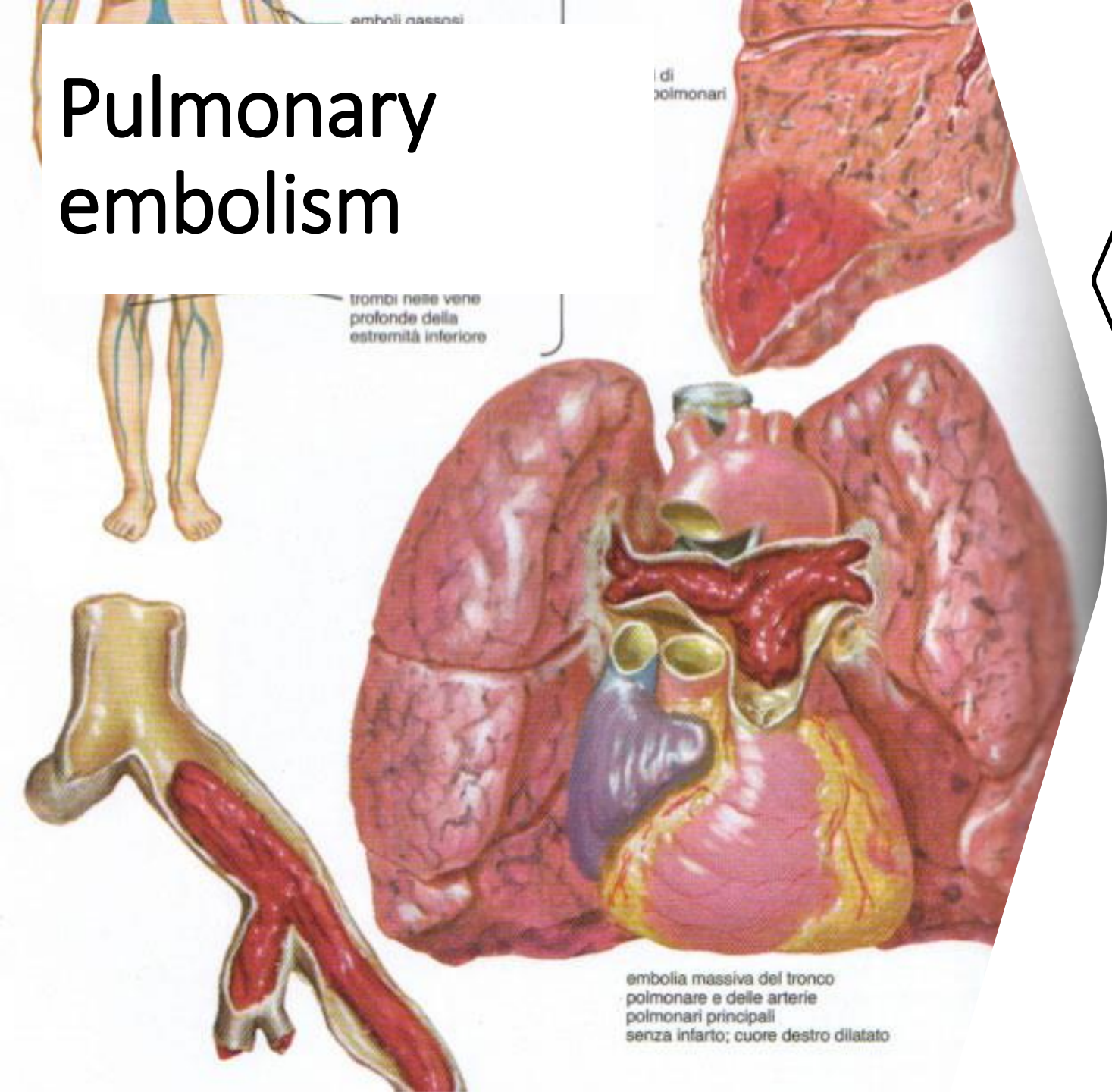
It is the **third most frequent cardiovascular disease** with an overall annual incidence of 100–200 per 100 000 inhabitants.

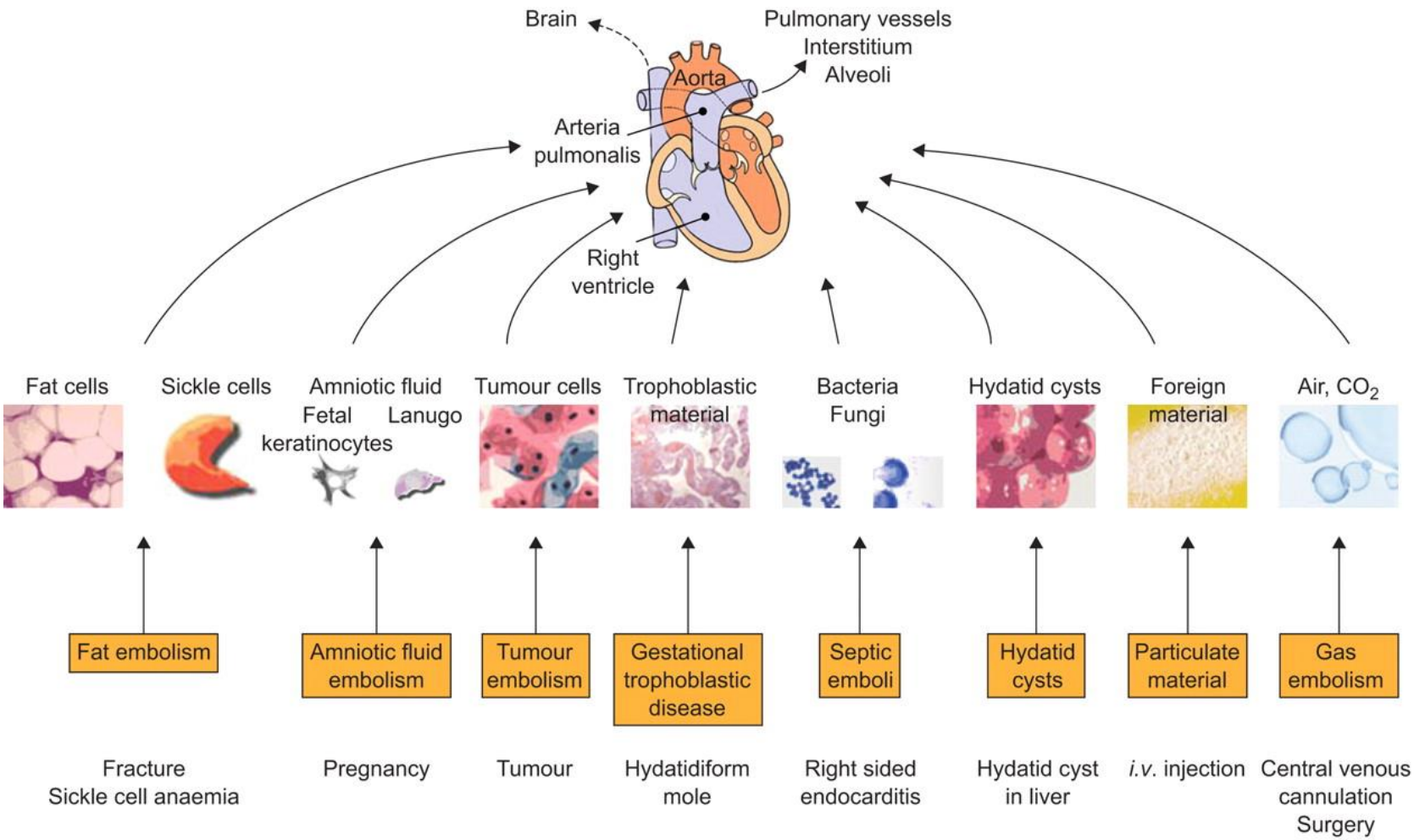
Deep vein thrombosis

- A blood clot that forms in a deep vein, usually the leg, groin or arm

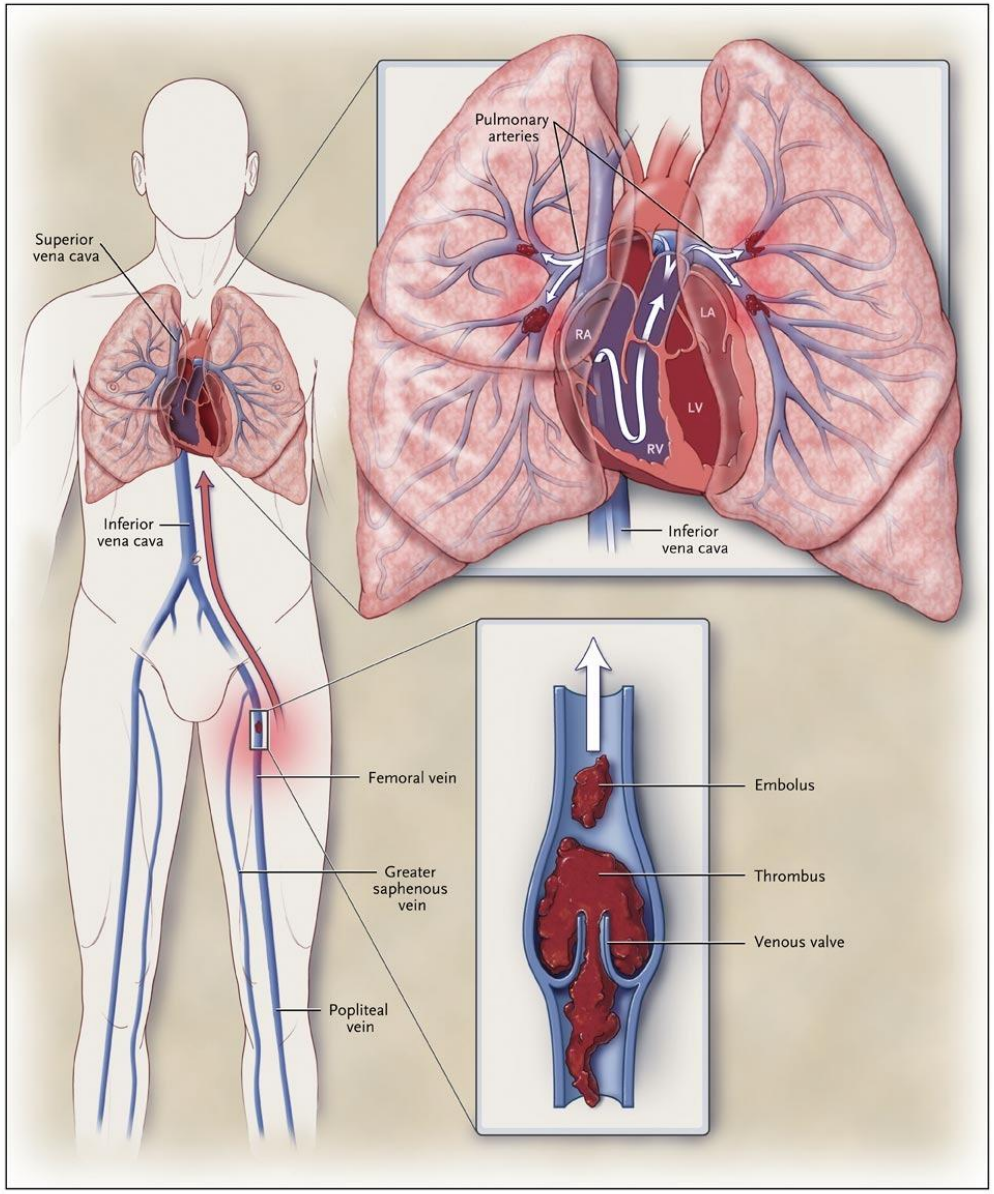


Pulmonary embolism





Jorens PG et al Eur Respir J 2009 34: 452-474

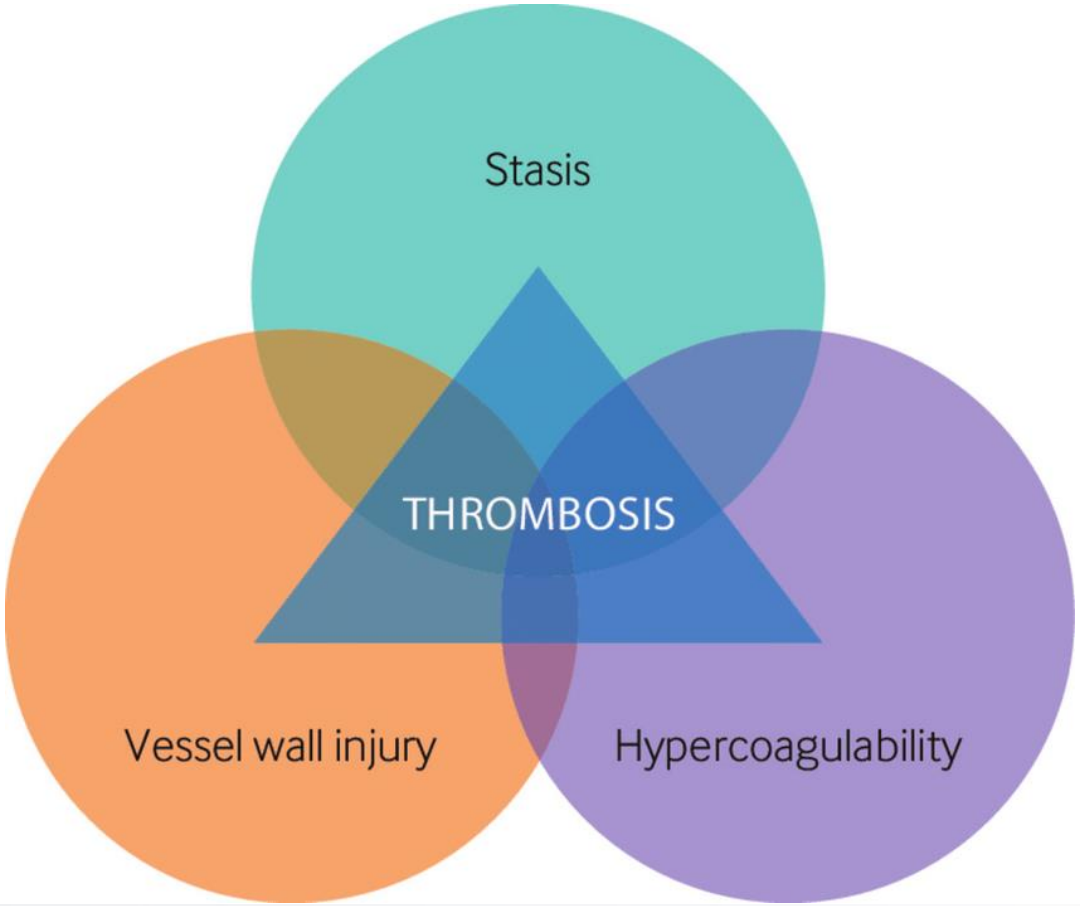


Small PE may pass unperceived, thanks to the pulmonary «filter» (while a small embolus in the systemic circulation can have severe consequences)

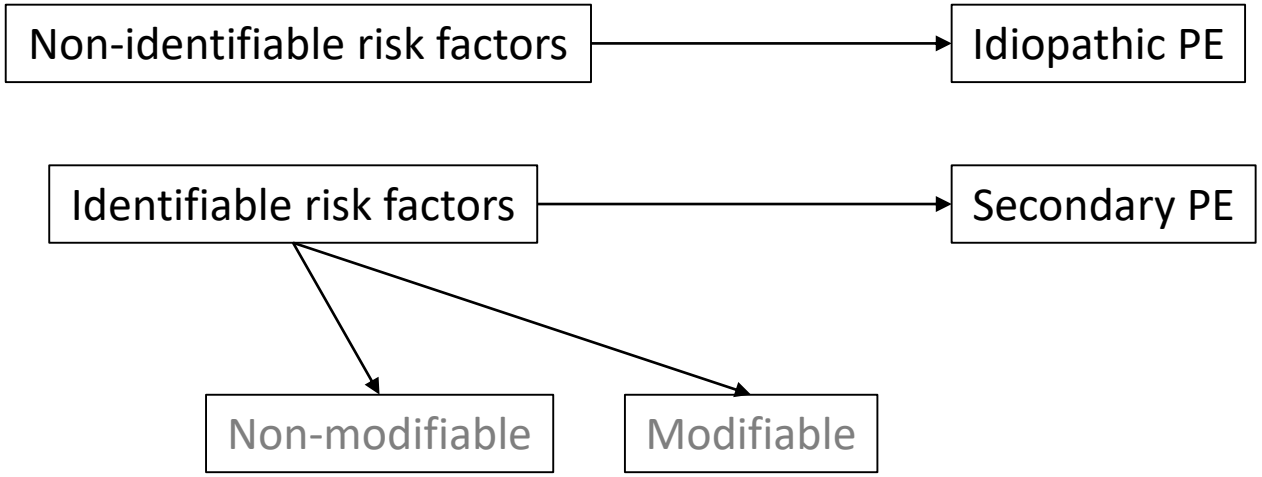
Large PE may give severe symptoms and hemodynamic instability

Tapson VF. N Engl J Med 2008;358:1037-1052.

Virchow's triad



PE, classification



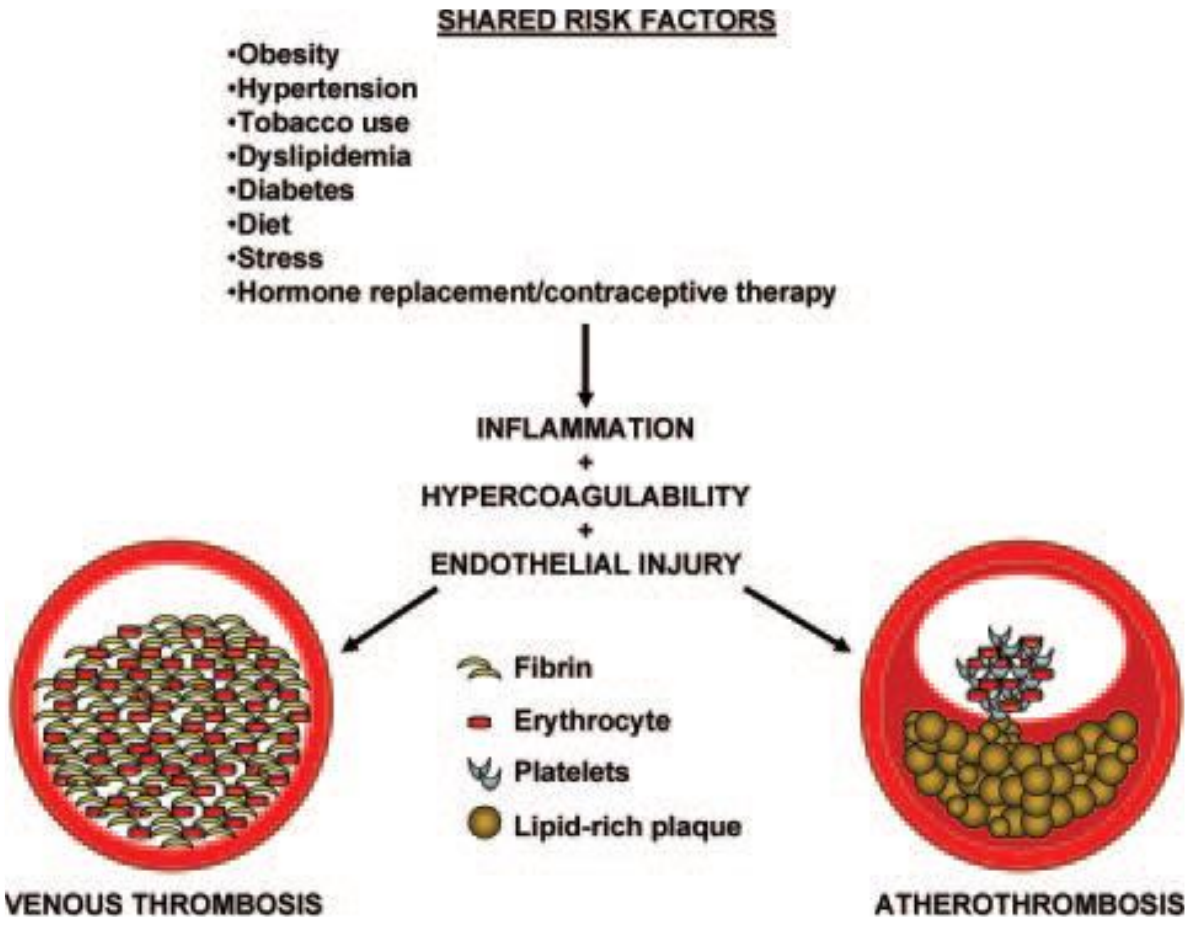
Risk factors

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

Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Auto–immune diseases
Blood transfusion
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Infection (specifically pneumonia, urinary tract infection and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Oral contraceptive therapy
Paralytic stroke
Postpartum period
Superficial vein thrombosis
Thrombophilia

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

Risk factors



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Arterio-venous continuum

Piazza G et al., Circulation 2010

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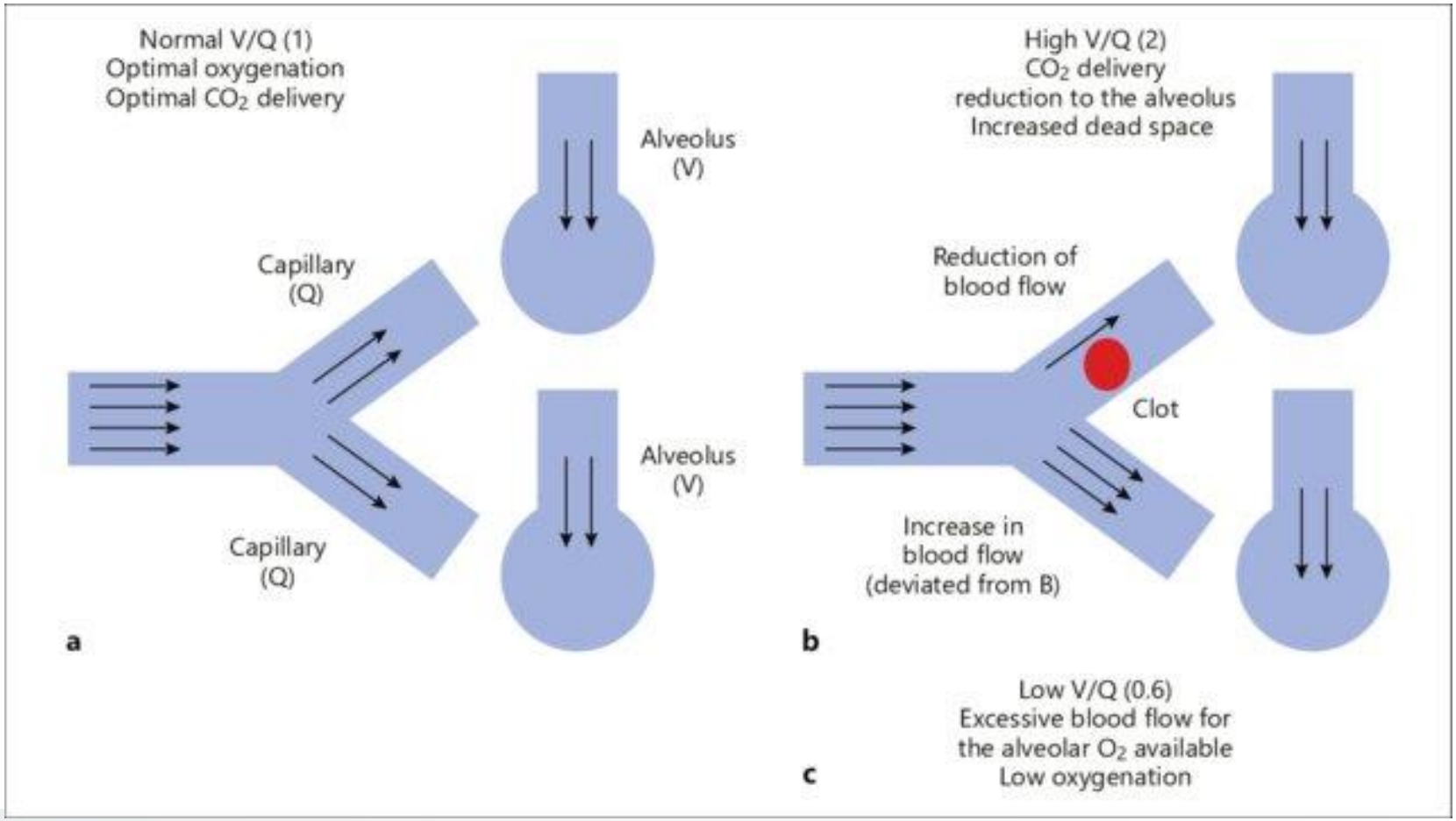
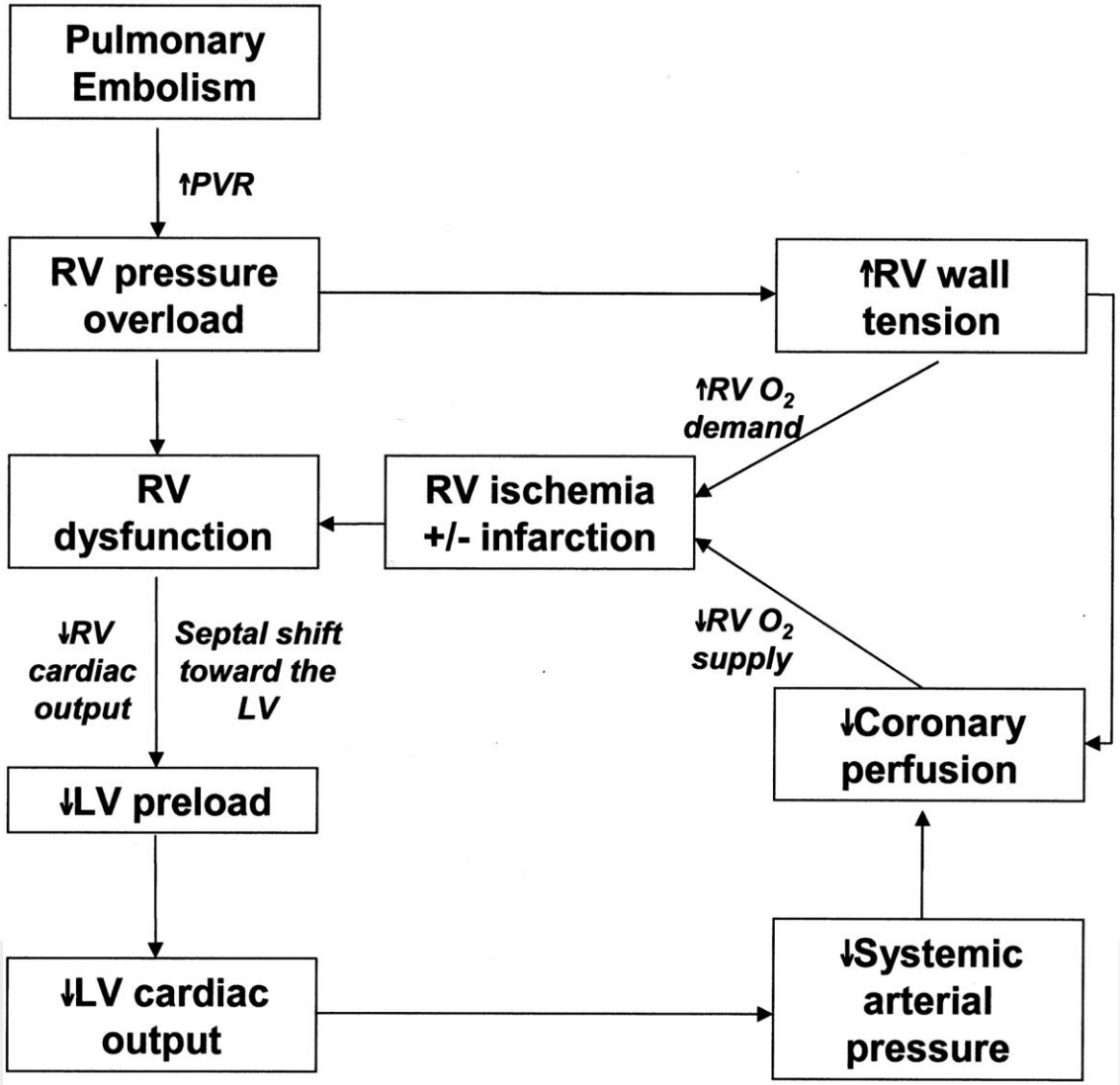
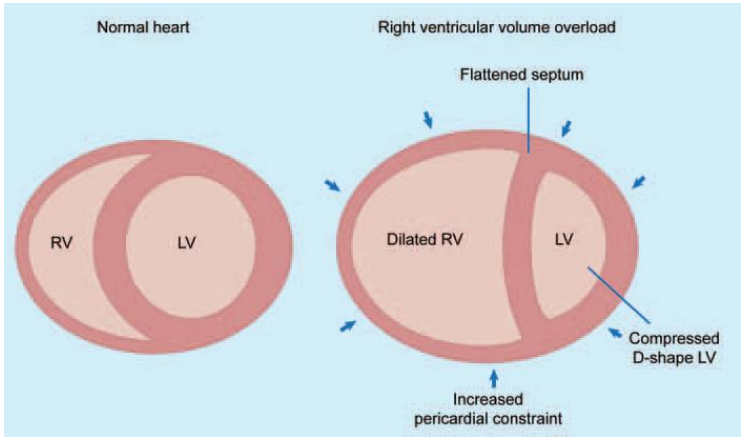
PE consequences: the alveolo-capillary perspective



Respiration 98(3):1-10. DOI: 10.1159/000501342

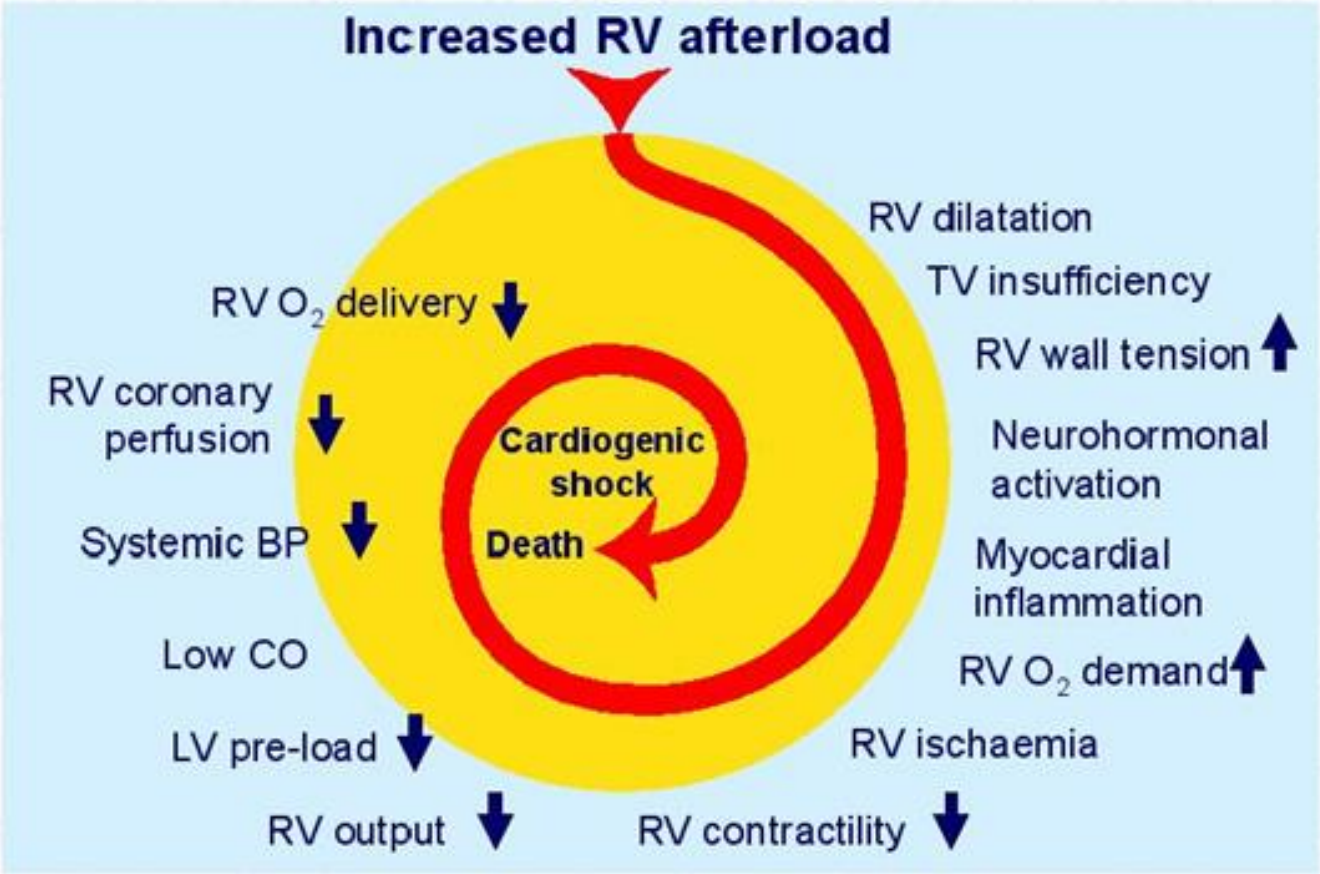
PE consequences: the circulatory perspective





doi.org/10.1161/CIRCULATIONAHA.106.620872

Key factors contributing to haemodynamic collapse in acute pulmonary embolism



BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

PE consequences: symptoms

- **Asymptomatic**
- Dyspnea
- Chest pain (RV ischemia or lung infarction)
- Palpitations
- Pre-syncope / syncope
- Hemoptisis
- Hypotension
- Shock

Aspecific symptoms
➔ Insidiuos condition

PE probability Geneva score

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		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE-unlikely	0–5	0–2
PE-likely	≥6	≥3

Pulmonary embolism: diagnosis
Blood tests

D-dimer (or D dimer) is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis.

In PE, d-dimer is generally high

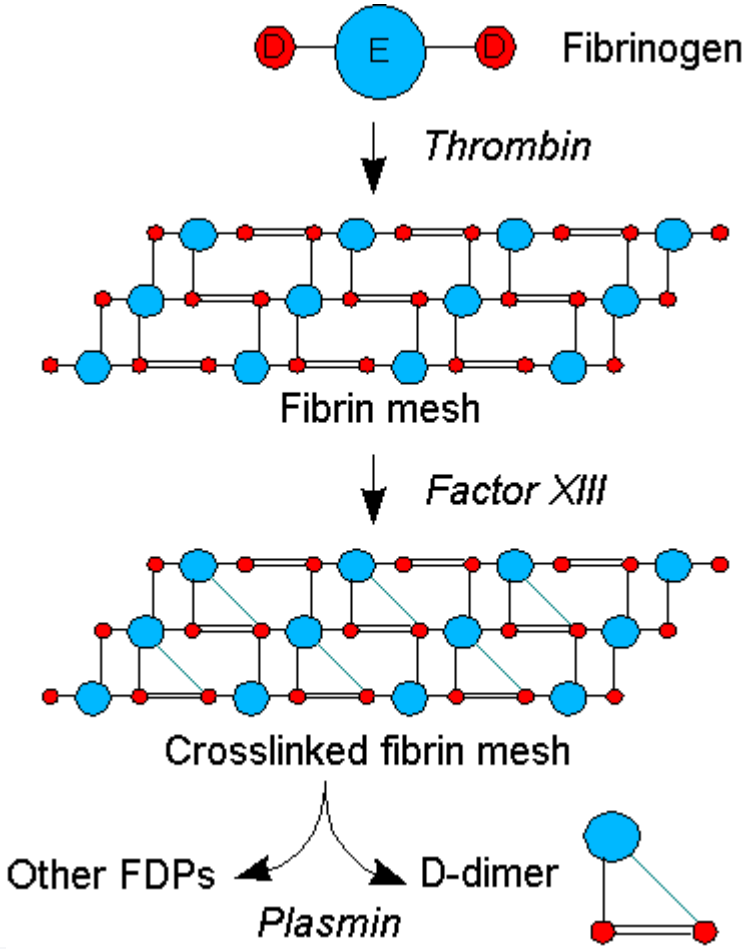
It has a high negative predictive value (low values virtually exclude PE) but a low positive predictive value

D-dimer should be < 500 ng/mL

Age-adjusted cut-offs have been developed to exclude PE in people > 50 years-old, according to the following rule:

Age-adjusted D-dimer cut-off < age x 10

Example: 78 years old person → age-adjusted d-dimer cut-off < 780 ng/mL



Righini M. Et al, JAMA 2014

Pulmonary embolism: diagnosis
Blood tests

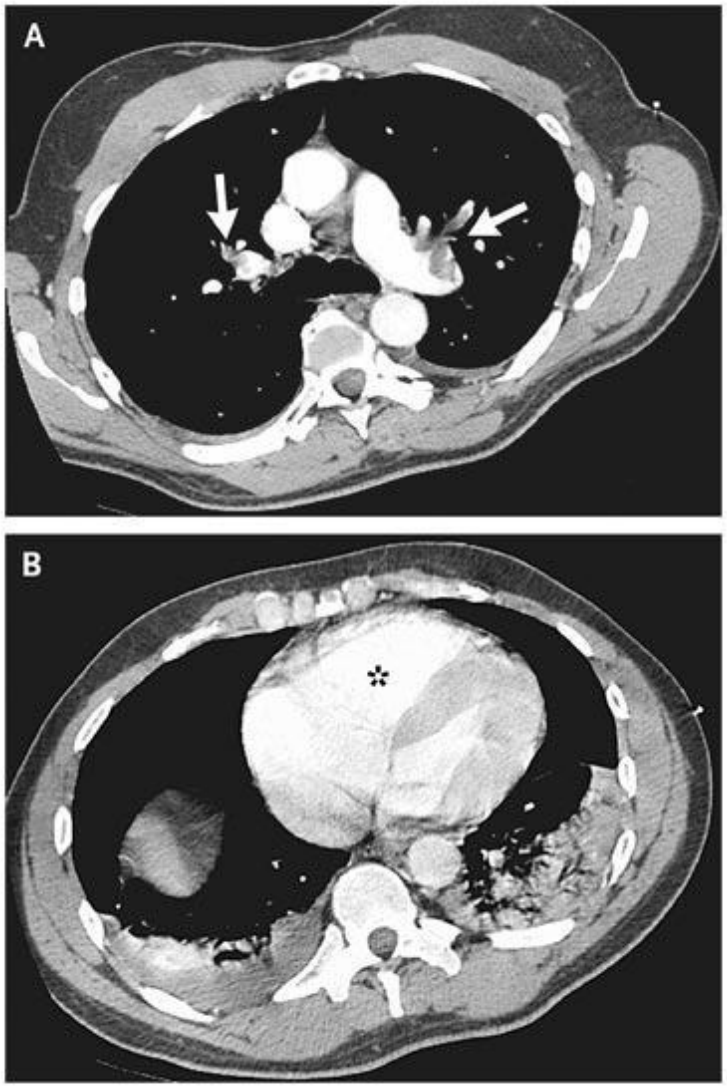
Troponins (cardiac-specific enzymes) and natriuretic peptides can be high, but only if PE is associated with significant right ventricular strain/overload.

Pulmonary embolism: diagnosis
Angio-CT of the chest

Cornerstone for diagnosis:

visualization of thrombi in the pulmonary arteries

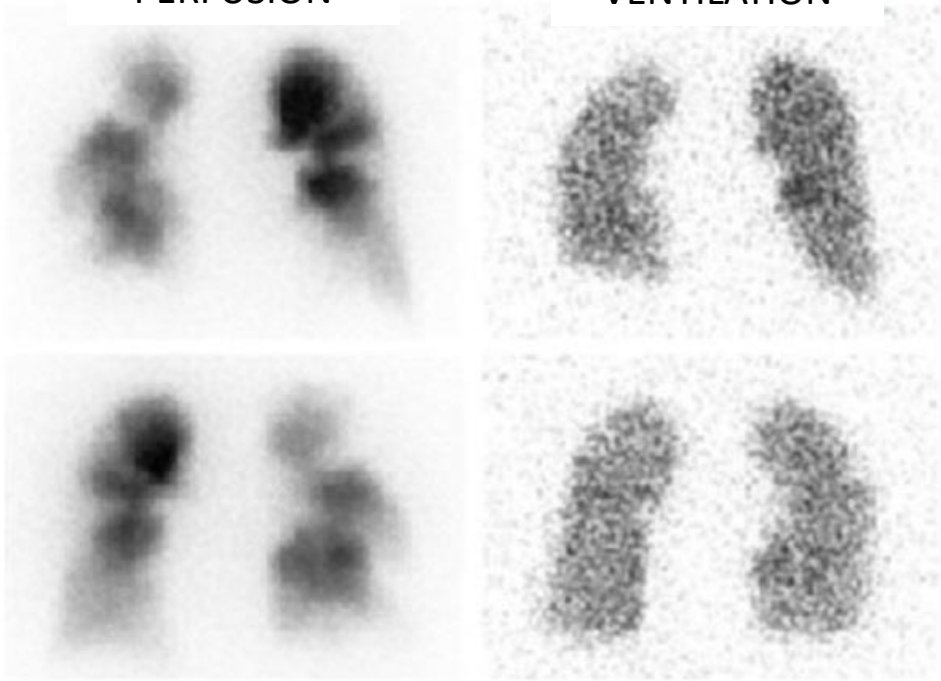
Assessment of signs of RV overload (RV dilation)



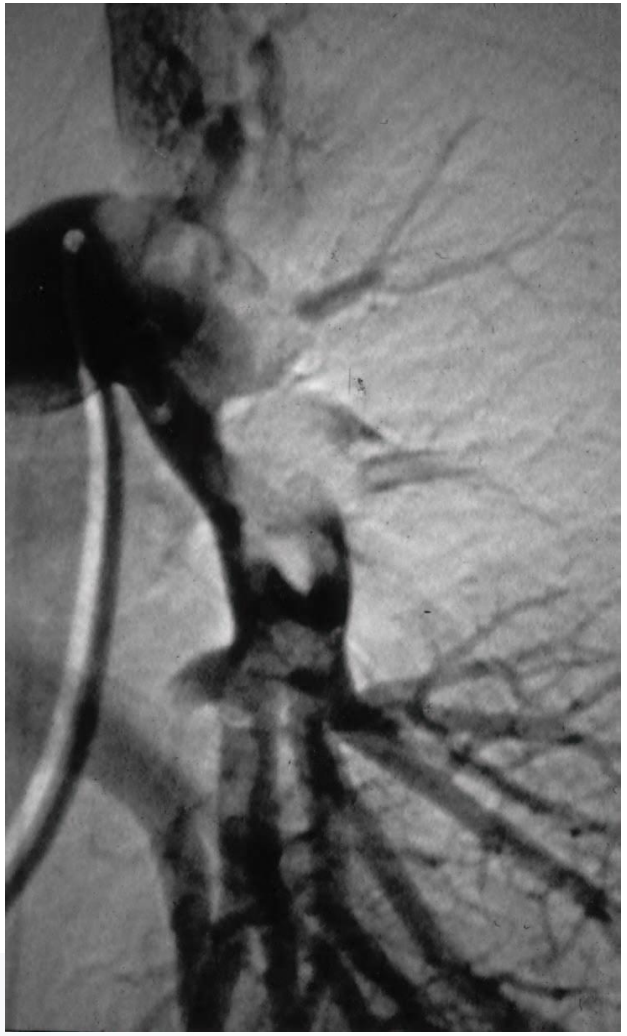
Alternative imaging techniques

V/Q scan (lung scintigraphy)

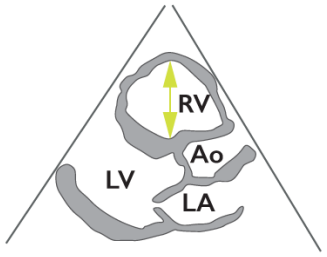
PERFUSION VENTILATION



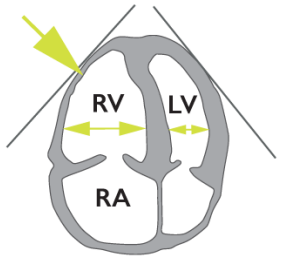
Pulmonary angiography



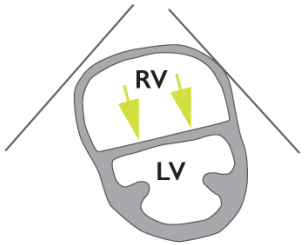
Complementary imaging techniques
Echocardiography



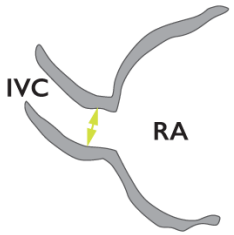
A. Enlarged right ventricle, parasternal long axis view



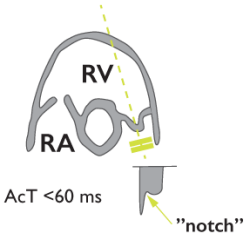
B. Dilated RV with basal RV/LV ratio >1.0, and McConnell sign (arrow), four chamber view

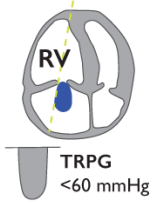


C. Flattened intraventricle septum (arrows) parasternal short axis view

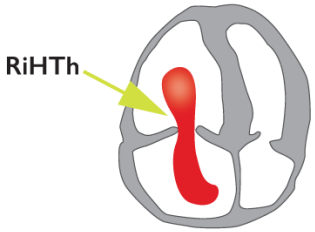


D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view

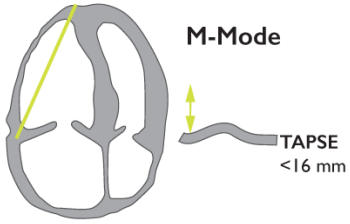




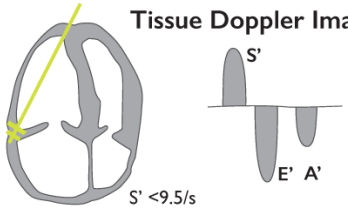
E. 60/60 sign: coexistence of acceleration time of pulmonary ejection <60 ms and midsystolic "notch" with mildy elevated (<60 mmHg) peak systolic gradient at the tricuspic valve



F. Right heart mobile thrombus detected in right heart cavities (arrow)



G. Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<16 mm)

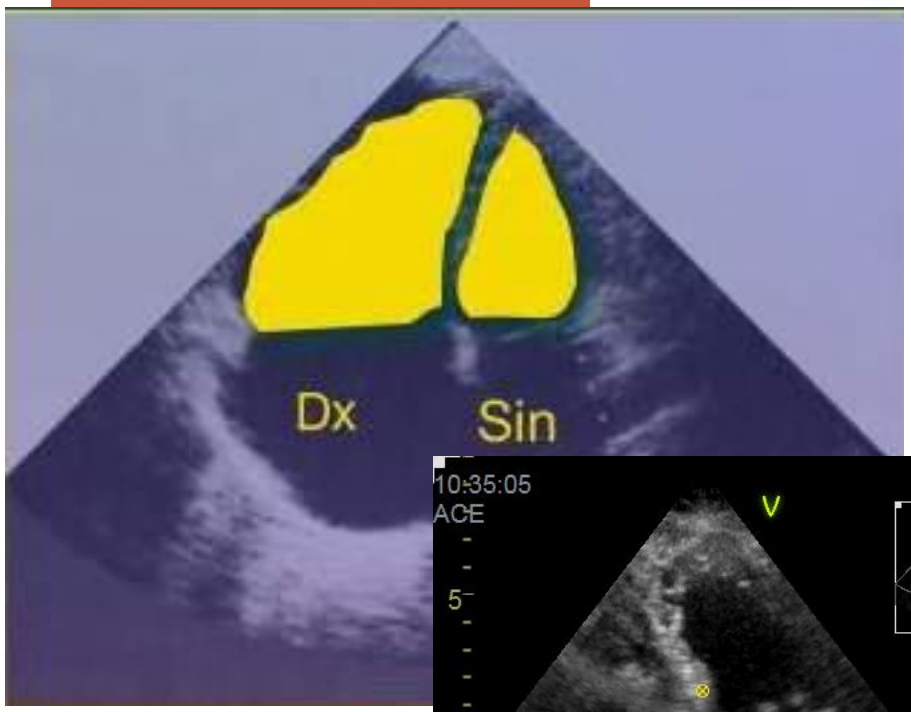


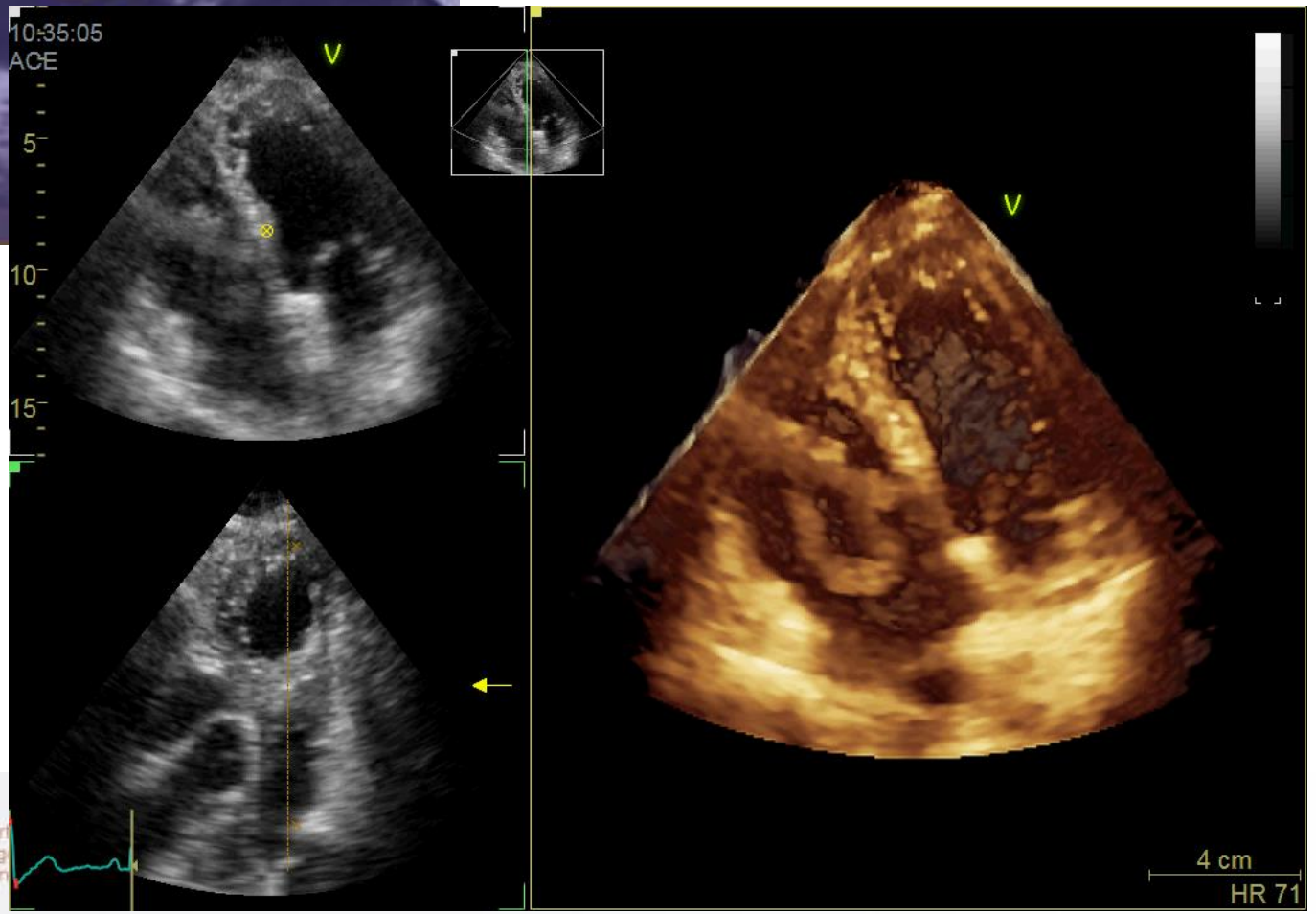
H. Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s)

Indirect clues to diagnosis (right chambers overload)

Severity of PE (compromised RV function → massive PE)

(Low sensitivity)


Dx
Sin


10:35:05
ACE
V
5
10
15
V
4 cm
HR 71

Complementary imaging techniques Echocardiography

Useful in differential diagnosis of causes of hemodynamic instability, such as:

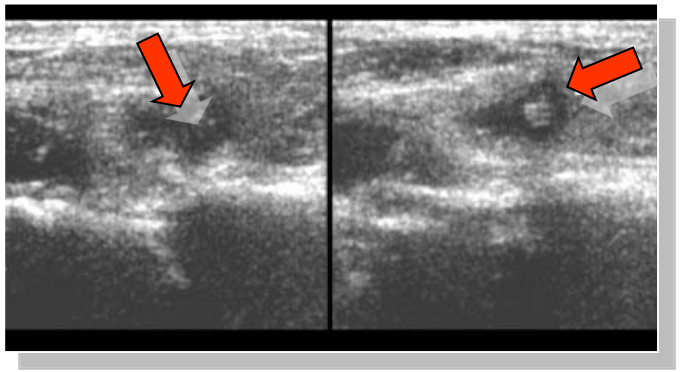
- Cardiac tamponade
- Aortic dissection
- Acute valvular dysfunction
- Hypovolemia
- Myocardial infarction

Complementary imaging techniques Echocardiography

Useful from a pathophysiological perspective for a better assessment of patients' symptoms:

- If pulmonary vascular obstruction is acute and the RV is not preconditioned, PAP will be normal or slightly increased
- It might be «paradoxically» low in case of acute and severe pulmonary vascular obstruction due to afterload mismatch with acute RV failure (acute cor pulmonare) and shock
- Only if the RV is «preconditioned» and pulmonary vascular obstruction is > 30-50%, the RV may generate a sPAP > 60-70 mmHg (e.g. in patients with CTEPH)

Complementary imaging techniques
Duplex ultrasound



Thrombi in the deep veins of the leg

High positive predictive value if PE is suspected

Low negative predictive value

Other findings

EKG :

- sinus tachycardia / atrial tachyarrhytmias,
- RV strain patterns/RV ischemia (e.g. negative T waves V1-V4, complete or incomplete new onset BBD, S1Q3T3)

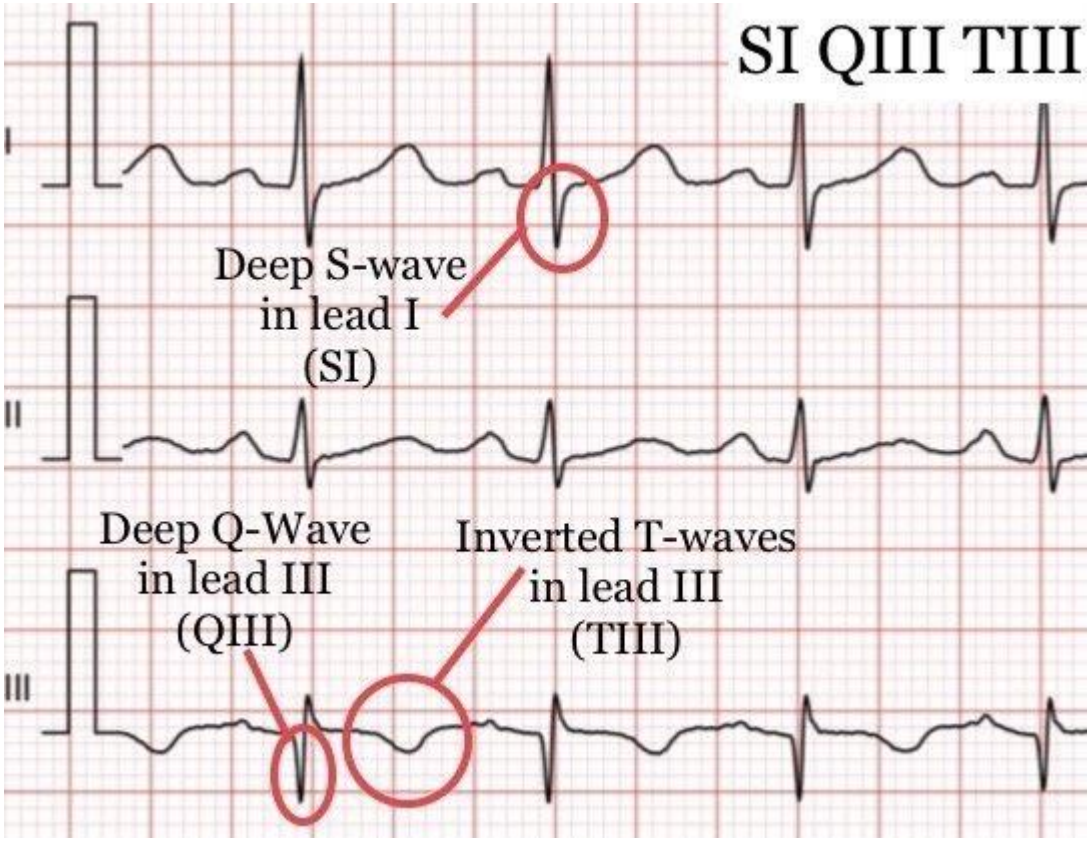
Chest X-ray :

- «paradoxycally» normal (unless other comorbidities are present) despite cardiorespiratory compromise

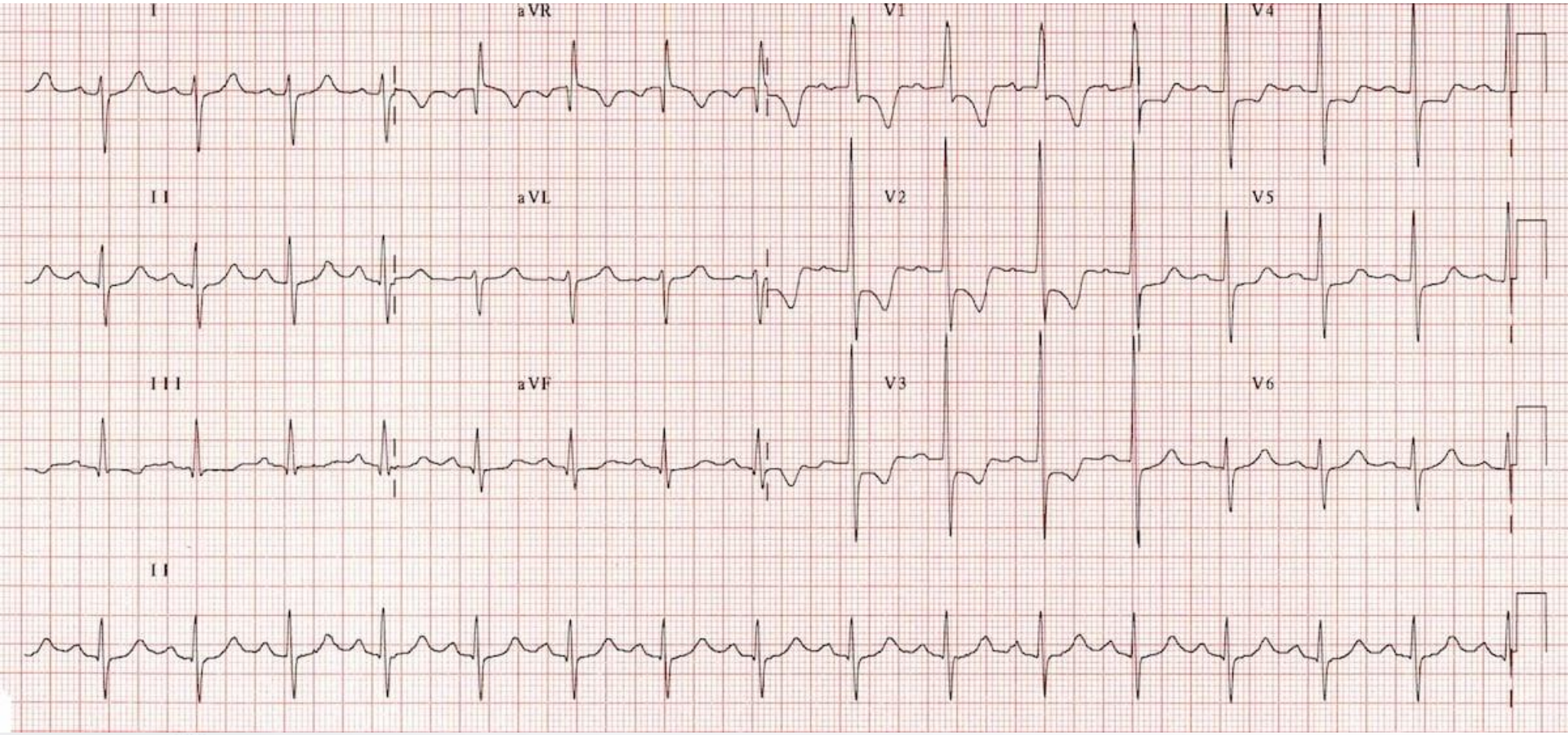
BGA :

- hypocapnic hypoxia (unless other comorbidities are present)

S1Q3T3


SI QIII TIII
I
Deep S-wave
in lead I
(SI)
II
Deep Q-Wave
in lead III
(QIII)
Inverted T-waves
in lead III
(TIII)
III

RV strain



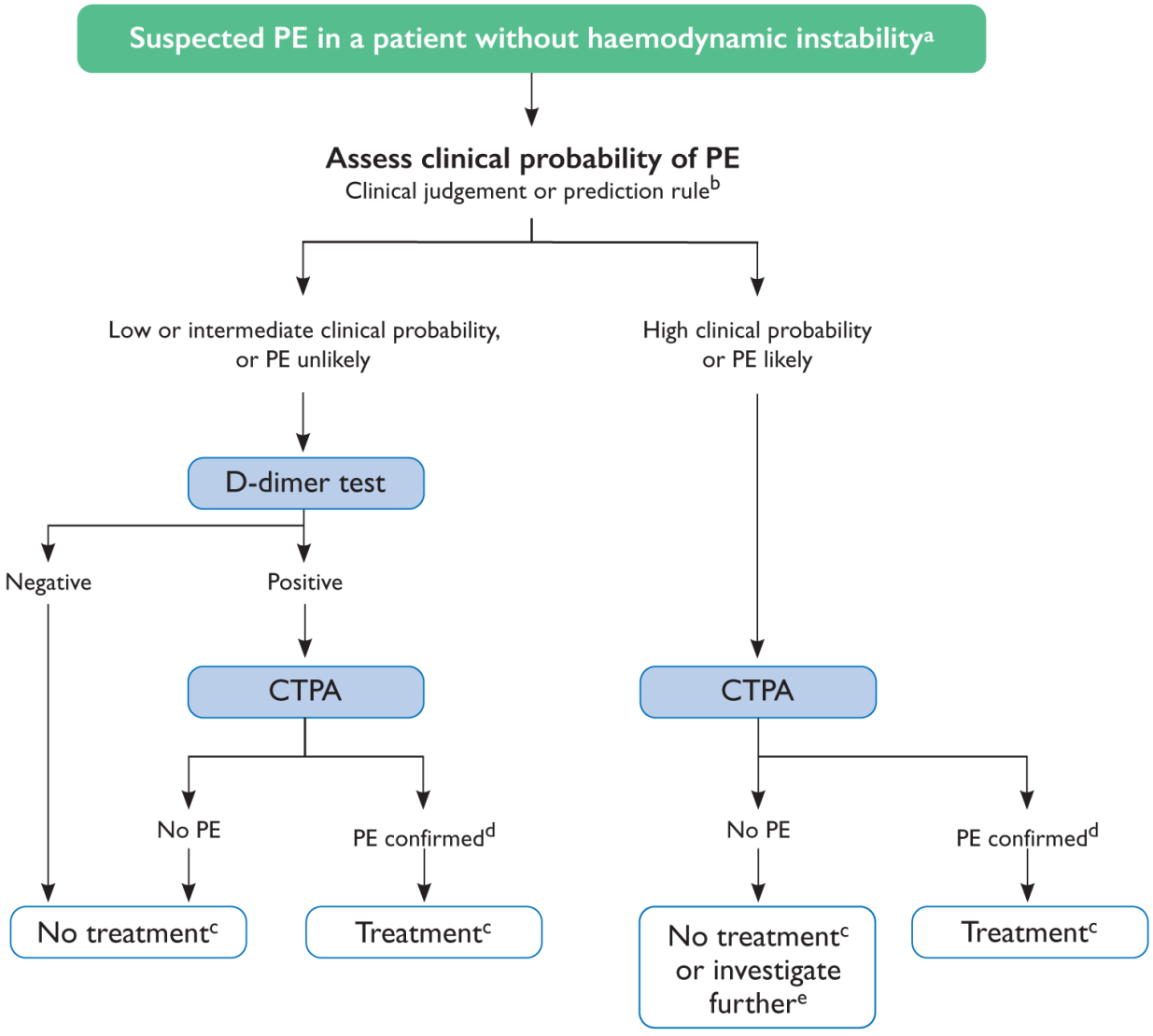
Pulmonary embolism
Diagnostic algorithms

Hemodynamic stability

Hemodynamic instability

https://doi.org/10.1093/eurheartj/ehz405

Diagnostic algorithm



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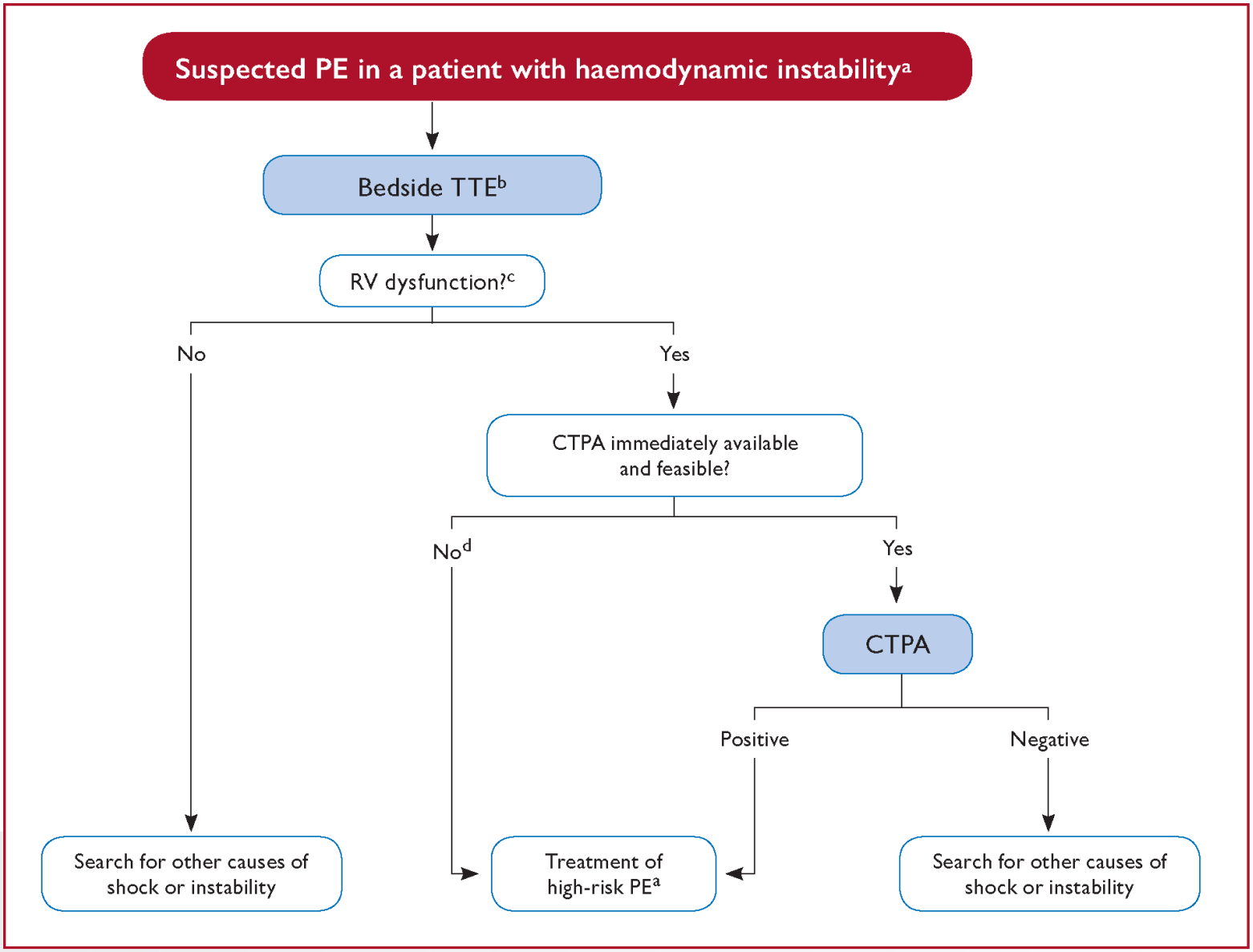

Pulmonary embolism. Risk stratification

Risk of early mortality		Indicatori di rischio			
		Shock or hypotension	Clinical scores, e.g. sPESI≥1	RV overload	
				imaging	biomarkers
High risk		+			
Intermediate risk	intermediate-high	-	+	+	+
	Intermediate-low	-	+	One or none positive	
Low risk		-	-	Optional	

PULMONARY EMBOLISM SEVERITY INDEX (PESI)

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10	–
Cancer	+30	1
Chronic heart failure	+10	1
Chronic pulmonary disease	+10	
Pulse rate ≥110 b.p.m.		
Systolic blood pressure <100		
Respiratory rate >30 breaths		
Temperature <36°C		
Altered mental status		
Arterial oxyhaemoglobin satu		

Original version	Simplified version
Risk strata	
Class I: ≤65 points very low 30-day mortality risk (0-1.6%) **Class II: 66-85 points** low mortality risk (1.7-3.5%)	**0 points** = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%)
Class III: 86-105 points moderate mortality risk (3.2-7.1%) **Class IV: 106-125 points** high mortality risk (4.0-11.4%) **Class V: >125 points** very high mortality risk (10.0-24.5%)	**≥1 point(s)** = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

The validation and reproducibility of the Pulmonary Embolism Severity Index, Chan CM et al, J Throm Haemost 2010, 8:1509-1514.

The RV in risk stratification

Echocardiography

- RV dilation
- RV dysfunction
- Thrombus in transit in right heart chamber

Chest CT

- RV dilation

Blood test

- High NTproBNP / BNP
- High Troponins

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Low risk		-	-	Optional	

Risk of mortality → treatment

Risk of early mortality		Treatment
High risk		Primary reperfusion*
Intermediate risk	Intermediate-high	Anticoagulant treatment; monitoring; «rescue» reperfusion*
	Intermediate-low	Anticoagulant treatment; hospitalization
Low risk		Anticoagulant treatment; rapid hospital discharge

***Reperfusion**: fibrinolytic drugs; surgical or percutaneous embolectomy

Supportive treatment
high risk PE with hemodynamic instability

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO[239]
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 μg/kg/min[a] [240]	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 μg/kg/min[241]	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias
Mechanical circulatory support		
Veno–arterial ECMO/extracorporeal life support[251,252,258]	Rapid short-term support combined with oxygenator	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team

Treatment of pulmonary embolism

Respiratory supporrt (oxygen, non invasive or mechanical ventilation)

Hemodynamic support (vasopressors)

Anticoagulant therapy

Inhibition of thrombus growth	Acceleration of thrombolysis	Prevention of recurrences
Anticoagulant therapy	*Fibrinolytic therapy*	*Oral anticoagulant therapy; vena cava filters*

Medical treatment

Fibrinolytic drugs (in high risk patients)

- Recombinant tissue plasminogen activator (rTPA)

Anticoagulant drugs

- Parenteral anticoagulation
  - Subcutaneous low molecular weight heparin (need to adjust for kidney function)
  - Unfractioned heparin (need to monitor APTT)
- Oral anticoagulation
  - Vitamin K antagonists (warfarin, acenocumarol: need to monitor INR)
  - Direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban)

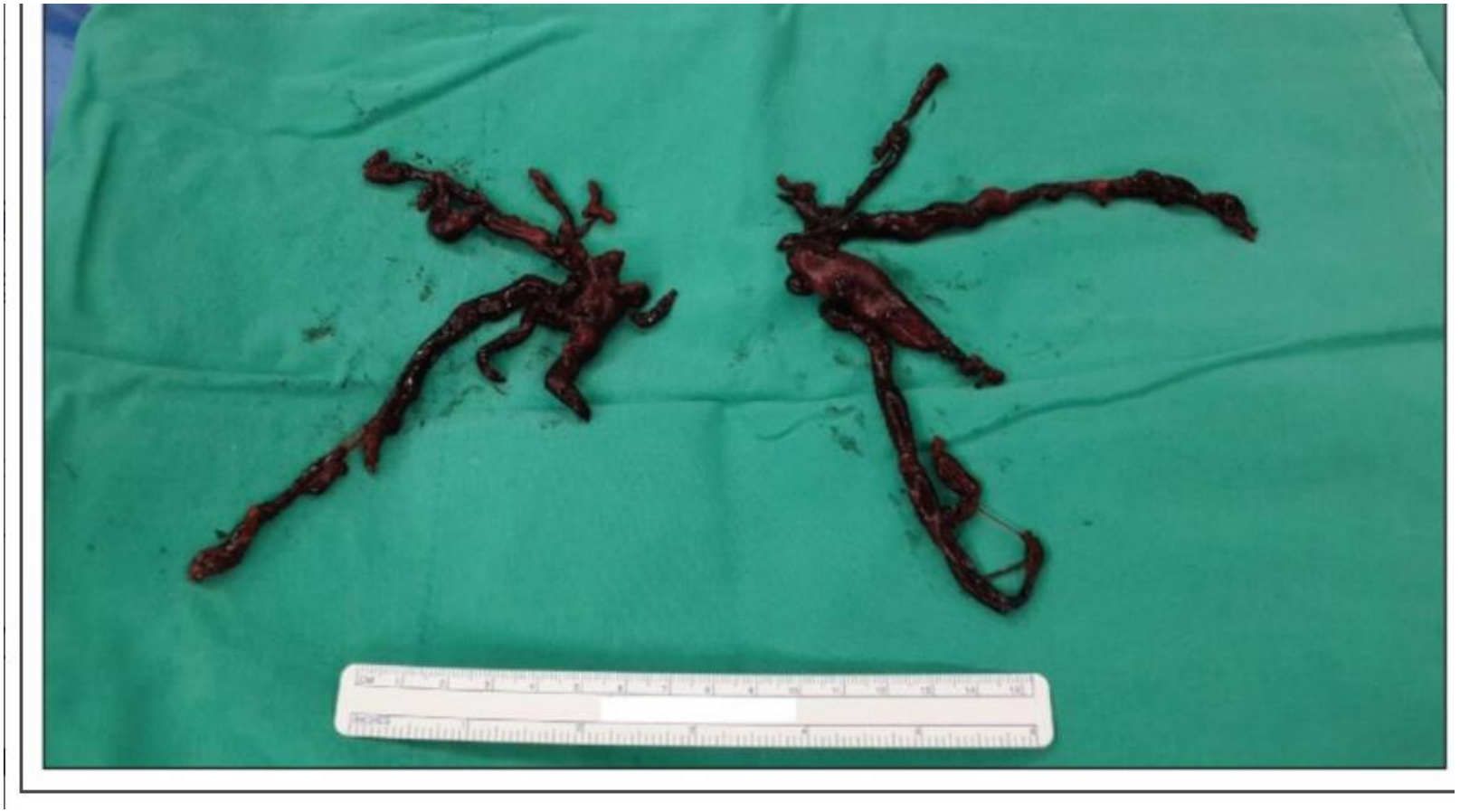
Thrombolytic regimens, doses and contraindications

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute**
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]	History of haemorrhagic stroke or stroke of unknown origin
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Ischaemic stroke in previous 6 months
	Accelerated regimen: 1.5 million IU over 2 h	Central nervous system neoplasm
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 3 million IU over 2 h	Bleeding diathesis
		Active bleeding
		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

BP = blood pressure; IU = international units; rtPA, recombinant tissue-type plasminogen activator.

[a]This is the accelerated regimen for rtPA in pulmonary embolism; it is not officially approved, but it is sometimes used in extreme haemodynamic instability such as cardiac arrest.

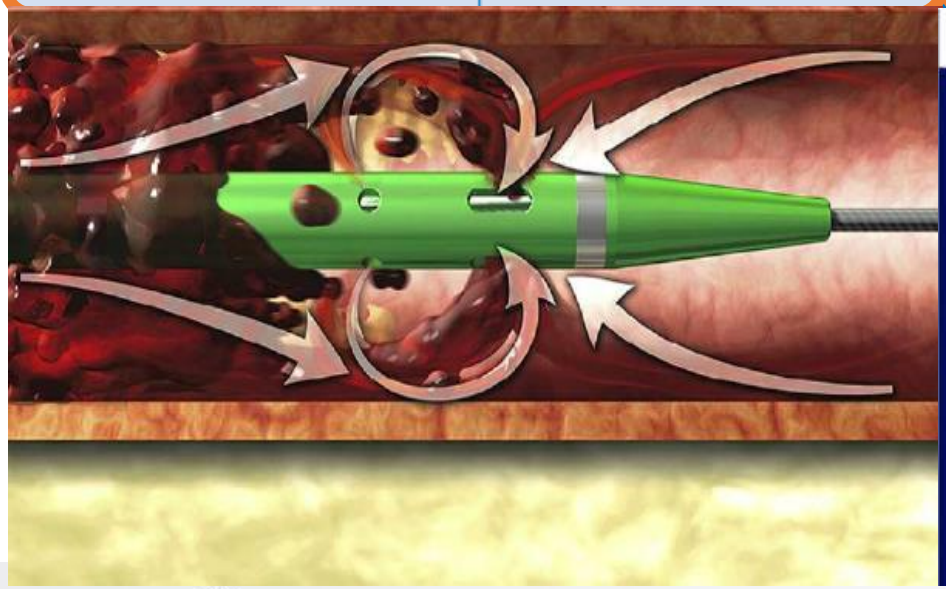
Surgical embolectomy

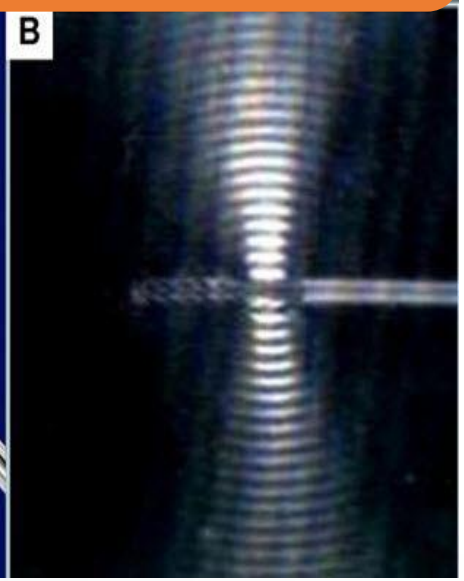


Rarely performed and only in high risk patients

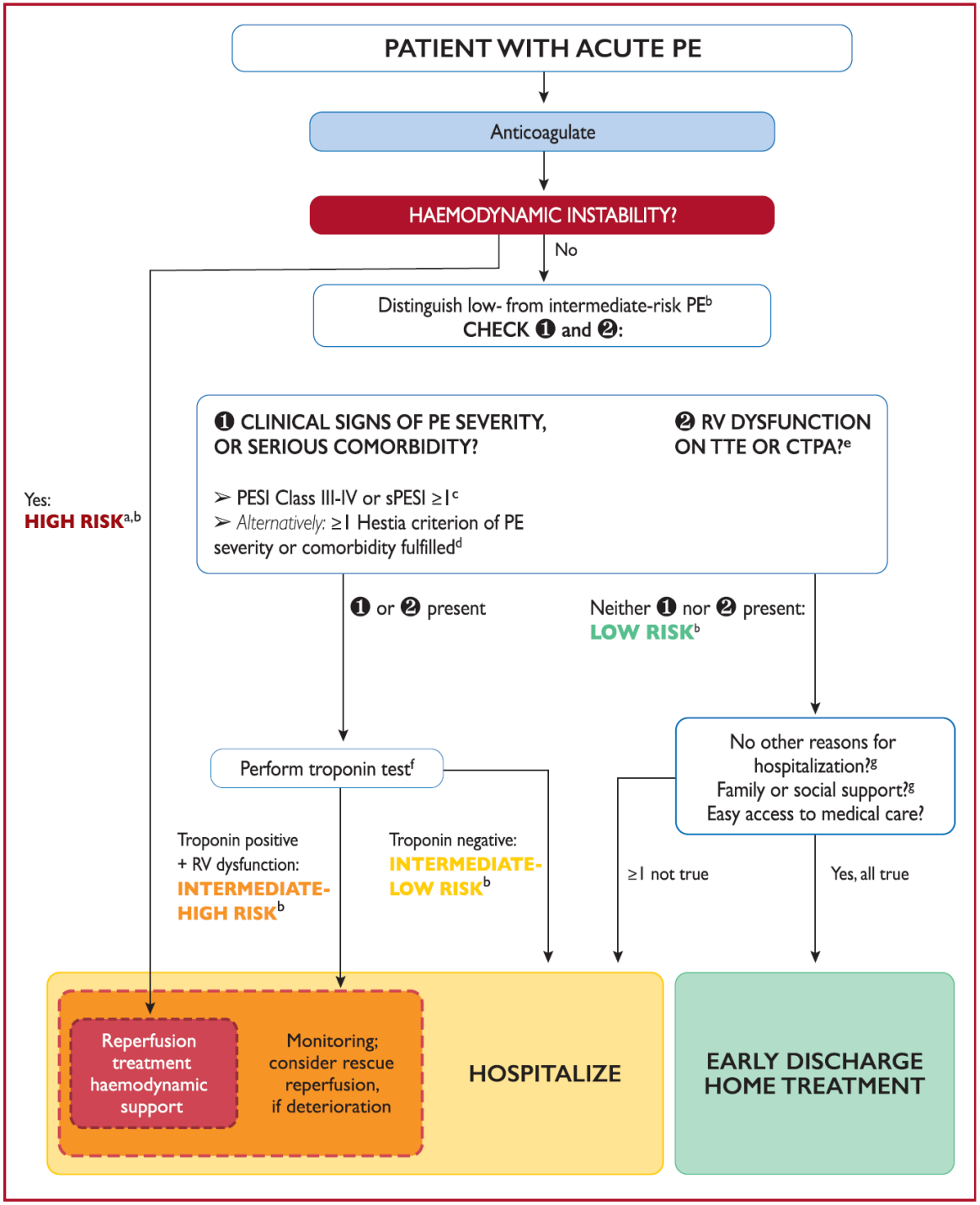
Percutaneous embolectomy

Catheter interventions without local thrombolysis		Catheter interventions with local thrombolysis	
Technique	**Device examples**	**Technique**	**Device examples**
Thrombus fragmentation	Pigtail catheter fragmentation Balloon angioplasty using peripheral balloon catheters	Catheter-directed thrombolysis (continuous infusion with or without bolus)	UniFuse® (AngioDynamics, Latham, NY, US) Cragg-McNamara® (ev3 Endovascular, Plymouth, MN, USA)
Rheolytic thrombectomy	AngioJet 6 F PE® (Bayer, Germany)	Ultrasound-assisted catheter-directed thrombolysis (continuous infusion with or without bolus)	EkoSonic® (EKOS, Bothell, WA, USA)





Kuo WT; J Vasc Interv Radiol 2009


PATIENT WITH ACUTE PE
Anticoagulate
HAEMODYNAMIC INSTABILITY?
No
Yes:
HIGH RISK[a,b]
Distinguish low- from intermediate-risk PE[b]
CHECK ❶ and ❷:
❶ CLINICAL SIGNS OF PE SEVERITY, OR SERIOUS COMORBIDITY?
➢ PESI Class III-IV or sPESI ≥1[c]
➢ Alternatively: ≥1 Hestia criterion of PE severity or comorbidity fulfilled[d]
❷ RV DYSFUNCTION ON TTE OR CTPA?[e]
❶ or ❷ present
Neither ❶ nor ❷ present:
LOW RISK[b]
Perform troponin test[f]
No other reasons for hospitalization?[g]
Family or social support?[g]
Easy access to medical care?
Troponin positive
+ RV dysfunction:
INTERMEDIATE-HIGH RISK[b]
Troponin negative:
INTERMEDIATE-LOW RISK[b]
≥1 not true
Yes, all true
Reperfusion treatment haemodynamic support
Monitoring; consider rescue reperfusion, if deterioration
HOSPITALIZE
EARLY DISCHARGE
HOME TREATMENT

Pulmonary embolism: prognosis

Mortality:

- At one month: 10%
- At two months: 10-20%

Thanks to anticoagulant therapy, PE completely resolves in 3-6 months

- Small, clinically meaningless lung perfusion defects can be evident in about 35% of patients
- Large, clinically relevant lung perfusion defects can persist in about 1% of patients, leading to chronic thromboembolic pulmonary hypertension

Pulmonary embolism: prognosis

Risk of recurrences:

- About 4.5% per year in idiopathic PE → 5 years recurrence as high as 20-30%

Favorable prognosis:

- Negative d-dimer one month after discontinuation of anticoagulant therapy

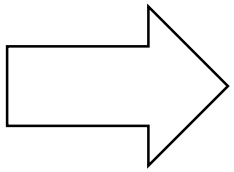
Medical treatment

Fibrinolytic drugs

- Recombinant tissue plasminogen activator (rTPA)

Anticoagulant drugs

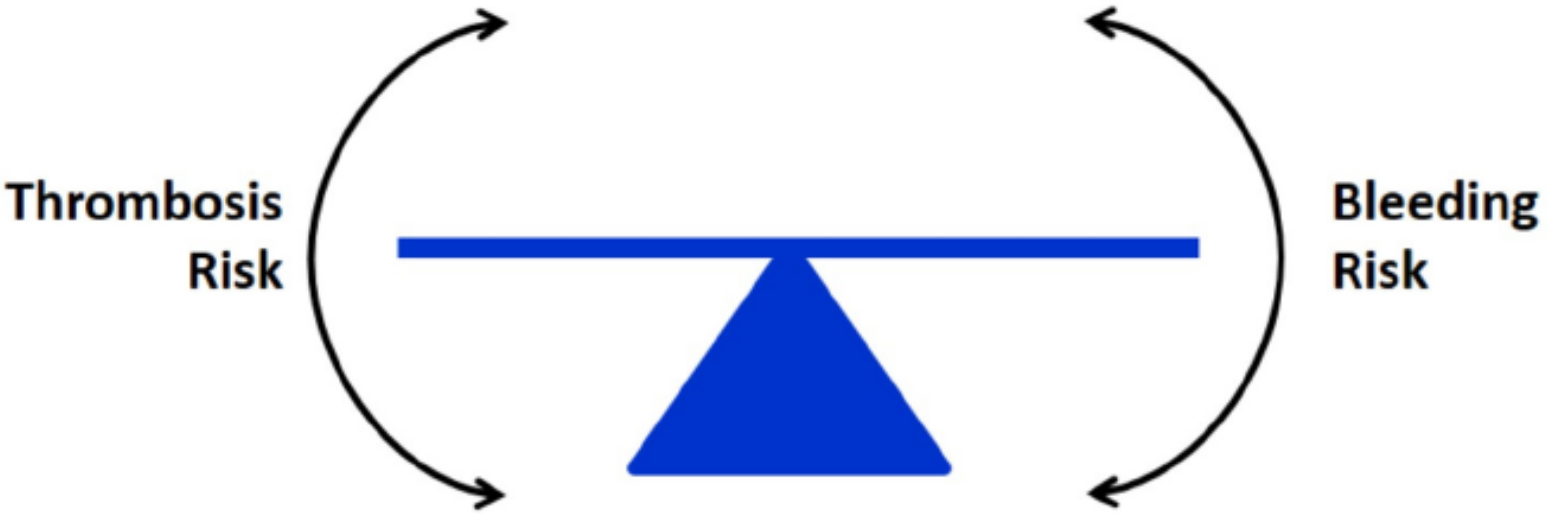
- Parenteral anticoagulation
  - Low molecular weight heparin
  - Unfractioned heparin
- Oral anticoagulation
  - Vitamin K antagonists
  - Direct oral anticoagulants



To be continued for at least 3-6 months after the acute event

The decision on the duration of anticoagulant therapy after PE is based on balancing the estimated risk of recurrences and the bleeding risk

PE
prognosis and long-term management

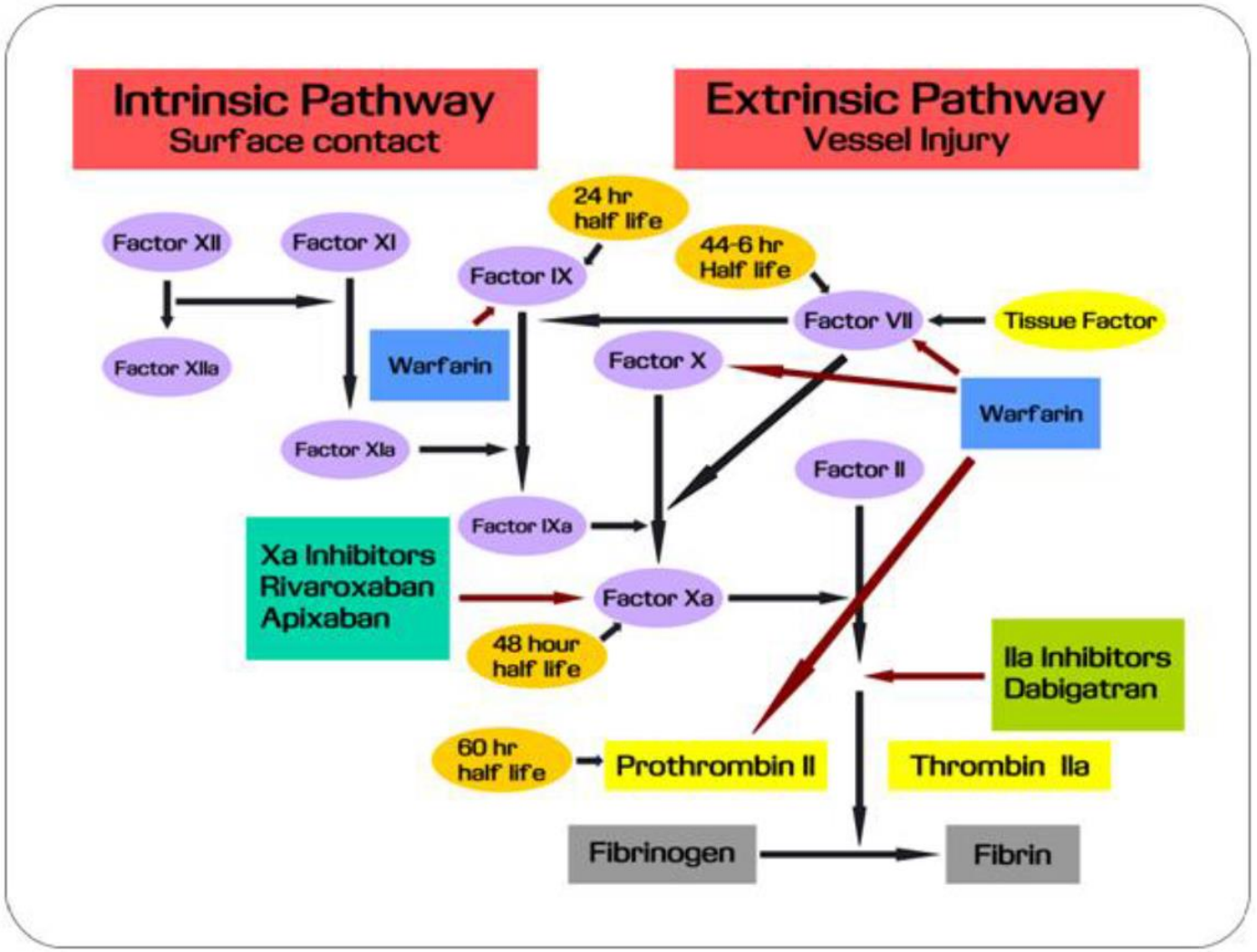


Long-term maintenance of anticoagulation is an individualized decision, based on estimated risk of recurrence of PE, perceived risk of bleeding and patients' preference.

Risk factors for PE recurrence

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

	Advantages	Disadvantages
VKA	▶ Mainstay of therapy since 1960[1] ▶ Can be used in severe renal impairment[2] ▶ Anticoagulation can be reversed[2]	▶ Slow onset/offset requires bridging[1] ▶ Numerous interactions (drugs and food)[1] ▶ Narrow therapeutic window[1] ▶ Inter-individual variability in dose response[1] ▶ Need for INR monitoring[1,2]
NOACs	▶ Predictable pharmacological profiles[1] ▶ No major interactions (food or drugs)[1] ▶ Do not require routine level monitoring[1] ▶ ACCP update recommending preferential use over VKA3	▶ No readily available monitoring for special circumstances (e.g. major bleeding, urgent procedure) ▶ No reversal agent for most (NB dabigatran) ▶ No long term data


Intrinsic Pathway
Surface contact
Extrinsic Pathway
Vessel Injury
24 hr
half life
44-6 hr
Half life
Factor XII
Factor XI
Factor IX
Factor VII
Tissue Factor
Factor XIIa
Warfarin
Factor X
Warfarin
Factor XIa
Factor II
Factor IXa
Xa Inhibitors
Rivaroxaban
Apixaban
Factor Xa
48 hour
half life
IIa Inhibitors
Dabigatran
60 hr
half life
Prothrombin II
Thrombin IIa
Fibrinogen
Fibrin

Apixaban

- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[1]
- Recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery[2]

Rivaroxaban

- Recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults[3,4]
- Recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery[5]

Dabigatran

- Recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery[6]
- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[7]

Edoxaban

- Recommended as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults[8]

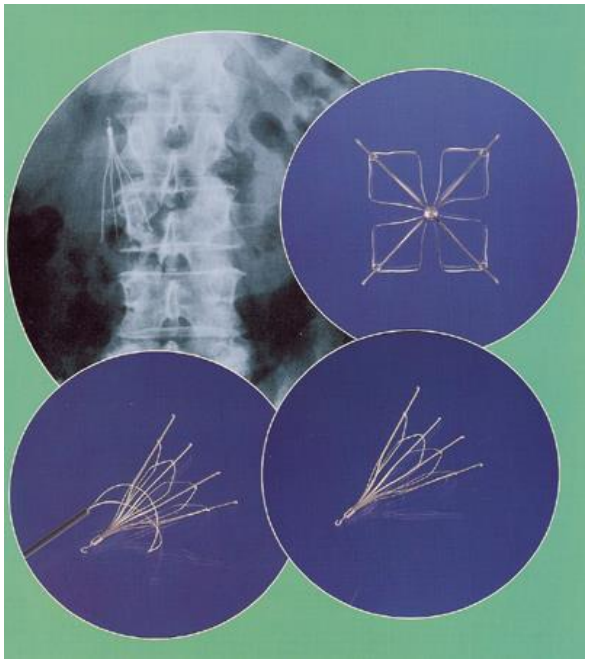
DOAC
Drug-drug interactions

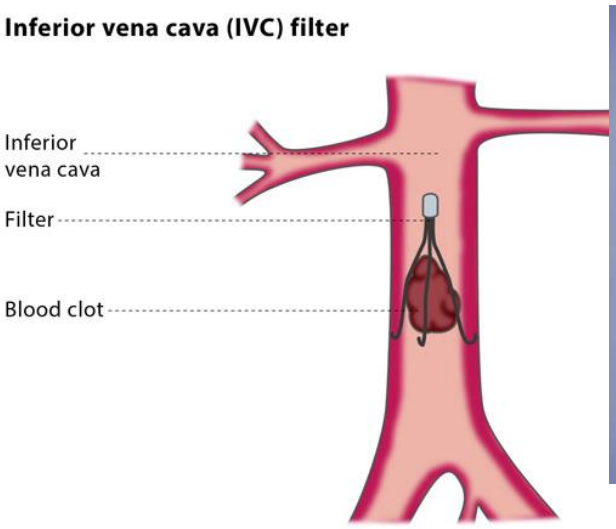
		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

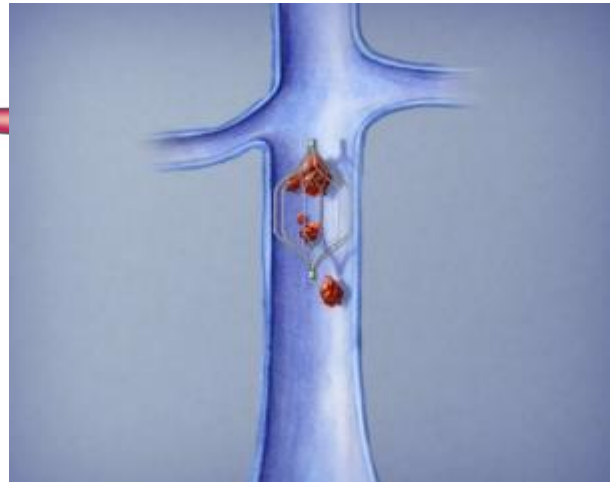
DOAC
Drug-drug interactions

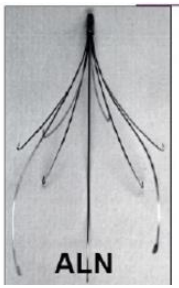
	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%	no data	no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12-30%	no data	no effect	no effect

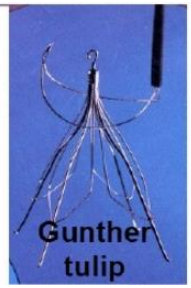
Inferior vena cava filters

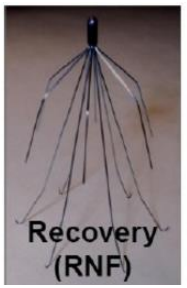




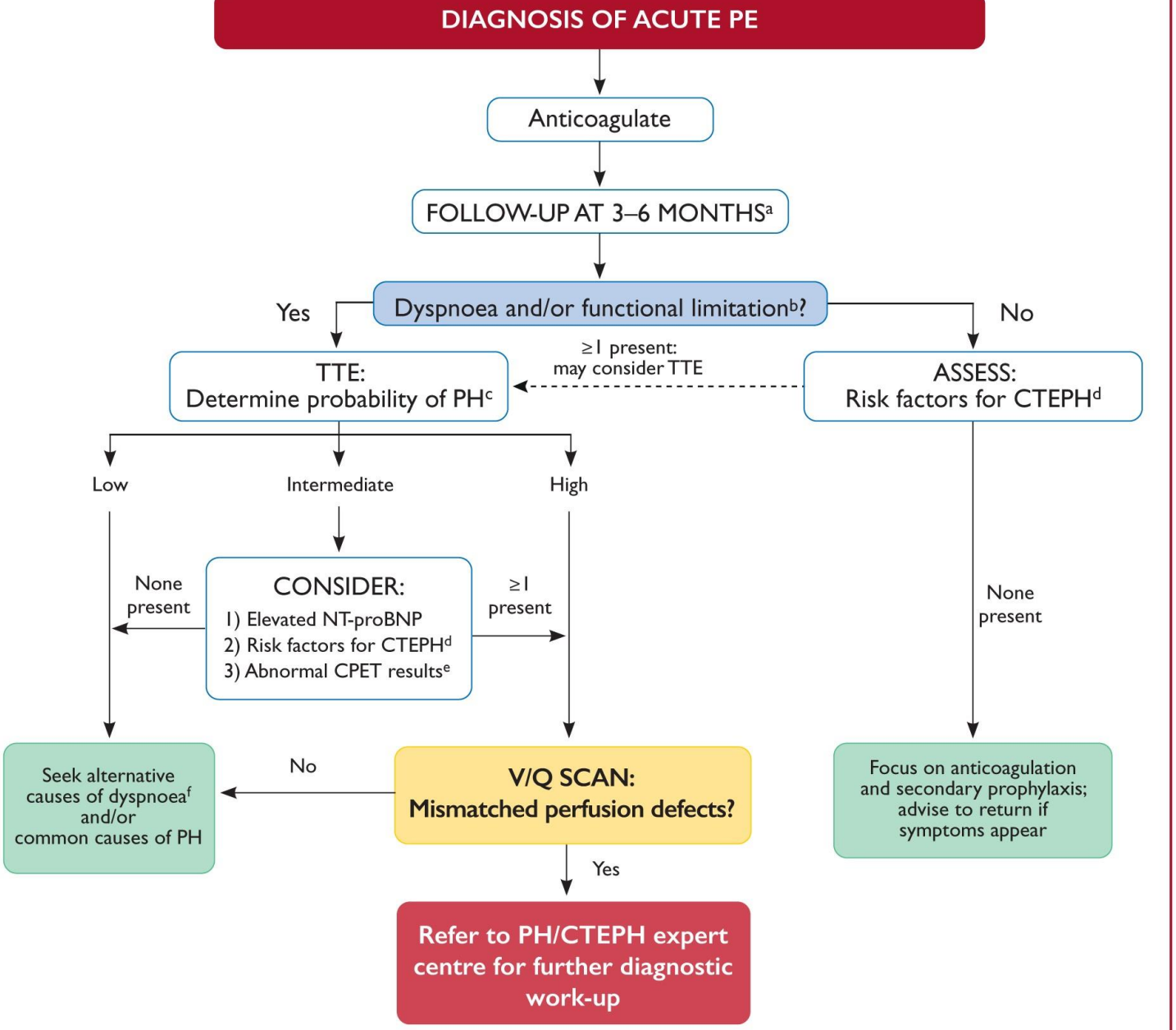








Venous filters are indicated in **patients with acute PE who have absolute contraindications to anticoagulant** drugs, and in patients with objectively confirmed **recurrent PE despite adequate anticoagulation treatment**


DIAGNOSIS OF ACUTE PE
Anticoagulate
FOLLOW-UP AT 3–6 MONTHS[a]
Dyspnoea and/or functional limitation[b]?
Yes
No
≥1 present: may consider TTE
TTE: Determine probability of PH[c]
ASSESS: Risk factors for CTEPH[d]
Low
Intermediate
High
None present
CONSIDER:
1) Elevated NT-proBNP
2) Risk factors for CTEPH[d]
3) Abnormal CPET results[e]
≥1 present
None present
Seek alternative causes of dyspnoea[f] and/or common causes of PH
No
V/Q SCAN: Mismatched perfusion defects?
Yes
Focus on anticoagulation and secondary prophylaxis; advise to return if symptoms appear
Refer to PH/CTEPH expert centre for further diagnostic work-up