ΝΕΕΣ ΚΑΤΕΥΘΥΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ ΓΙΑ ΤΗΝ ΠΝΕΥΜΟΝΙΚΗ ΕΜΒΟΛΗ

ΜΠΟΥΛΙΑ ΣΤΑΥΡΟΥΛΑ

ΕΠΙΜΕΛΗΤΡΙΑ Α`

ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΝΟΣΟΚΟΜΕΙΟ ΕΥΑΓΓΕΛΙΣΜΟΣ

ΕΝΩΣΗ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΠΡΟΣΩΠΙΚΟΥ
Γ.Ν.Α. «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ» (Ε.Ε.Π.Ν.Ε.)

25ο Ετήσιο Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης Γ.Ν.Α. «Ο Ευαγγελισμός»

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

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–61
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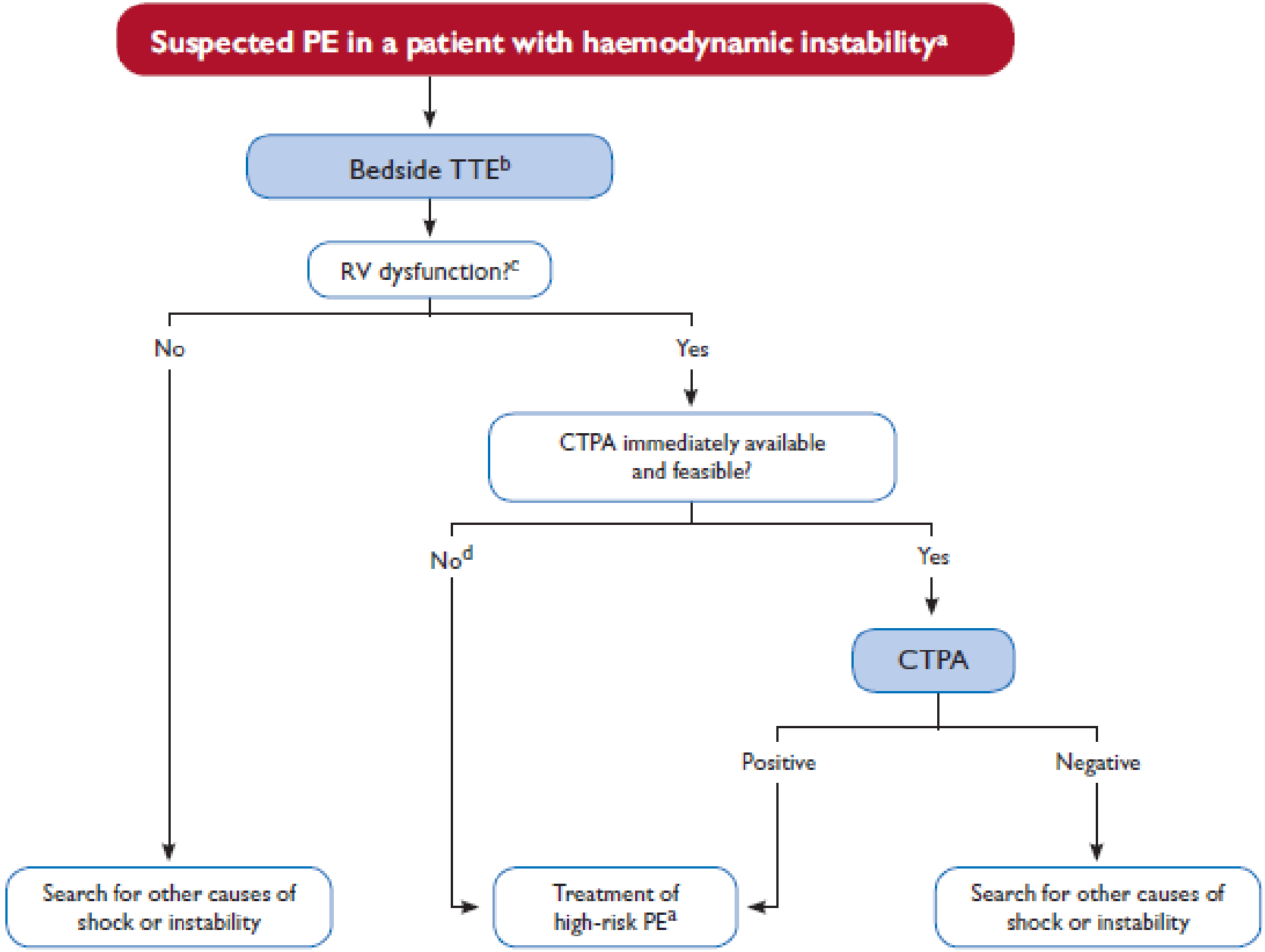
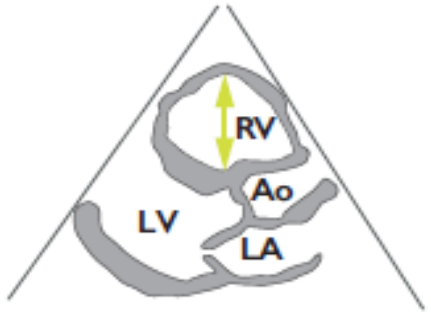
ΟΡΙΣΜΟΣ ΑΙΜΟΔΥΝΑΜΙΚΗΣ ΑΣΤΑΘΕΙΑΣ

Table 4 **Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)**

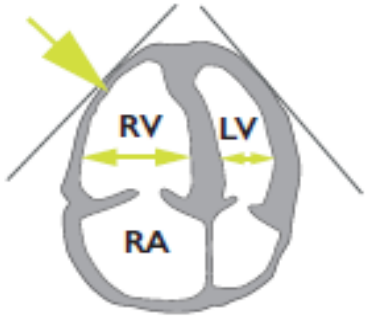
(1) Cardiac arrest	(2) Obstructive shock[68–70]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	


Suspected PE in a patient with haemodynamic instability[a]
Bedside TTE[b]
RV dysfunction?[c]
No
Yes
CTPA immediately available and feasible?
No[d]
Yes
CTPA
Positive
Negative
Search for other causes of shock or instability
Treatment of high-risk PE[a]
Search for other causes of shock or instability

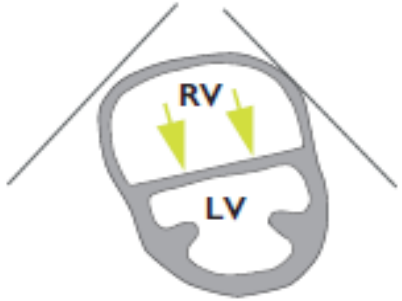
Graphic representation of transthoracic echocardiographic parameters



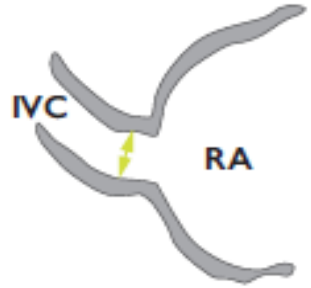
A. Enlarged right ventricle, parasternal long axis view



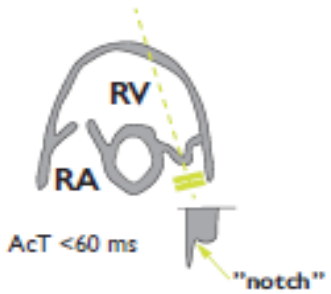
B. Dilated RV with basal RV/LV ratio >1.0, and McConnell sign (arrow), four chamber view

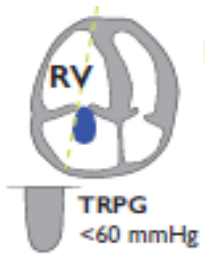


C. Flattened intraventricle septum (arrows) parasternal short axis view



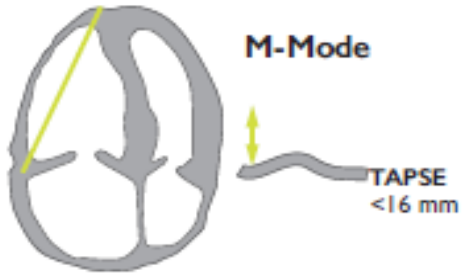
D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view



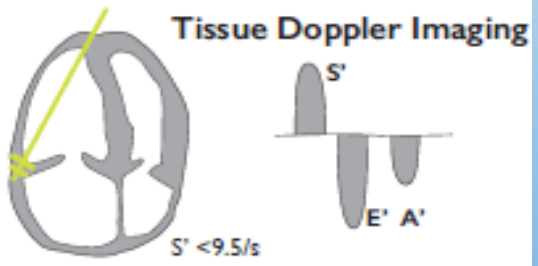


E. 60/60 sign: coexistence of acceleration time of pulmonary ejection <60 ms and midsystolic "notch" with mildy elevated (<60 mmHg) peak systolic gradient at the tricuspic valve

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)

Without Haemodynamic Instability

Clinical evaluation		
It is recommended that the diagnostic strategy be based on clinical probability, assessed either by clinical judgement or by a validated prediction rule.[89,91,92,103,134,170–172]	I	A

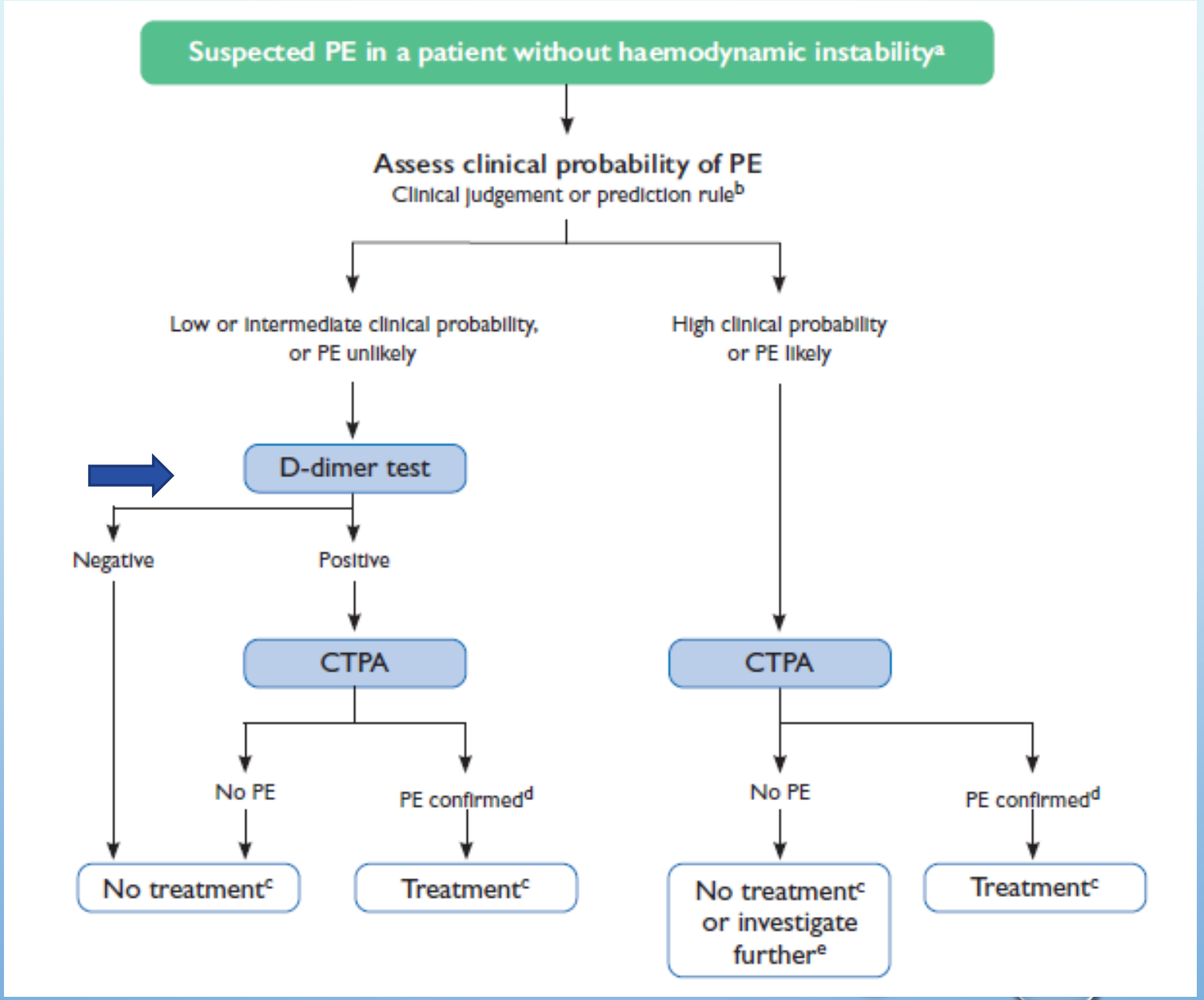
REVISED GENEVA

ΚΤΙΜΗΣΗ ΚΛΙΝΙΚΗΣ ΠΙΘΑΝΟΤΗΤΑΣ ΠΕ

WELLS RULE

ΚΛΙΝΙΚΗ ΠΙΘΑΝΟΤΗΤΑ	ΕΠΙΒΕΒΑΙΩΣΗ ΠΕ
ΧΑΜΗΛΗ	10%
ΜΕΣΗ	30%
ΥΨΗΛΗ	65%
PE-LIKELY	12%
PE-UNLIKELY	30%

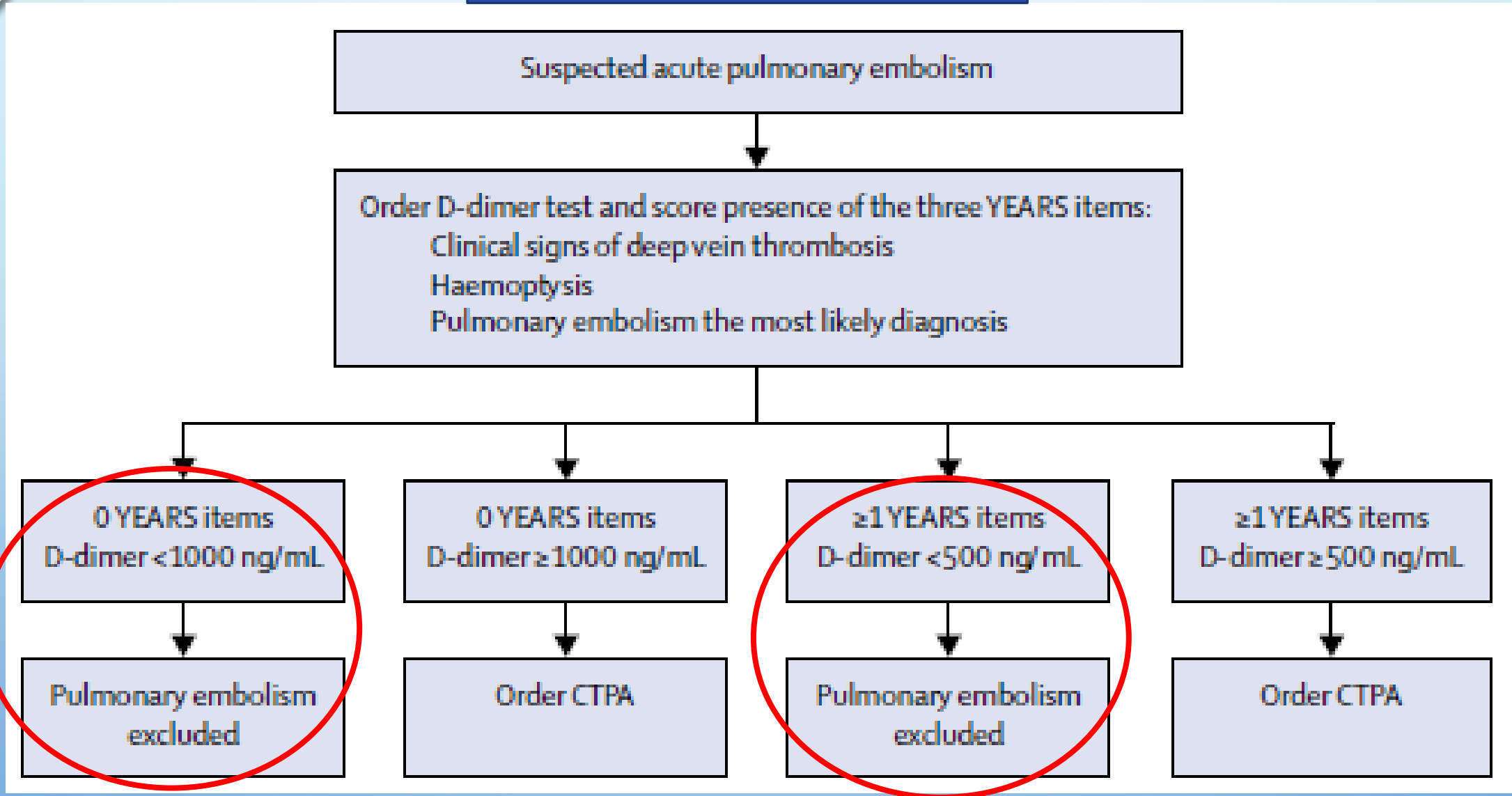
Diagnostic algorithm for patients with suspected pulmonary embolism without haemodynamic instability.



D-DIMER

	CLASS	LEVEL
Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are PE-unlikely, to reduce the need for unnecessary imaging and irradiation.[101–103,122,164,171,173,174]	I	A
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.[175,176]	III	A
As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age-adjusted cut-off (age × 10 μg/L, in patients aged >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or those that are PE-unlikely.[106]	IIa	B
As an alternative to the fixed or age-adjusted D-dimer cut-off, D-dimer levels adapted to clinical probability[c] should be considered to exclude PE.[107]	IIa	B

YEARS MODEL

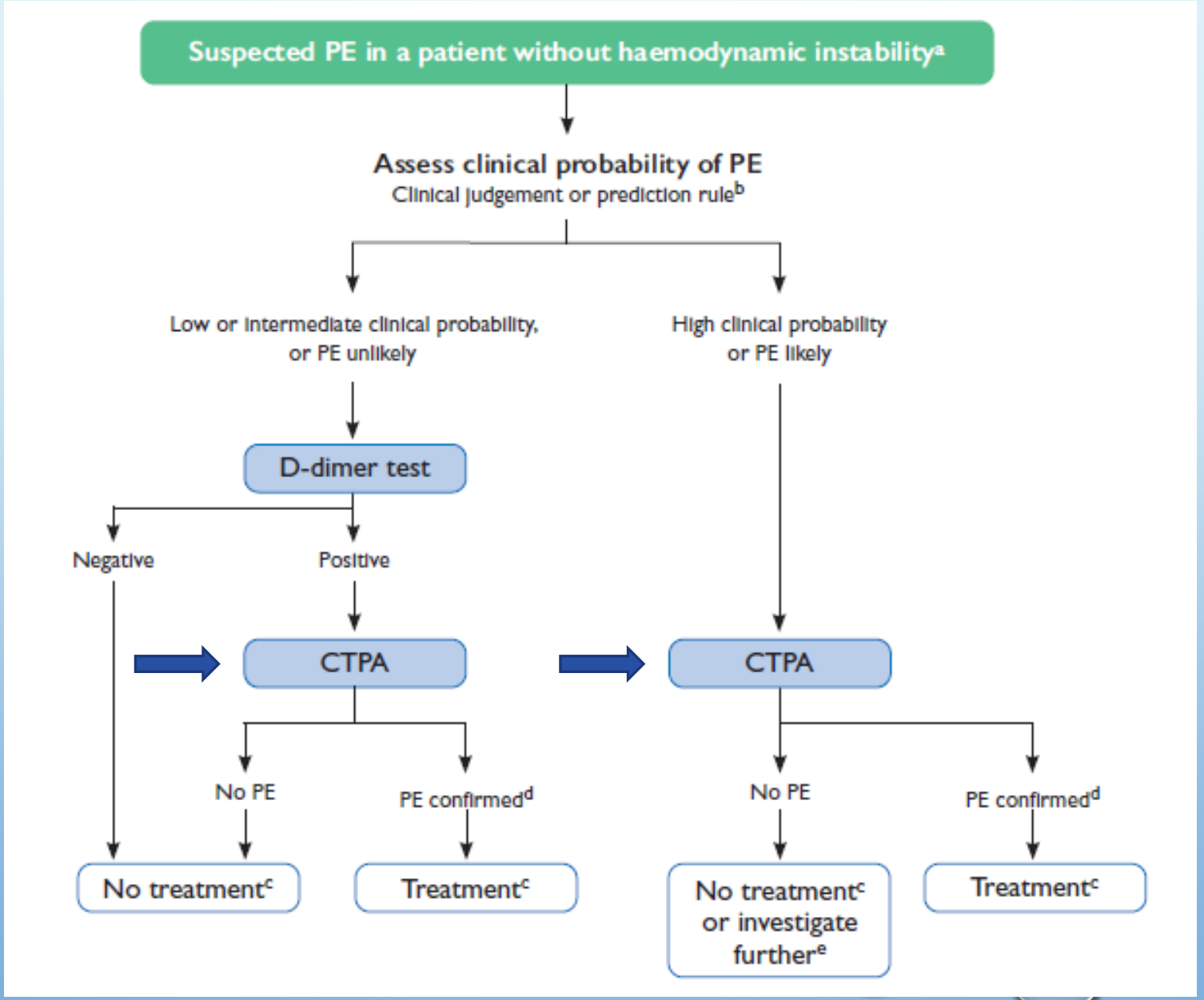


THE LANCET
2017

D-dimer

D-dimer threshold	No CTPA	Reduction
<500 ng/ml	34%	
<age adjusted	37%	8.7%
YEARS	48%	14%

Diagnostic algorithm for patients with suspected pulmonary embolism without haemodynamic instability.



CTPA

	CLASS	LEVEL
It is recommended to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or who is PE-unlikely.[101,122,164,171]	I	A
It is recommended to accept the diagnosis of PE (without further testing) if CTPA shows a segmental or more proximal filling defect in a patient with intermediate or high clinical probability.[115]	I	B
It should be considered to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with high clinical probability or who is PE-likely.[171]	IIa	B
Further imaging tests to confirm PE may be considered in cases of isolated subsegmental filling defects.[115]	IIb	C
CT venography is not recommended as an adjunct to CTPA.[115,164]	III	B

V/Q Scintigraphy

	CLASS	LEVEL
It is recommended to reject the diagnosis of PE (without further testing) if the perfusion lung scan is normal.[75,122,134,174]	I	A
It should be considered to accept that the diagnosis of PE (without further testing) if the V/Q scan yields high probability for PE.[134]	IIa	B
A non-diagnostic V/Q scan should be considered as exclusion of PE when combined with a negative proximal CUS in patients with low clinical probability, or who are PE-unlikely.[75,122,174]	IIa	B

V/Q SPECT

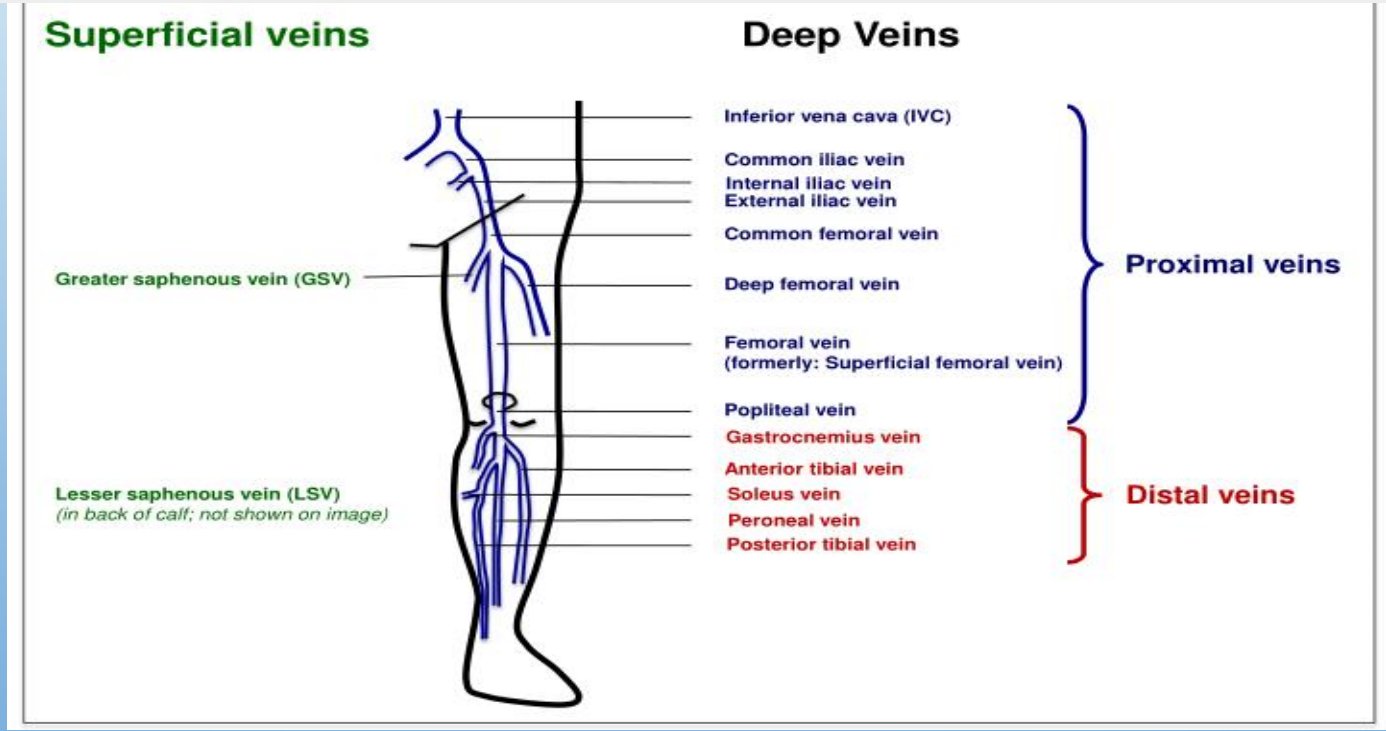
V/Q SPECT may be considered for PE diagnosis.[121,126–128]	IIb[d]	B

MRA

MRA is not recommended for ruling out PE.[139,140]	III	A

LOWER LIMB CUS

	CLASS	LEVEL
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.[164,165]	I	A
If CUS shows only a distal DVT, further testing should be considered to confirm PE.[177]	IIa	B
If a positive proximal CUS is used to confirm PE, assessment of PE severity should be considered to permit risk-adjusted management.[178,179]	IIa	C



ΑΠΕΙΚΟΝΙΣΤΙΚΕΣ ΤΕΧΝΙΚΕΣ

	Strengths	Weaknesses/limitations	Radiation issues[a]

CTPA	• 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
		• Radiation exposure
		• Exposure to iodine contrast:
		  ○ 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
			• Radiation effective dose 3–10 mSv[b]
			• Significant radiation exposure to young female breast tissue

Planar V/Q scan	• Almost no contraindications • Relatively inexpensive • Strong validation in prospective management outcome studies	• 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	• Lower radiation than CTPA, effective dose ~2 mSv[b]
V/Q SPECT	• Almost no contraindications • Lowest rate of non-diagnostic tests (<3%) • High accuracy according to available data • Binary interpretation ('PE' vs. 'no PE')	• Variability of techniques • Variability of diagnostic criteria • Cannot provide alternative diagnosis if PE excluded • No validation in prospective management outcome studies	• Lower radiation than CTPA, effective dose ~2 mSv[b]
Pulmonary angiography	• Historical gold standard	• Invasive procedure • Not readily available in all centres	• Highest radiation, effective dose 10–20 mSv[b]

PE SEVERITY AND THE RISK OF EARLY DEATH

Initial risk stratification of suspected or confirmed PE, based on the presence of haemodynamic instability, is recommended to identify patients at high risk of early mortality.[218,219,235]	I	B
In patients without haemodynamic instability, further stratification of patients with acute PE into intermediate- and low-risk categories is recommended.[179,218,219,235]	I	B
In patients without haemodynamic instability, use of clinical prediction rules integrating PE severity and comorbidity, preferably the PESI or sPESI, should be considered for risk assessment in the acute phase of PE.[178,226,229]	IIa	B
Assessment of the RV by imaging methods[c] or laboratory biomarkers[d] should be considered, even in the presence of a low PESI or a negative sPESI.[234]	IIa	B

PESI

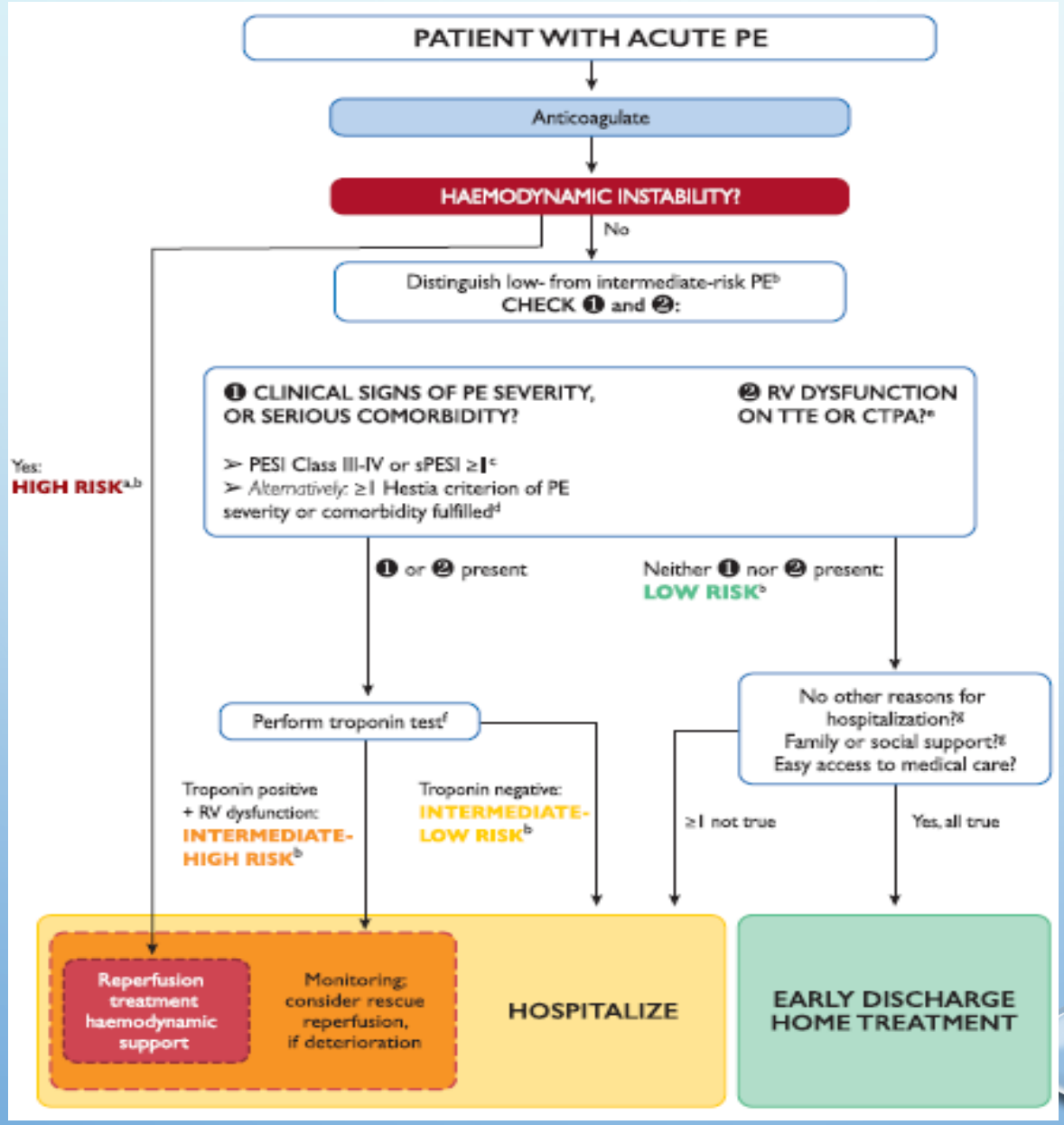
Parameter	Original version[226]	Simplified version[229]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point

Risk strata[a]	
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%)

EARLY MORTALITY RISK

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

RISK-ADJUSTED MANAGEMENT STRATEGY FOR ACUTE PULMONARY EMBOLISM



Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided.[c] 178,206,317–319	IIa	A

HESTIA CRITERIA

Criterion/question
Is the patient haemodynamically unstable?[a]
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk of bleeding?[b]
More than 24 h of oxygen supply to maintain oxygen saturation >90%?
Is PE diagnosed during anticoagulant treatment?
Severe pain needing i.v. pain medication for more than 24 h?
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, or no support system)?
Does the patient have a CrCl of <30 mL/min?[c]
Does the patient have severe liver impairment?[d]
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

ΘΕΡΑΠΕΙΑ

Α.ΥΠΟΞΥΓΟΝΑΙΜΙΑ

- ΡΙΝΙΚΗ ΚΑΝΟΥΛΑ ΣΕ SaO2<90%
- HFO
- ΜΕΜΑ
- ΔΙΑΣΩΛΗΝΩΣΗ
  - ↓PEEP
  - TV:6 Ml/kgr
  - P plateau <30cm H2O

Β. ΑΙΜΟΔΥΝΑΜΙΚΗ ΥΠΟΣΤΗΡΙΞΗ

ΘΕΡΑΠΕΙΑ ΔΕ ΚΑΡΔΙΑΚΗΣ ΑΝΕΠΑΡΚΕΙΑΣ

Treatment Of RV Failure In Acute High-Risk PE

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 and/or dobutamine should be considered in patients with high-risk PE.		IIa C
Mechanical circulatory support		
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.[d 252]		IIb C

ΘΕΡΑΠΕΙΑ

Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE,[c] while diagnostic workup is in progress.	I	C

UFH

- αιμοδυναμική αστάθεια
- GFR≤30ml/min
- νοσογόνος παχυσαρκία

It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C

ΧΑΜΗΛΟΥ ΜΒ ΗΠΑΡΙΝΕΣ ΚΑΙ FONDAPARINUX

	Dosage	Interval
Enoxaparin	1.0 mg/kg	Every 12 h
	or	
	1.5 mg/kg[a]	Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b]	Every 12 h[b]
	10 mg (body weight >100 kg)	

If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.[262,309–311]

I

A

NOACS

When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.[260,261,312–314]	I	A
NOACs are not recommended in patients with severe renal impairment,[d] during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.[260,261,312–314]	III	C

NOACS

Characteristics[a]	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Time to peak effect	1–2 h	1–3 h	1–2 h	2–4 h
Half-life	8–14 h	14–17 h	5–11 h	7–11 h
Renal elimination	27%	80%	50%	33%
Caveats due to interactions with concomitant medication[b]	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors). Concomitant use with strong CYP3A4 and P-gp inducers (rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's Wort) may lead to an ~50% reduction in apixaban exposure.	Strong P-gp inhibitors (systemic ketoconazole, cyclosporine, itraconazole, and dronedarone) are contraindicated. Concomitant treatment with tacrolimus is not recommended. Concomitant administration of P-gp inducers (rifampicin, St John's wort, carbamazepine, and phenytoin) is expected to result in decreased dabigatran plasma concentrations and should be avoided.	In patients concomitantly taking edoxaban and the P-gp inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg edoxaban o.d.	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors)
Further conditions in which NOACs are contraindicated or not recommended[c]	CrCl <15 mL/min. Severe hepatic impairment (Child–Pugh C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min. Concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL/min.	CrCl <15 mL/min. Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min (FDA); CrCl <15 mL/min (EMA). Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.
Reversal agent	Andexanet	Idarucizumab	Andexanet	Andexanet

VKA

When patients are treated with a VKA, over-lapping with parenteral anticoagulation is rec-ommended until an INR of 2.5 (range 2.0–3.0) is reached.[315,316]	I	A

Αντιφωσφολιπιδικό Σύνδρομο

ΘΕΡΑΠΕΙΕΣ ΕΠΑΝΑΙΜΑΤΩΣΗΣ
ΘΡΟΜΒΟΛΥΣΗ

Systemic thrombolytic therapy is recommended for high-risk PE. [282]	I	B
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE. [c,f 179]	III	B
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment. [282]	I	B

ΘΕΡΑΠΕΙΕΣ ΕΠΑΝΑΙΜΑΤΩΣΗΣ
ΘΡΟΜΒΟΛΥΣΗ

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

ΘΕΡΑΠΕΙΕΣ ΕΠΑΝΑΙΜΑΤΩΣΗΣ

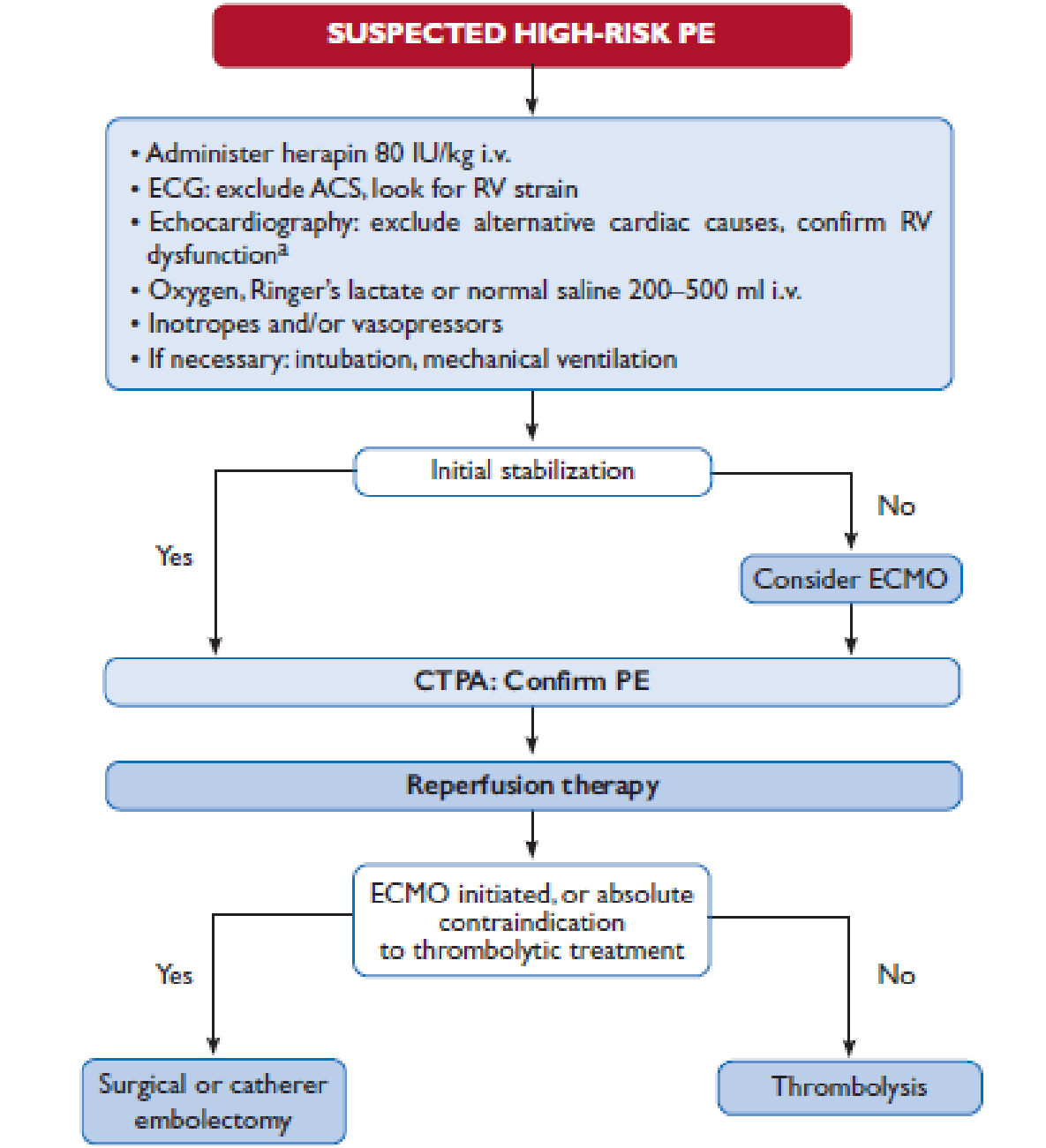
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[d]	I	C
Percutaneous catheter-directed tre… should be considered for pati… high-risk PE, in whom thromb… contraindicated or has failed.[d]	IIa	C
As an alter… rescue thrombolytic therapy, su… bolectomy[e] or percutaneous ca…irected treatment[e] should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C

If appropriate expertise and resources are available on-site.

ΦΙΛΤΡΑ ΚΚΦ

IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in cases of PE recurrence despite therapeutic anticoagulation.	IIa	C
Routine use of IVC filters is not recommended.[302–304]	III	A

EMERGENCY MANAGEMENT OF PATIENTS WITH SUSPECTED HIGH-RISK PULMONARY EMBOLISM



DURATION OF ANTICOAGULATION IN PATIENTS WITHOUT CANCER

Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE.[347]	I	A

Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months.[331,340,341]	I	B

DURATION OF ANTICOAGULATION

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

DURATION OF ANTICOAGULATION

Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor.[358]	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome.[359]	I	B

Patients in whom extension of anticoagulation beyond 3 months should be considered[c,d]		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor.[330,331,347,351–353]	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome.[330,352,353]	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor.[330,331,352]	IIa	C

EXTENDED ANTICOAGULATION

NOAC dose in extended anticoagulation[e]		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation.[352,353]	IIa	A

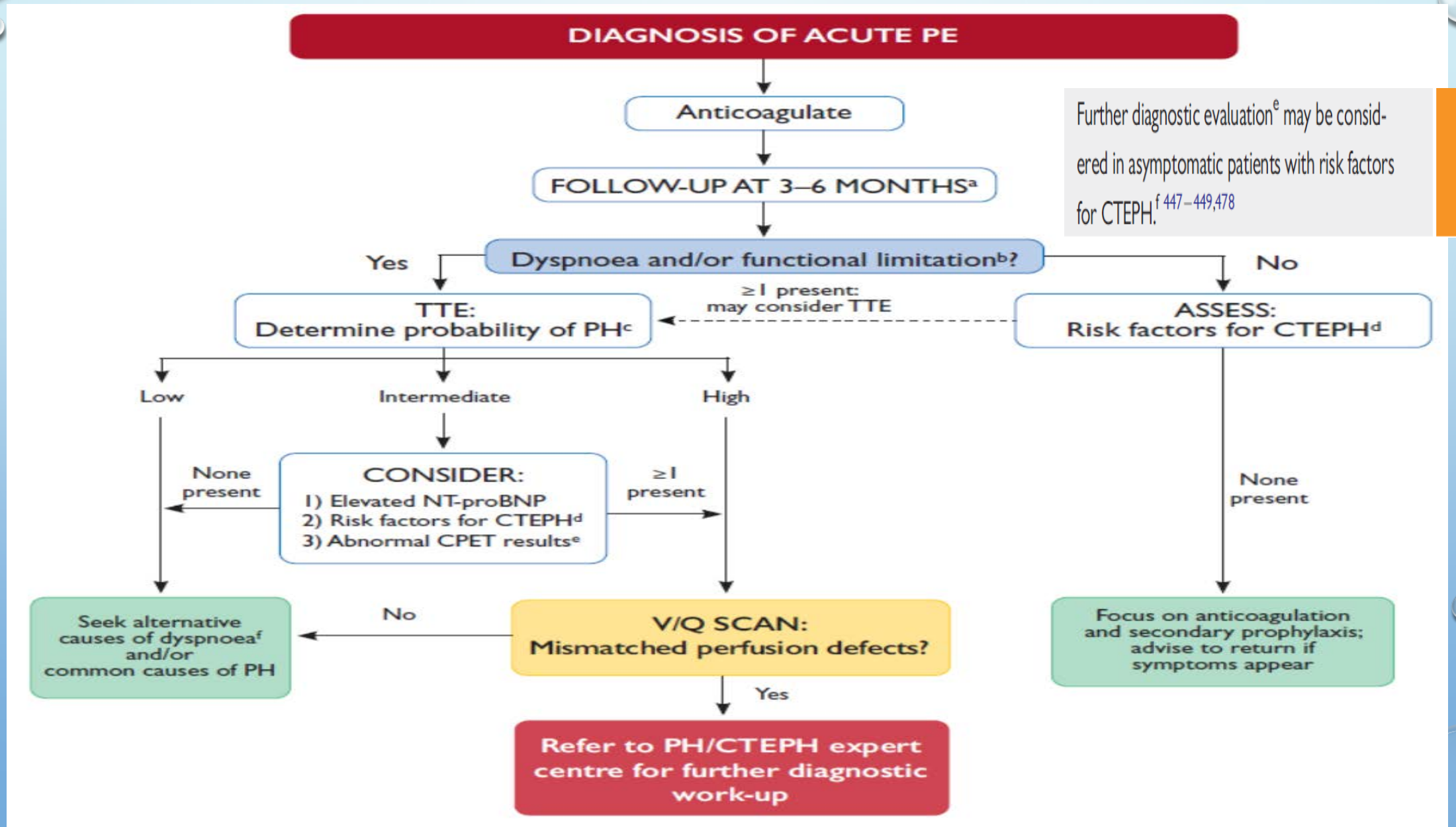
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal[f] function, and bleeding risk be reassessed at regular intervals.[259]	I	C

DURATION OF ANTICOAGULATION

Recurrence Risk Vs Bleeding Risk

Prediction model	Prediction model	Parameters	Points	Categories of bleeding risk	Validation status
Vienna prediction model[33–35]	OBRI[44]	Age ≥65 years History of stroke History of gastrointestinal bleeding Recent myocardial infarction, renal insufficiency, diabetes, or anaemia	1 1 1 1	0: low 1–2: intermediate 3–4: high	Validation showed modest accuracy in VKA cohorts (reviewed in Klok *et al.*[45]) No data in patients treated with NOACs
HERDOO2[36,37]	Kuijer *et al.*[46]	Age ≥60 years Female sex Malignancy	1.6 1.3 2.2	0: low 1–3: intermediate >3: high	
DASH tool[38,39]	RIETE[47]	Age >75 years Recent bleeding Cancer Creatinine >1.2 mg/dL Anaemia PE (vs. DVT) index event	1 2 1 1.5 1.5 1	0: low 1–4: intermediate >4: high	
DAMOVES[40,41]	HAS-BLED[48,49]	Uncontrolled hypertension Abnormal liver/renal function Previous stroke Bleeding history or predisposition Labile INR (time in therapeutic range <60%) Age >65 years Concomitant drugs or alcohol	1 1 1 1 1 1 1	0–2: low ≥3: high	
Ottawa[a 42,43]	VTE-BLEED[50]	Active cancer Male patient with uncontrolled hypertension Anaemia History of bleeding Age ≥60 years Renal dysfunction (CrCl 30–60 mL/min)	1.5 2 1 1.5 1.5 1.5	0–1: low ≥2: high	Validated in *post hoc* analysis of RCTs testing NOACs vs. VKAs after initial LMWH treatment[50,51]

LONG-TERM SEQUELAE



Further diagnostic evaluation[e] may be considered in asymptomatic patients with risk factors for CTEPH.[f 447–449,478]	IIb	C

DYSPNOEA

Supplementary Table 16 **Assessment of the severity of dyspnoea**

Grade/ functional class	Medical Research Council scale	World Health Organization functional class
1	Not troubled by breathlessness except on strenuous exercise	No limitation of physical activity; ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
2	Short of breath when hurrying or walking up a slight hill	Slight limitation of physical activity, but comfortable at rest; ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
3	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace	Marked limitation of physical activity, but comfortable at rest; less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
4	Stops for breath after walking ~100 m or after a few minutes on level ground	Inability to carry out any physical activity without symptoms; manifest signs of right heart failure; dyspnoea and/or fatigue may even be present at rest; discomfort is increased by any physical activity
5	Too breathless to leave the house, or becomes breathless while dressing or undressing	

ECHO- PH

Supplementary Table 17 Echocardiographic probability of pulmonary hypertension

Peak tricuspid regurgitation velocity (m/s)	Presence of other echocardiographic PH signs[a]	Echocardiographic probability of PH
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Supplementary Table 18 Echocardiographic signs of pulmonary hypertension

A: the ventricles[a]	B: pulmonary artery[a]	C: IVC and RA[a]
RV/LV basal diameter ratio >1.0	AcT <105 ms and/or mid-systolic notching	Inferior vena cava diameter >21 mm with decreased respiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

CTEPH RISK FACTORS

Table 13 Risk factors and predisposing conditions for chronic thromboembolic pulmonary hypertension[447–449]

Findings related to the acute PE event (obtained at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3–6 month follow-up)
Previous episodes of PE or DVT	Ventriculo-atrial shunts
Large pulmonary arterial thrombi on CTPA	Infected chronic i.v. lines or pacemakers
Echocardiographic signs of PH/RV dysfunction[a]	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease[b]	Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
	Non-O blood group
	Hypothyroidism treated with thyroid hormones
	History of cancer
	Myeloproliferative disorders
	Inflammatory bowel disease
	Chronic osteomyelitis

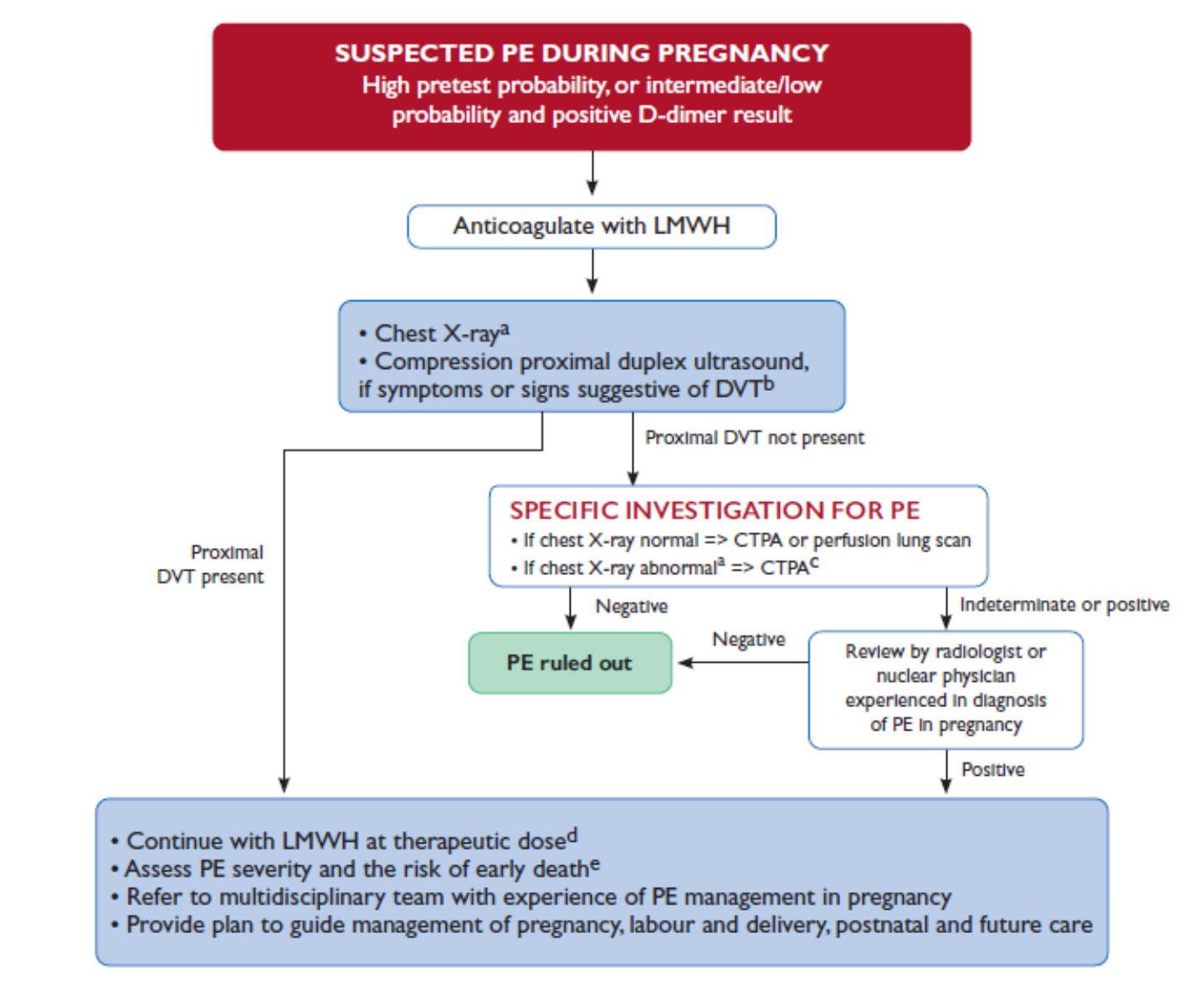
ΚΑΡΚΙΝΟΣ & ΠΕ

For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363]	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366]	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367]	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378]	IIa	B
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.[376,377]	IIa	B

ΚΑΡΚΙΝΟΣ & ΠΕ

Anticoagulation in the patient with PE and cancer, after the first 6 months	If cancer still active:[e] • Continue anticoagulation LMWH or, alternatively, edoxaban or rivaroxaban, as recommended in *section 8.4* If cancer in remission: • Continue oral anticoagulation (NOAC or VKA); alternatively, consider discontinuing if the bleeding risk is high. • In either case, periodically reassess the risk–benefit ratio of continuing/resuming anticoagulation.	• In the absence of conclusive evidence, the decision to continue or stop after the first 6 months of anticoagulation should be made on a case-by-case basis after considering the success of anticancer therapy, the estimated overall risk of VTE recurrence (*Supplementary Table 13*), the bleeding risk (*Supplementary Table 14*), and the preference of the patient.

ΕΓΚΥΜΟΣΥΝΗ & ΠΕ



ΕΓΚΥΜΟΣΥΝΗ & ΠΕ

Diagnosis		
Formal diagnostic assessment with validated methods is recommended if PE is suspected during pregnancy or in the post-partum period.[388,391]	I	B
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period.[388,391]	IIa	B
In a pregnant patient with suspected PE (particularly if she has symptoms of DVT), venous CUS should be considered to avoid unnecessary irradiation.[388]	IIa	B
Perfusion scintigraphy or CTPA (with a low-radiation dose protocol) should be considered to rule out suspected PE in pregnant women; CTPA should be considered as the first-line option if the chest X-ray is abnormal.[385,386]	IIa	C

ΕΓΚΥΜΟΣΥΝΗ & ΠΕ

Treatment		
A therapeutic, fixed dose of LMWH based on early pregnancy body weight is the recommended therapy for PE in the majority of pregnant women without haemodynamic instability.[408,410]	I	B
Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE.[421]	IIa	C
Insertion of a spinal or epidural needle is not recommended, unless ≥24 h have passed since the last therapeutic dose of LMWH.	III	C
Administration of LMWH is not recommended within 4 h of removal of an epidural catheter.	III	C
NOACs are not recommended during pregnancy or lactation.	III	C

Amniotic fluid embolism		
Amniotic fluid embolism should be considered in a pregnant or post-partum woman with otherwise unexplained cardiac arrest, sustained hypotension, or respiratory deterioration, especially if accompanied by disseminated intravascular coagulation.[422,425,426]	IIa	C

SPECIFIC CLINICAL SITUATIONS

Clinical setting	Suggested management[a]	Comments
Subsegmental PE	Single subsegmental PE in an outpatient without cancer and without proximal DVT: • Clinical surveillance. Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: • Anticoagulant treatment. Multiple subsegmental PE: • Anticoagulant treatment.	• Poor interobserver agreement for the diagnosis of subsegmental PE; diagnosis to be confirmed by an experienced thoracic radiologist. • Suggestion based on indirect evidence, only limited data available.
Incidental PE	If single subsegmental PE: • Proceed as above. In all other cases: • Anticoagulant treatment.	• Suggestion based on retrospective cohort data.
Management of acute PE in a patient with active bleeding	• Insert inferior vena cava filter (preferably retrievable). • Reassess the possibility of anticoagulation as soon as the bleeding has ceased and the patient is stabilized, and remove the filter as soon as anticoagulant treatment is resumed.	

SPECIFIC CLINICAL SITUATIONS

PE diagnosis and anticoagulation in the elderly, frail patients, and patients with polypharmacy	• Assess clinical probability of PE as in the non-frail patient, but caution needed in the nursing home setting as clinical prediction rules may be unreliable.[27] • Generally prefer NOACs over VKAs in elderly and frail patients, but observe the following: a. Avoid NOACs in patients with severe renal impairment.[b] b. Consult the drugs' summary of product characteristics and the updated European Heart Rhythm Association guide[19] for possible interactions between NOACs and the patient's concomitant medication. • Reassess, at regular intervals, drug tolerance and adherence, hepatic and renal function, and the patient's bleeding risk	• Number of diseases mimicking PE symptoms increases with age, making diagnostic delay more common. • These patients have been poorly represented in clinical trials. Whatever the treatment (VKAs or NOACs), these patients are at high risk of bleeding.
Initial anticoagulation in a patient with acute PE and end-stage renal disease	• Administer UFH; consider anti-Xa (rather than aPTT) monitoring.[28]	• No truly safe anticoagulation option available, although LMWH with anti-Xa monitoring is also used in clinical practice.

SPECIFIC CLINICAL SITUATIONS

Duration of anticoagulation in a young female patient suffering acute PE while on oral contraceptives	If patient was taking an oestrogen-containing contraceptive, and especially if PE occurred in the first 3 months of initiation of contraception: • Discontinue hormonal contraceptives after discussing alternative methods of contraception; consider discontinuing anticoagulation after 3 months.	• The risk of VTE attributable to oestrogen–progestin contraception (or hormonal treatment) depends on the specific compound and the presence of concomitant thrombophilia, and is associated with the time interval
	All other cases: • Manage chronic anticoagulation as after acute PE occurring in the absence of identifiable risk factors. • Consider using a validated prediction model for quantification of the risk for VTE recurrence (*Supplementary Table 14*); for example, the HERDOO2 score: a. hyperpigmentation, oedema, or redness in either leg; b. D-dimer level ≥250 μg/L; c. obesity with body mass index ≥30; d. older age (essentially 0 in this case). A score of 0 or 1 may help identify young women who can safely discontinue anticoagulant treatment. • Advise patient on the need for prophylaxis with LMWH in case of pregnancy.	between the initiation of hormonal treatment and the occurrence of acute PE.[29,30]

2019

6.8 Recommendations for multidisciplinary pulmonary embolism teams

Recommendation	Class[a]	Level[b]
Set-up of a multidisciplinary team and a programme for the management of high- and (in selected cases) intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa	C

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ

Table 12 Estimated amounts of radiation absorbed in procedures used to diagnose pulmonary embolism (based on various references[385,392–398])

Test	Estimated foetal radiation exposure (mGy)[a]	Estimated maternal radiation exposure to breast tissue (mGy)[a]
Chest X-ray	<0.01	<0.1
Perfusion lung scan with technetium-99m-labelled albumin		
Low dose: ~40 MBq	0.02–0.20	0.16–0.5
High dose: ~200 MBq	0.20–0.60	1.2
Ventilation lung scan	0.10–0.30	<0.01
CTPA	0.05–0.5	3–10

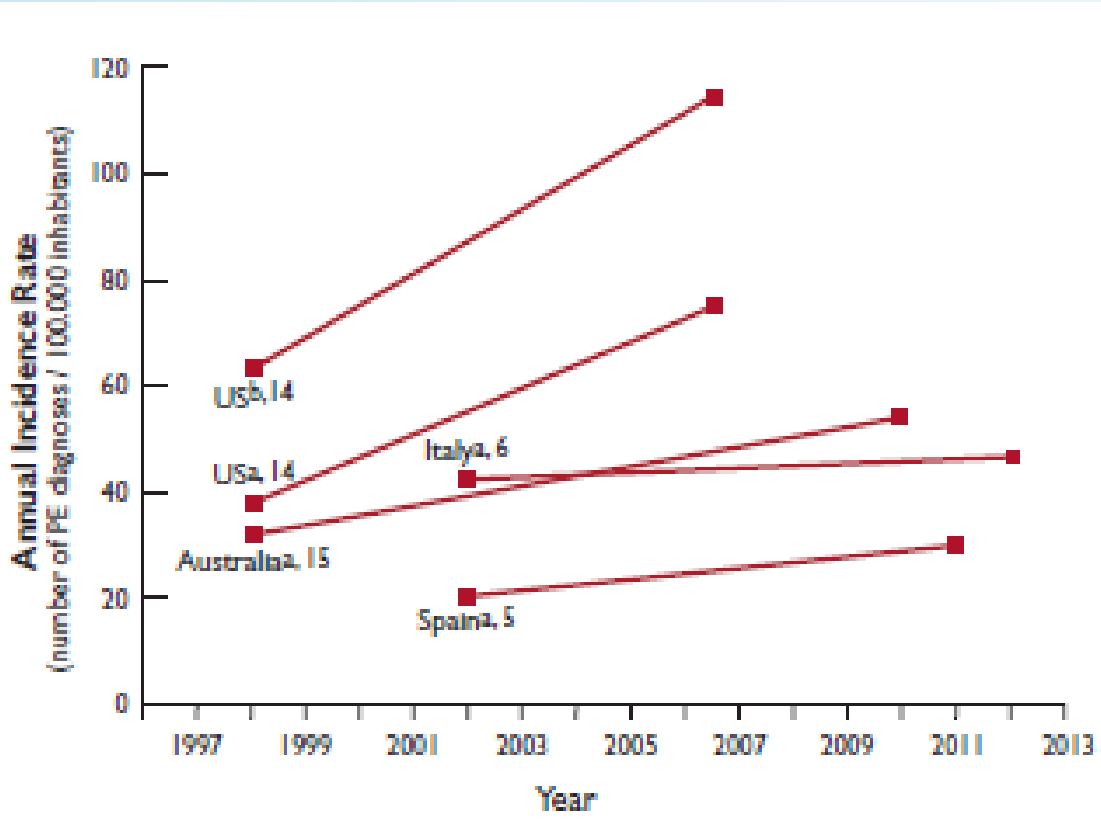
CTPA = computed tomography pulmonary angiography; mGy = milligray; MBq = megabecquerel; PE = pulmonary embolism.

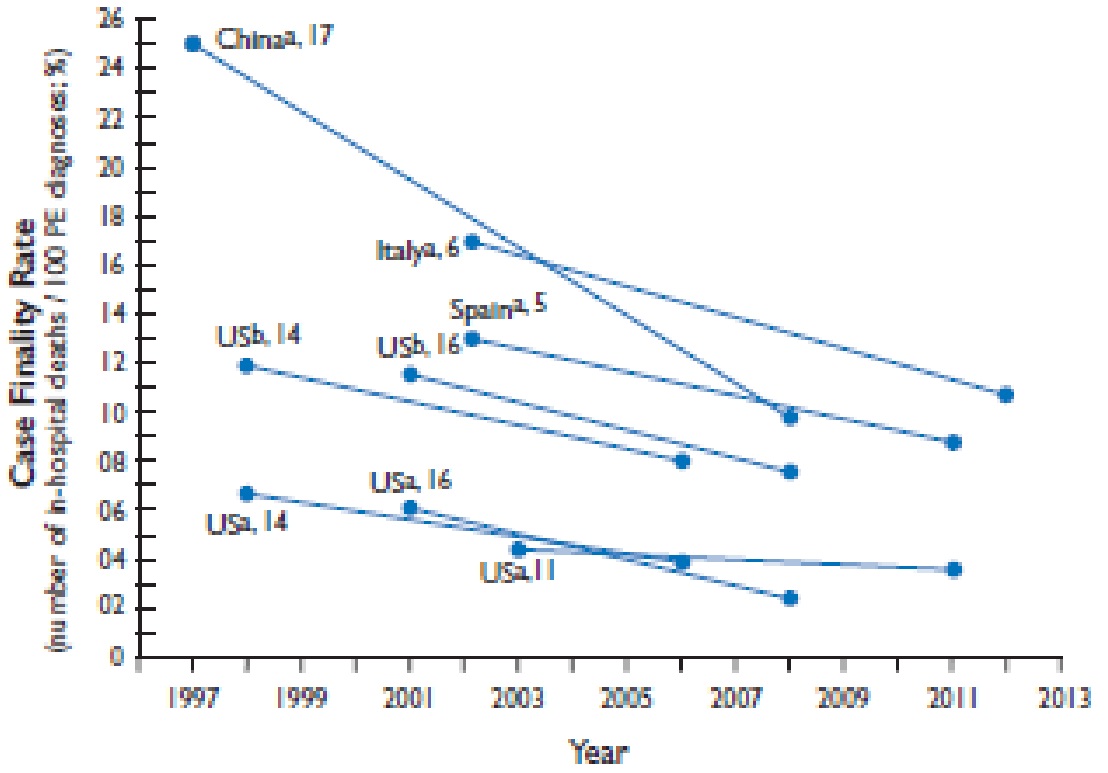
[a]In this section, absorbed radiation dose is expressed in mGy to reflect the radiation exposure to single organs, or the foetus, as a result of various diagnostic techniques. Compare with *Table 6*, in which effective radiation dose is expressed in millisieverts to reflect the effective doses of all organs that have been exposed.

ΠΝΕΥΜΟΝΙΚΗ ΕΜΒΟΛΗ

- ΘΡΟΜΒΟΕΜΒΟΛΙΚΗ ΝΟΣΟΣ = DVT ΚΑΙ ΠΕ
- $3^{Ο}$ ΣΕ ΣΥΧΝΟΤΗΤΑ ΟΞΥ ΚΑΡΔΙΑΓΓΕΙΑΚΟ ΣΥΝΔΡΟΜΟ ΠΑΓΚΟΣΜΙΩΣ, ΜΕΤΑ ΤΟ ΟΕΜ ΚΑΙ ΤΟ ΕΓΚΕΦΑΛΙΚΟ
- ΗΛΙΚΙΑ>80 ΕΤΩΝ⟶ Χ 8⬆ ΣΥΧΝΟΤΗΤΑΣ VTE ΣΥΓΚΡΙΤΙΚΑ ΜΕ < 50 ΕΤΩΝ

ΠΝΕΥΜΟΝΙΚΗ ΕΜΒΟΛΗ





ΚΛΙΝΙΚΗ ΕΙΚΟΝΑ

ΑΡΤΗΡΙΑΚΗ ΠΙΕΣΗ

ΜΑΚΡΟΧΡΟΝΙΑ ΘΕΡΑΠΕΙΑ ΚΑΙ ΠΡΟΦΥΛΑΞΗ ΠΡΟΛΗΨΗ ΥΠΟΤΡΟΠΗΣ

Supplementary Table 13 Validated prediction models for quantification of the risk of recurrent venous thromboembolism

Prediction model	Parameters	Points	Categories of recurrence risk	Risk group (for VTE recurrence) studied	Type of studies	Number of PE patients included	Remarks
Vienna prediction model[31–33]	• Male sex • Proximal DVT • Pulmonary embolism • D-dimer (continuous value)	n.a.	Continuous (nomogram)	Unprovoked VTE	Cohorts database (derivation, validation)	Derivation study: 438 (47% of cohort) Validation study: 291 (32%)	
HERDOO2[34,37]	• Hyperpigmentation, oedema or leg redness • D-dimer ≥250 µg/L (on VKAs) • Body mass index ≥30 kg/m² • Age ≥65 years	1 1 1 1	0–1 points: low risk; ≥2 points: high risk	Unprovoked VTE (derivation); unprovoked VTE, or with minor risk factors (validation)	Management study (derivation, internal validation)	Derivation study: 327 (49%) Management study: 1434 (39%)	Only applicable in women
DASH to a[38,39]	• D-dimer (post-VKA) normal or abnormal • Age <50 years • Male sex • Hormonal therapy	2 1 1 −2	≤1 points: low risk; ≥2 points: high risk	Unprovoked VTE, or minor risk factors	Cohorts database (derivation, external validation)	Not reported	
DAMDVES[40,41]	• Age (continuous) • Sex • Obesity • Abnormal D-dimer • Factor VIII (continuous) • Genetic thrombophilia • Varicose veins	n.a.	Continuous (nomogram)	Unprovoked VTE	Prospective cohort (derivation) Retrospective cohort (external validation)	Derivation study: 270 (68%) Validation study: not reported	

Ottawa[42,43]	• Female sex
	• Primary tumour site:
	  • lung
	  • breast
	• Tumour Node Metastasis stage I
	• History of VTE
		1
		1
		−1
		−2
		1
			≤0: low risk;
			≥1: high risk
				Patients with cancer	Retrospective cohort (derivation)
					Two RCTs (external validation)
						Not reported	Only applicable in patients with cancer

PULMONARY EMBOLISM RULE-OUT CRITERIA PERC

- AGE <50
- HR<100 BPM
- SAT O2>94%
- ΟΙΔΗΜΑ ΚΑ
- ΑΙΜΟΠΤΥΣΗ
- ΠΡΟΣΦΑΤΟ ΤΡΑΥΜΑ-ΧΕΙΡΟΥΡΓΕΙΟ
- ΧΡΗΣΗ ΟΡΜΟΝΩΝ
- DVT

ΝΟ

↓ΚΛΙΝΙΚΗ ΠΙΘΑΝΟΤΗΤΑ

ΜΑΚΡΟΧΡΟΝΙΑ ΘΕΡΑΠΕΙΑ

Prediction model	Parameters	Points	Categories of bleeding risk	Validation status
OBRI[44]	Age ≥65 years	1	0: low	Validation showed modest accuracy in VKA cohorts (reviewed in Klok *et al*[45])
	History of stroke	1	1–2: intermediate	
	History of gastrointestinal bleeding	1	3–4: high	
	Recent myocardial infarction, renal insufficiency, diabetes, or anaemia	1		No data in patients treated with NOACs
Kuijer *et al*[46]	Age ≥60 years	1.6	0: low	
	Female sex	1.3	1–3: intermediate	
	Malignancy	2.2	>3: high	
RIETE[47]	Age >75 years	1	0: low	
	Recent bleeding	2	1–4: intermediate	
	Cancer	1	>4: high	
	Creatinine >1.2 mg/dL	1.5		
	Anaemia	1.5		
	PE (vs. DVT) index event	1		
HAS-BLED[48,49]	Uncontrolled hypertension	1	0–2: low	
	Abnormal liver/renal function	1	≥3: high	
	Previous stroke	1		
	Bleeding history or predisposition	1		
	Labile INR (time in therapeutic range <60%)	1		
	Age >65 years	1		
	Concomitant drugs or alcohol	1		
VTE-BLEED[50]	Active cancer	1.5	0–1: low	Validated in *post hoc* analysis of RCTs testing NOACs vs. VKAs after initial LMWH treatment[50,51]
	Male patient with uncontrolled hypertension	2	≥2: high	
	Anaemia	1		
	History of bleeding	1.5		
	Age ≥60 years	1.5		
	Renal dysfunction (CrCl 30–60 mL/min)	1.5		

ΚΙΝΔΥΝΟΣ ΑΙΜΟΡΡΑΓΙΑΣ

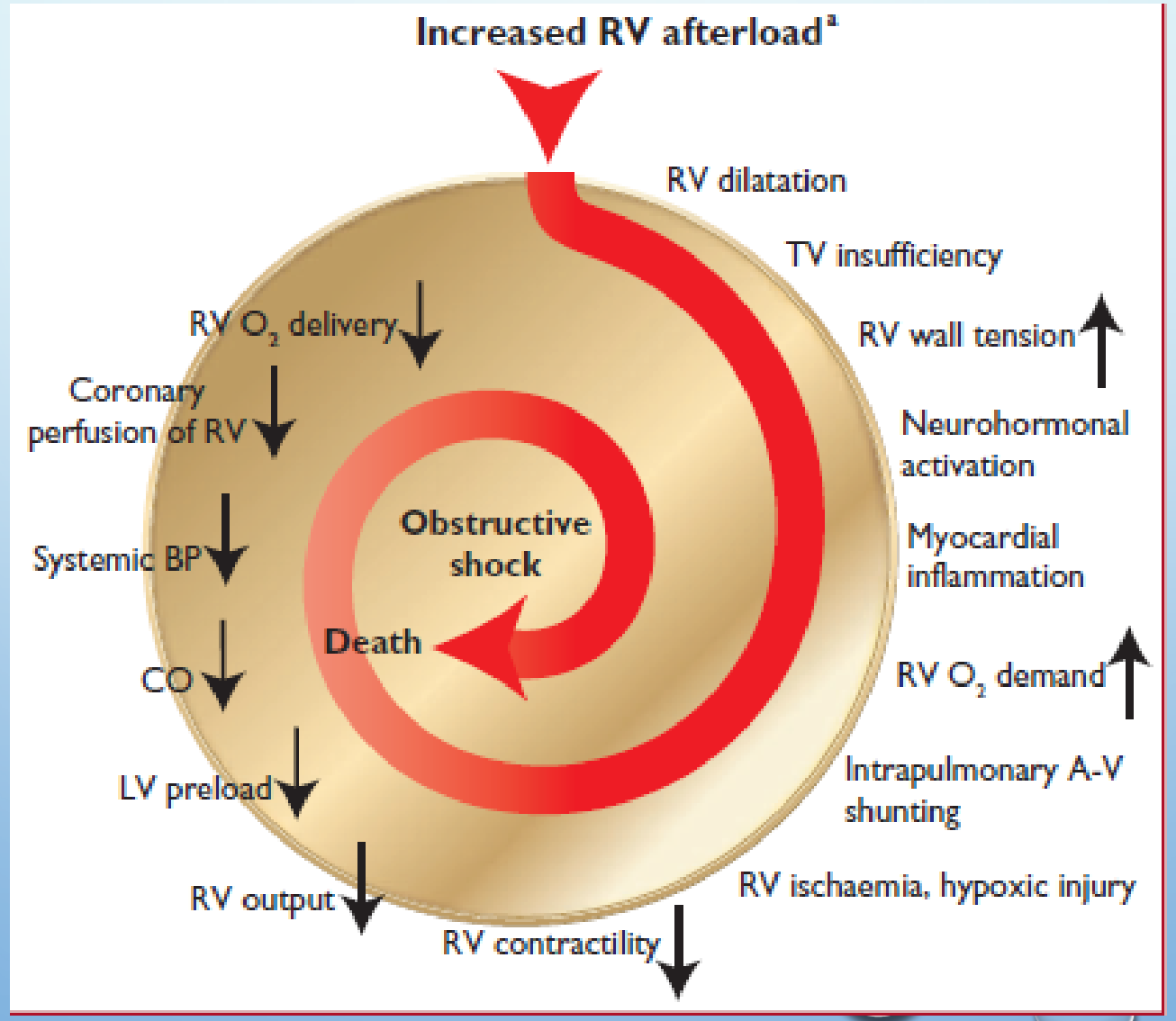
Prediction model	Parameters	Points	Categories of bleeding risk	Validation status
OBRI[44]	Age ≥65 years History of stroke History of gastrointestinal bleeding Recent myocardial infarction, renal insufficiency, diabetes, or anaemia	1 1 1 1	0: low 1–2: intermediate 3–4: high	Validation showed modest accuracy in VKA cohorts (reviewed in Klok *et al.*[45]) No data in patients treated with NOACs
Kuijer *et al.*[46]	Age ≥60 years Female sex Malignancy	1.6 1.3 2.2	0: low 1–3: intermediate >3: high	
RIETE[47]	Age >75 years Recent bleeding Cancer Creatinine >1.2 mg/dL Anaemia PE (vs. DVT) index event	1 2 1 1.5 1.5 1	0: low 1–4: intermediate >4: high	
HAS-BLED[48,49]	Uncontrolled hypertension Abnormal liver/renal function Previous stroke Bleeding history or predisposition Labile INR (time in therapeutic range <60%) Age >65 years Concomitant drugs or alcohol	1 1 1 1 1 1 1	0–2: low ≥3: high	
VTE-BLEED[50]	Active cancer Male patient with uncontrolled hypertension Anaemia History of bleeding Age ≥60 years Renal dysfunction (CrCl 30–60 mL/min)	1.5 2 1 1.5 1.5 1.5	0–1: low ≥2: high	Validated in *post hoc* analysis of RCTs testing NOACs vs. VKAs after initial LMWH treatment[50,51]

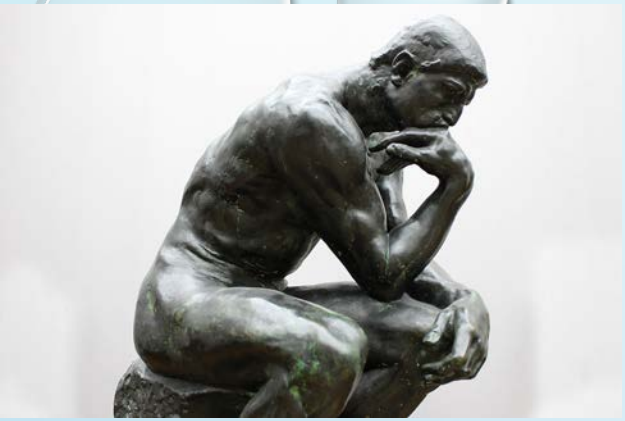
ΥΠΟΤΡΟΠΙΑΖΟΥΣΑ ΠΕ

Prediction model	Parameters	Points	Categories of recurrence risk	Risk group (for VTE recurrence) studied	Type of studies	Number of PE patients included	Remarks
Vienna prediction model[33–35]	• Male sex • Proximal DVT • Pulmonary embolism • D-dimer (continuous value)	n.a.	Continuous (nomogram)	Unprovoked VTE	Cohorts database (derivation, validation)	Derivation study: 438 (47% of cohort) Validation study: 291 (32%)	
HERDOO2[36,37]	• Hyperpigmentation, oedema or leg redness • D-dimer ≥250 μg/L (on VKAs) • Body mass index ≥30 kg/m^2 • Age ≥65 years	1 1 1 1	0–1 points: low risk; ≥2 points: high risk	Unprovoked VTE (derivation); unprovoked VTE, or with minor risk factors (validation)	Management study (derivation, internal validation)	Derivation study: 327 (49%) Management study: 1634 (59%)	Only applicable in women
DASH tool[38,39]	• D-dimer (post-VKA; normal or abnormal) • Age <50 years • Male sex • Hormonal therapy	2 1 1 −2	≤1 points: low risk; ≥2 points: high risk	Unprovoked VTE, or minor risk factors	Cohorts database (derivation, external validation)	Not reported	
DAMOVES[40,41]	• Age (continuous) • Sex • Obesity • Abnormal D-dimer • Factor VIII (continuous) • Genetic thrombophilia • Varicose veins	n.a.	Continuous (nomogram)	Unprovoked VTE	Prospective cohort (derivation) Retrospective cohort (external validation)	Derivation study: 270 (68%) Validation study: not reported	

Ottawa[a] [42,43]	• Female sex
	• Primary tumour site:
	  • lung
	  • breast
	• Tumour Node Metastasis stage I
	• History of VTE
		1
		1
		−1
		−2
		1
			≤0: low risk;
			≥1: high risk
				Patients with cancer	Retrospective cohort (derivation)
					Two RCTs (external validation)
						Not reported	Only applicable in patients with cancer

ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ ΠΕ





EARLY DISCHARGE

Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided.[c] [178,206,317–319]	IIa	A