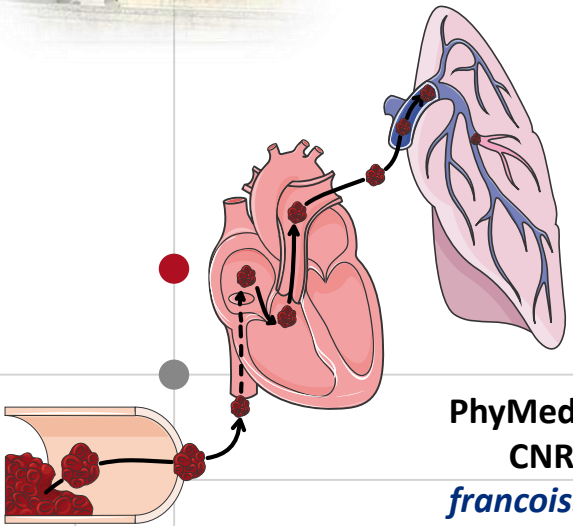
Marrakech, Octobre 2019

New ESC guidelines:

pulmonary embolism



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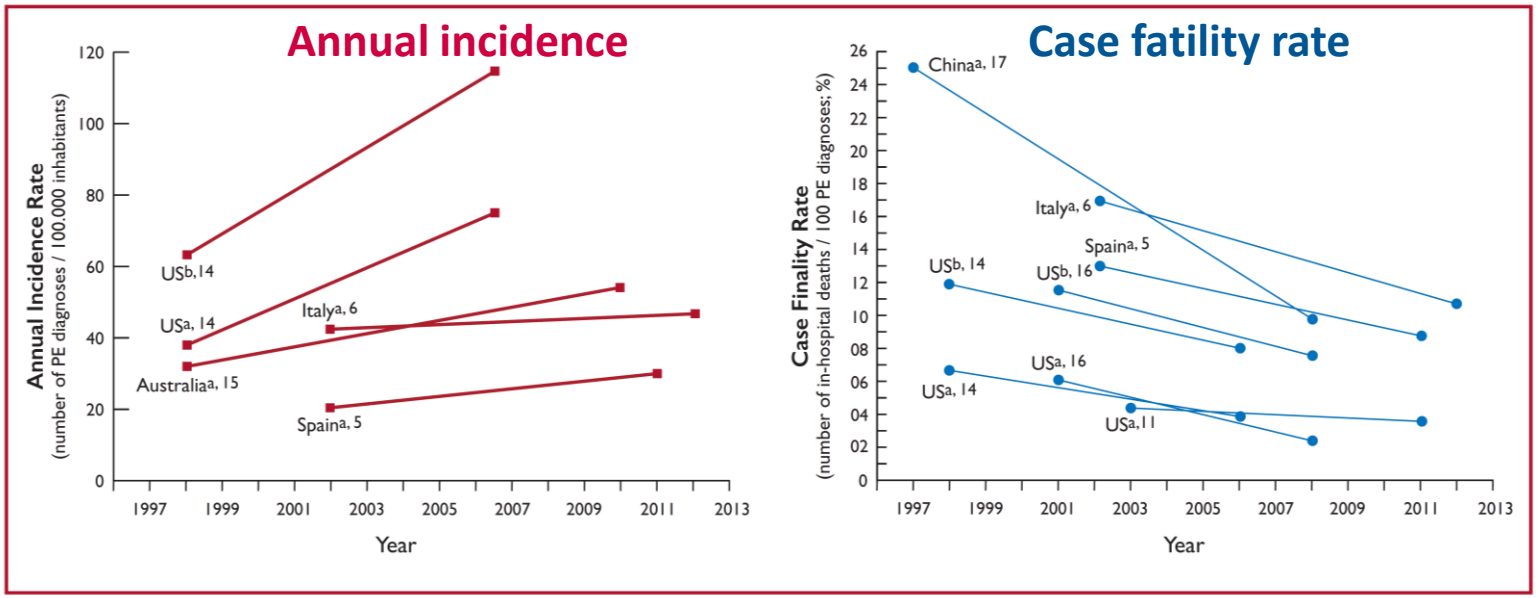
Conflicts of interest

Affiliation/Financial Relationship	Company
• Grant/Research Support	• **Servier, Medtronic, Astra-Zeneca**
• Consulting Fees/Honoraria	• **Amgen, Sanofi, Medtronic, Novartis, SJM, AZ, MSD, Actelion, Thoratec, Pfizer, Vitalaire, BMS, Bayer, boehringer**
• Major Stock Shareholder/Equity	
• Royalty Income	• **0**
• Ownership/Founder	• **0**
• Intellectual Property Rights	• **0**
• Other Financial Benefit	• **0**

Epidemiology



Konstantinides SV, et al.
***J Am Coll Cardiol*. 2016** Mar 1;67(8):976-90.

Case report

Medical history

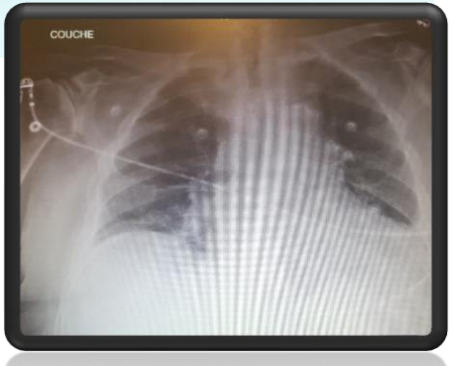
- Medical:
  - Chronic renal insufficiency
  - Ischemic stroke
  - Chondrocalcinosis
  - Pneumopathies (infections)
  - Parkinson's disease
- Surgery
  - Minor but various
- Diabetes, hypertension

Treatments

- Bisoprolol 2,5mg
- Aspirin 75mg
- Amlodipine 5mg
- Trinitrine 15mg/24h
- Prednisone 5mg
- Sertraline 75mg
- Furosemide 20mg
- Levodopa 50/12,5mg
- And many others
- …

Aguilhon S, Vandenberghe D, Roubille F.
***Int J Cardiol.* 2017.**

History



- Acute chest pain
- Prehospital managment
  - 100/60 mmHgAP 85% mmHg O2 saturation
- Emergency room
  - Transient hypoTA; 6L O2 ; T 38°C
  - Ronchi, limbs oedema, rales
- Biology:
    - CRP 209 mg/L, WBC 12 000, PCT 0,4
  - NT-proBNP 27 000 ng/L; hs tr
  - c
  - B
    - PH 7,4, pCO2 33, PO2 95, Bicar 20

Managment

- **Renal echography: normal**
- **Chest X-ray: cardiomegaly**
- **Treatments:**

Is this patient at risk for PE?

Aguilion S, Vandenberghe D, Roubille F. *Int J Cardiol.* 2017.

Risk factors for PE

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Table 3 **Predisposing factors for venous thromboembolism (data modified from Rogers *et al.*[23] and Anderson and Spencer[24])**

Strong risk factors (OR > 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 VTE
Spinal cord injury

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
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia
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

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Is PE likely?

PE-ESC guidelines 2019: revised GENEVA cliniqal prediction rule for PE

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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

b.p.m. = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

History

- Biology:
  - CRP 209 mg/L, WBC 12 000, PCT 0,4
  - NT-proBNP 27 000 ng/L; hs troponin 320->340 ng/L (normal<14)
  - creatinin 280 µM (basal 200)
  - Blood gases
    - PH 7,4, pCO2 33, PO2 95, Bicar 20

- Biology:
  - D-Dimeres: 750 ng/L

What do you think about D-Dimeres value?

PE-ESC guidelines 2019: what is new?

Diagnosis	
A 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

PE-ESC guidelines 2019: what is new?

From: **Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism: The ADJUST-PE Study**

Study Results According to D-Dimer Assays

Table 3. Study Results According to D-Dimer Assays

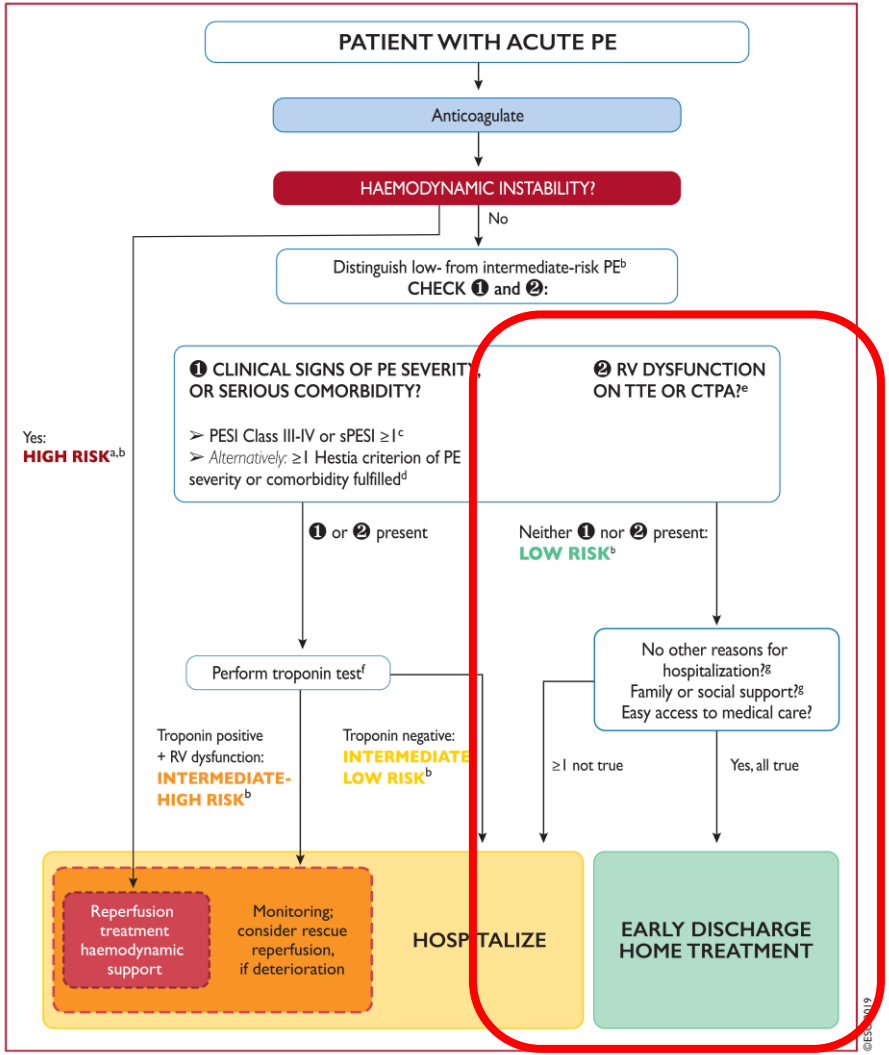
D-Dimer Assay	Low/Intermediate or Unlikely Clinical Probability, No. of Patients	D-Dimer <500 µg/L	3-mo Thromboembolism Risk		D-Dimer ≥500 µg/L and <Age-Adjusted Cutoff	3-mo Thromboembolism Risk	
			No. of Events/ Total Patients	% (95% CI)		No. of Events/ Total Patients	% (95% CI)
VIDAS D-Dimer Exclusion	1345	423	0/417	0.0 (0.0-0.9)	130	0/127	0.0 (0.0-2.9)
Innovance D-Dimer	838	202	1/202	0.5 (0.1-2.8)	103	1/103	1.0 (0.2-5.3)
STA-Liatest D-Dimer	389	132	0/132	0.0 (0.0-2.8)	49	0/47	0.0 (0.0-7.6)
D-Dimer HS 500	185	32	0/31	0.0 (0.0-11.0)	23	0/23	0.0 (0.0-14.3)
Second-generation Tina-quant	128	26	0/26	0.0 (0.0-12.9)	32	0/31	0.0 (0.0-11.0)
Cobas h 232	13	2	0/2	0.0 (0.0-65.8)	0		
Total	2898	817	1/8	0 0.1 (0.0-0.7)	337	1/331	0.3 (0.1-1.7)

JAMA. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135

Hospitalization in internal medicine

Would you hospitalize this patient?

Aguilhon S, Vandenberghe D, Roubille F. *Int J Cardiol.* 2017.


PATIENT WITH ACUTE PE
Anticoagulate
HAEMODYNAMIC INSTABILITY?
No
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]
Yes:
HIGH RISK[a,b]
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

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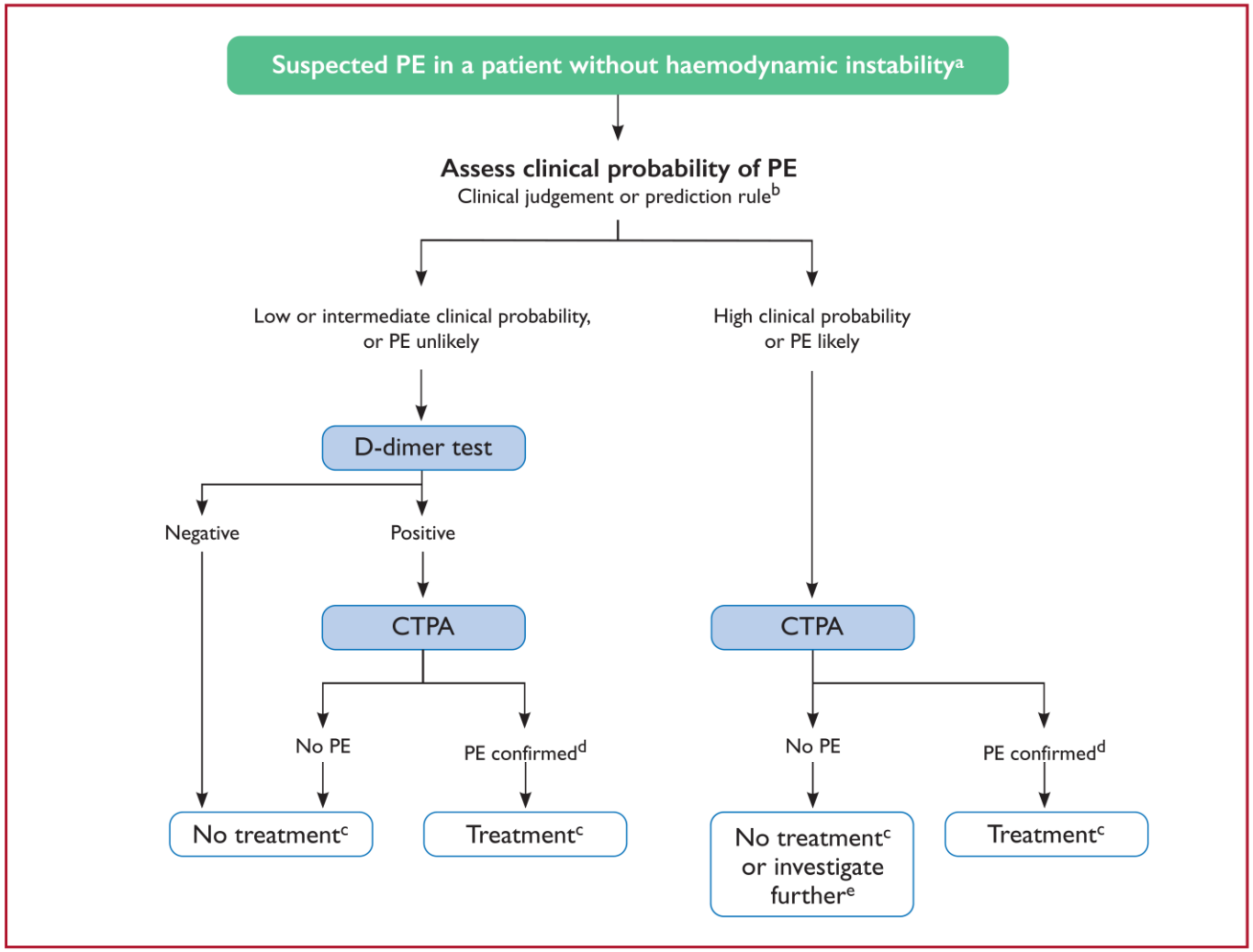
In case of established PE,
is this patient at high risk?



Instability

Risk assessment
A clear definition of haemodynamic instability and high-risk PE is provided (*Table 4*).
Assessment of PE severity and early PE-related risk is recommended, in addition to comorbidity/aggravating conditions and overall death risk.
A clear word of caution that RV dysfunction may be present, and affect early outcomes, in patients at 'low risk' based on clinical risk scores.

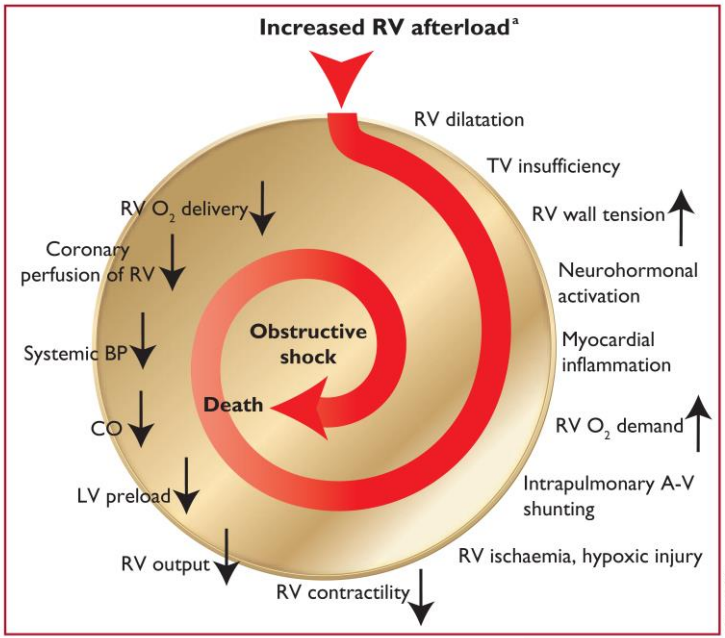


Table 4 **Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)**

(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)	

BP = blood pressure.

Interest of the PESI score

Parameter	Original version[214]	Simplified version[218]
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 blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+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%) **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%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

ESC 2014

Interest of the PESI score

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Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	
Temperature <36 °C	+20 points	
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	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%)

88+10+20+30+60>125

Barco S, et al; PEITHO Investigators.
Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials.
Eur Respir J. 2018 Jan 18;51(1).

ESC 2014

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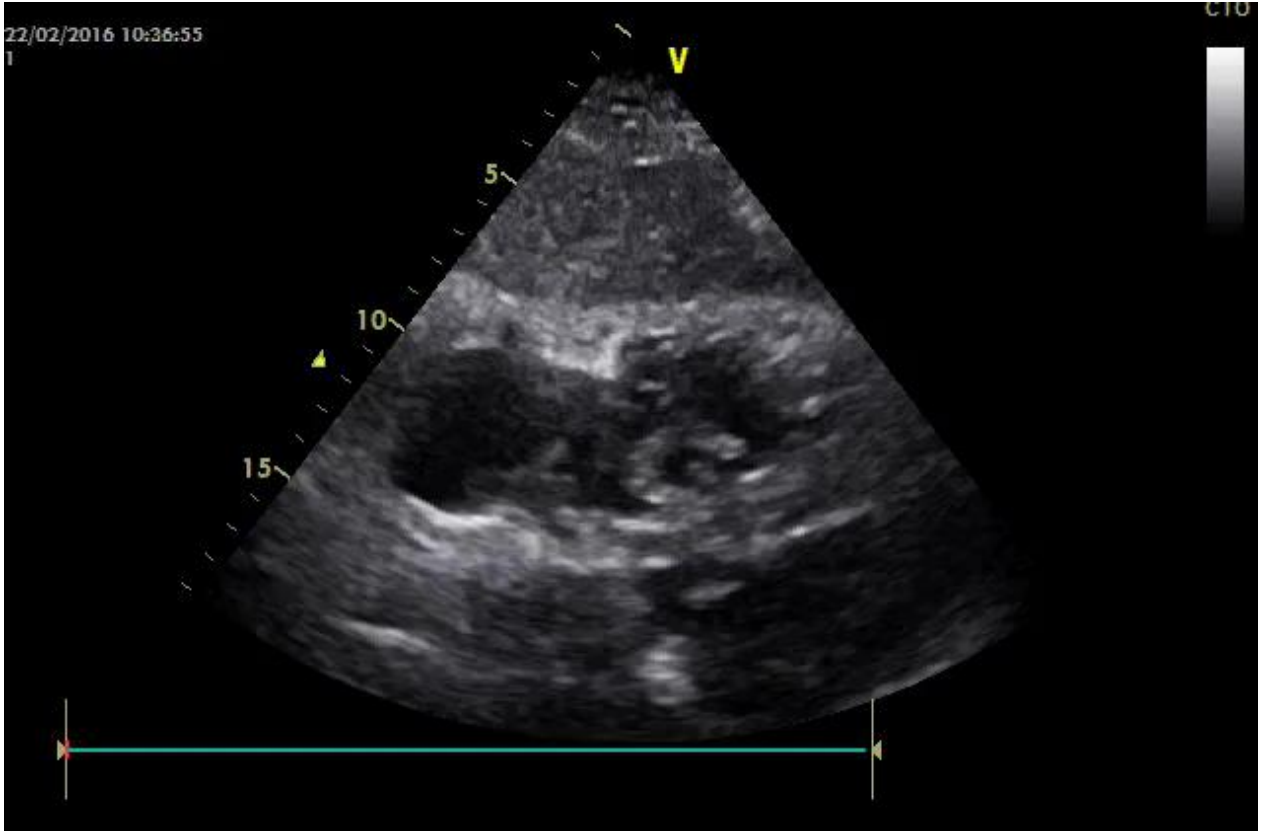
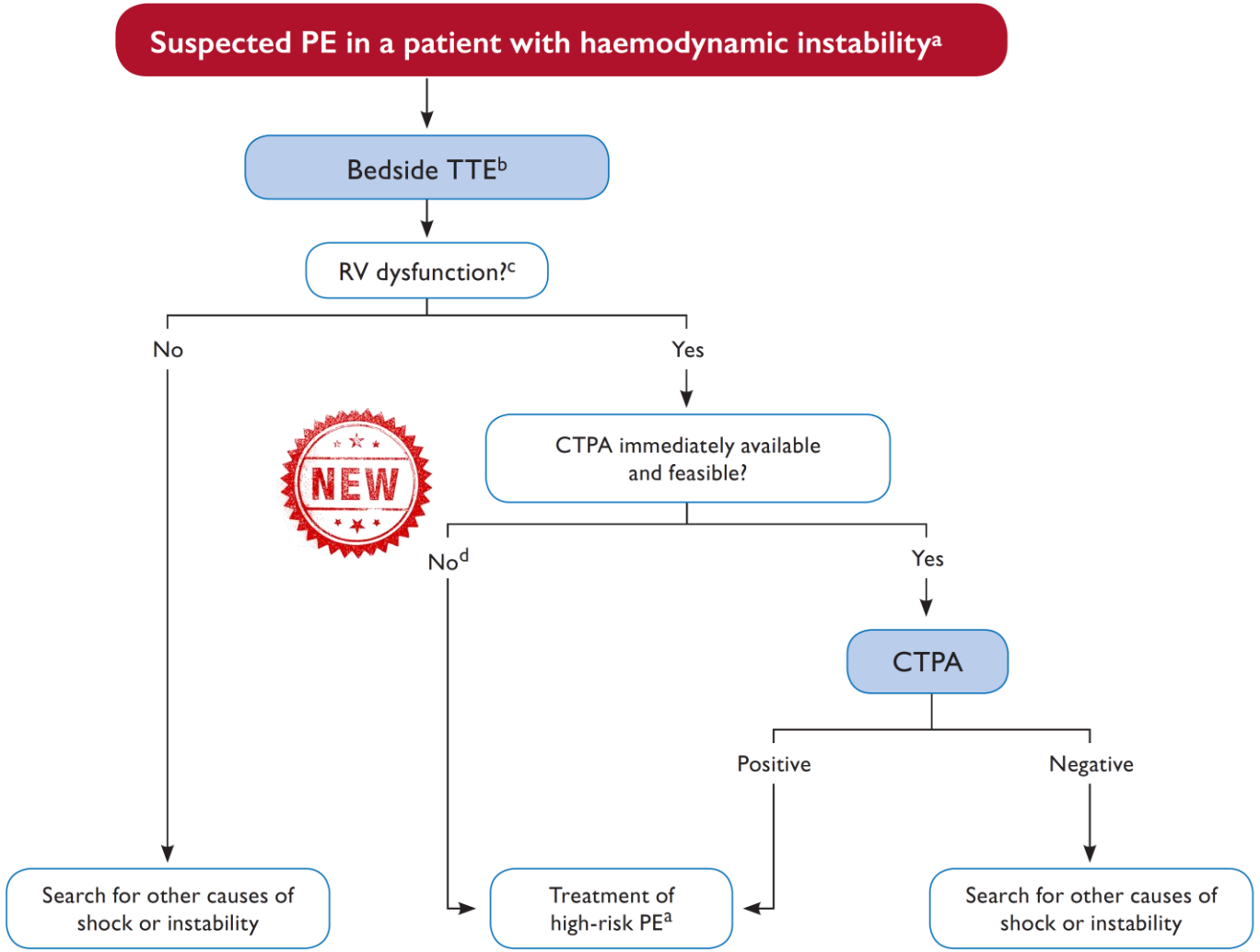
Hospitalization in internal medicine

- **Echography by the fellow**



Aguilhon S, Vandenberghe D, Roubille F. *Int J Cardiol.* 2017.



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Right heart failure: how to manage it?

Table 9 Treatment of right ventricular failure in acute high-risk pulmonary embolism

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

CO = cardiac output; BP = blood pressure; ECMO = extracorporeal membrane oxygenation; RV = right ventricle/ventricular.
[a]Epinephrine is used in cardiac arrest.

Treatment: Low/intermediate risk PE?

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6.7 Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism

Recommendations	Class[a]	Level[b]
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
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.[262,309–311]	I	A
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
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached.[315,316]	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
Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment.[282]	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy[e] or percutaneous catheter-directed treatment[e] should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE.[c,f 179]	III	B

NEW

Anticoagulation: how long?

Recommendations	Class[a]	Level[b]
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
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
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
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.[355–357]	IIb	B
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

Anticoagulation: how long in case of cancer?

Recommendations	Class[a]	Level[b]
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

Pregnancy

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

SUSPECTED PE DURING PREGNANCY
High pretest probability, or intermediate/low probability and positive D-dimer result

Anticoagulate with LMWH

- Chest X-ray[a]
- Compression proximal duplex ultrasound, if symptoms or signs suggestive of DVT[b]

Proximal DVT present

Proximal DVT not present

SPECIFIC INVESTIGATION FOR PE
- If chest X-ray normal => CTPA or perfusion lung scan
- If chest X-ray abnormal[a] => CTPA[c]

Negative

Indeterminate or positive

PE ruled out

Negative

Review by radiologist or nuclear physician experienced in diagnosis of PE in pregnancy

Positive

- Continue with LMWH at therapeutic dose[d]
- Assess PE severity and the risk of early death[e]
- Refer to multidisciplinary team with experience of PE management in pregnancy
- Provide plan to guide management of pregnancy, labour and delivery, postnatal and future care

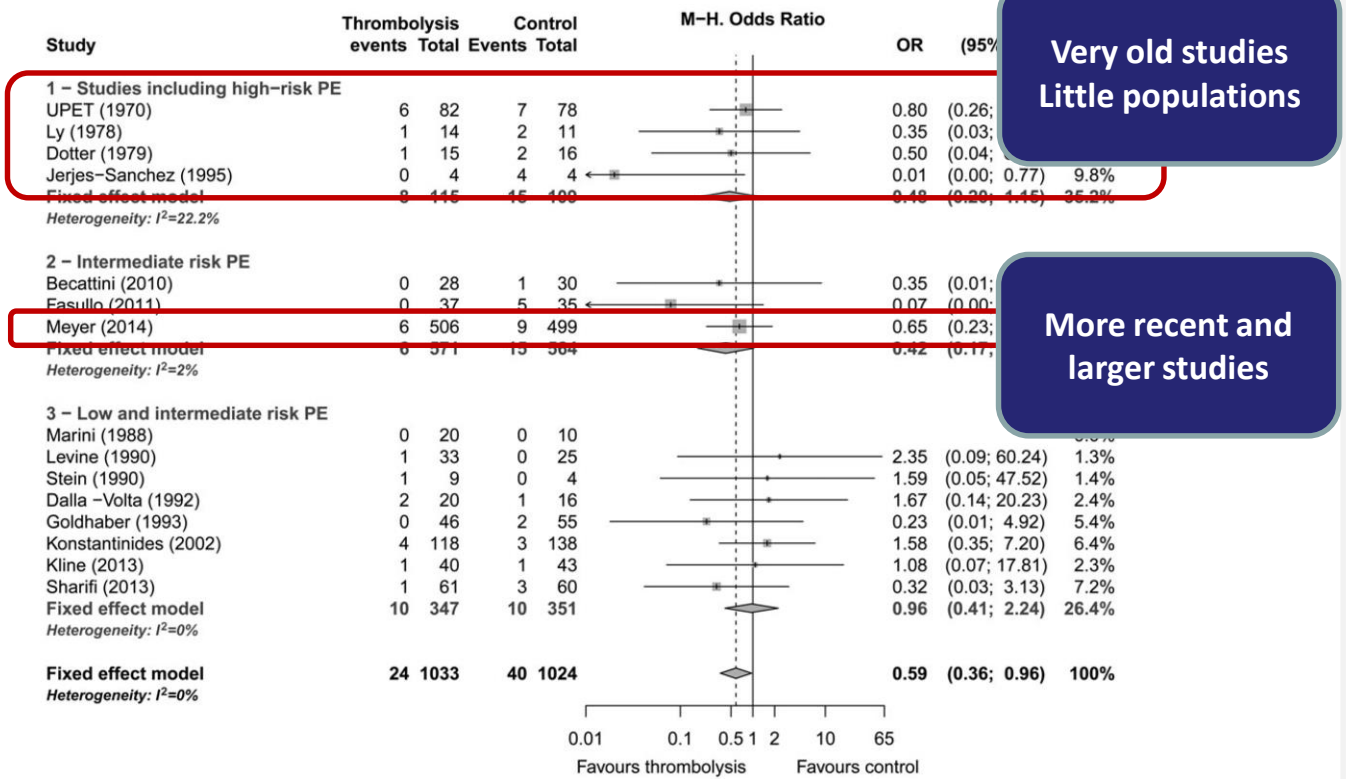
Follow-up?

Routine clinical evaluation[c] of patients 3–6 months after the acute PE episode is recommended.[288,352,353,437]	I	B
An integrated model of patient care after PE (involving hospital specialists, appropriately qualified nurses, and primary care physicians) is recommended to ensure optimal transition from hospital to community care.	I	C
In symptomatic patients with mismatched perfusion defects persisting on V/Q scan[d] beyond 3 months after acute PE, referral to a PH/CTEPH expert centre is recommended, after taking into account the results of echocardiography, natriuretic peptide levels, and/or [477]	I	C
Further diagnostic evaluation[e] should be considered in patients with persistent or new-onset dyspnoea/exercise limitation after PE.	IIa	C
Further diagnostic evaluation[e] may be considered in asymptomatic patients with risk factors for CTEPH[f] [447–449,478]	IIb	C

PE-ESC guidelines 2019: what is new?

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

Interest of thrombolytics in PE: early mortality

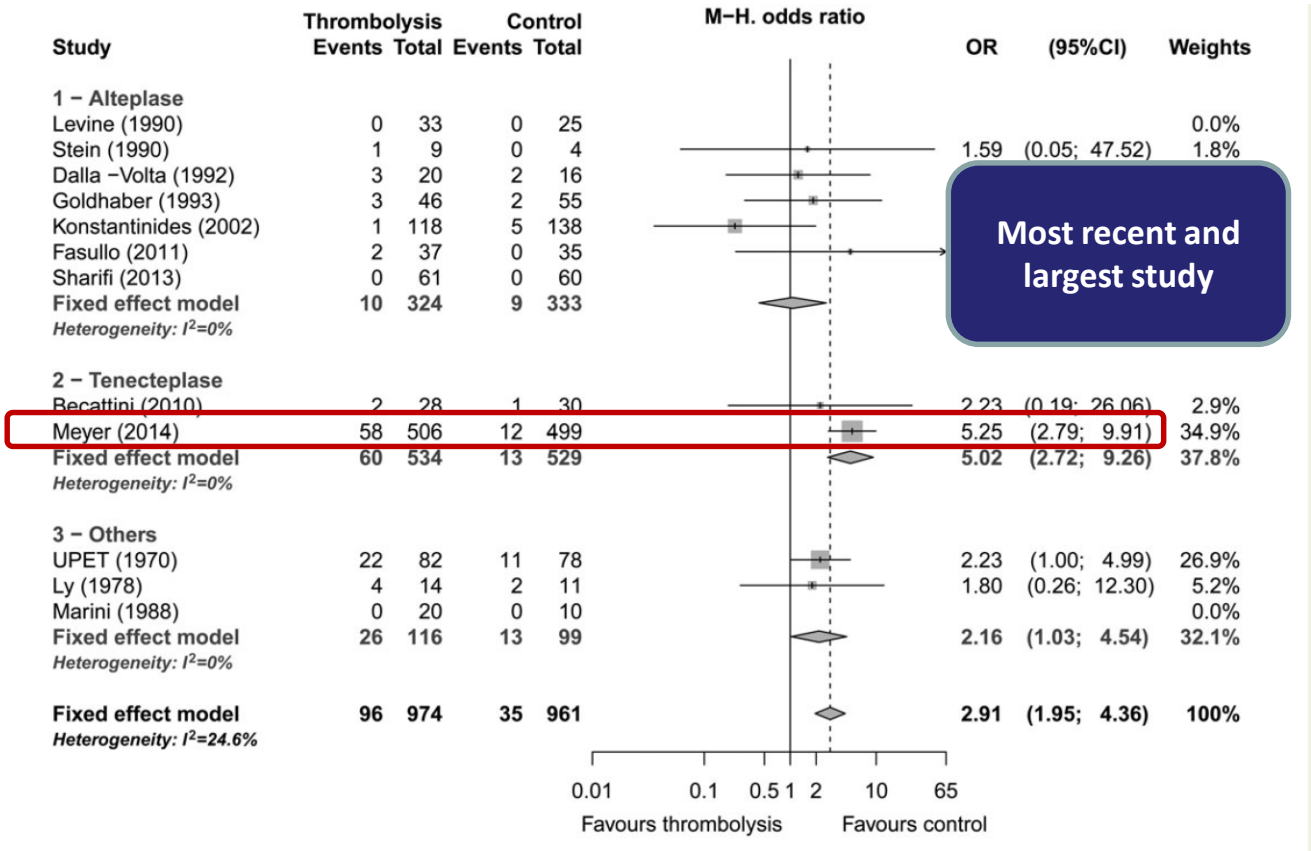


Very old studies
Little populations

More recent and larger studies

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis
***Eur Heart J*. 2014;36(10):605-614.**

Interest of thrombolytics in PE: major bleeding



Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

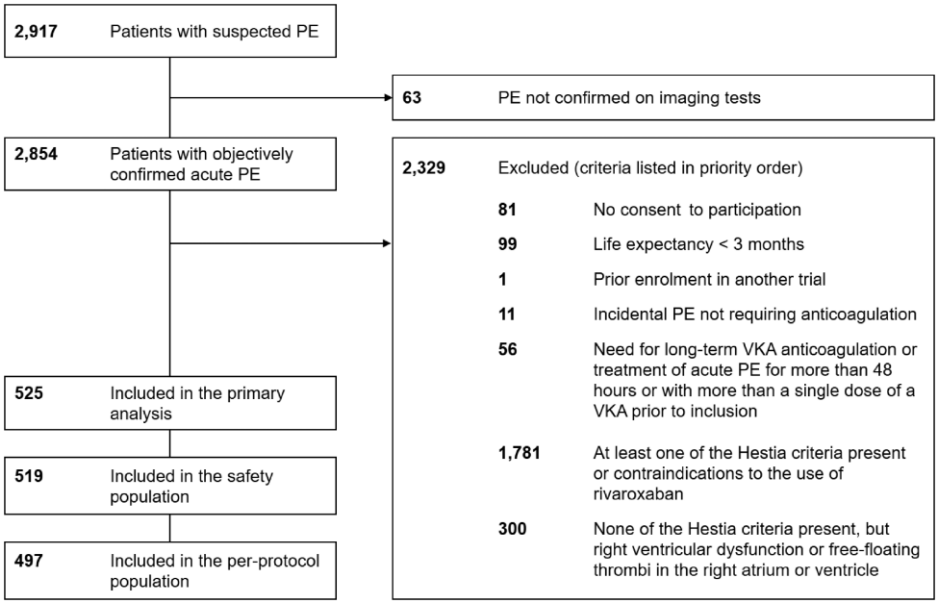
***Eur Heart J*. 2014;36(10):605-614.**

Early discharge?

Recommendation	Class[a]	Level[b]
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

Early discharge?

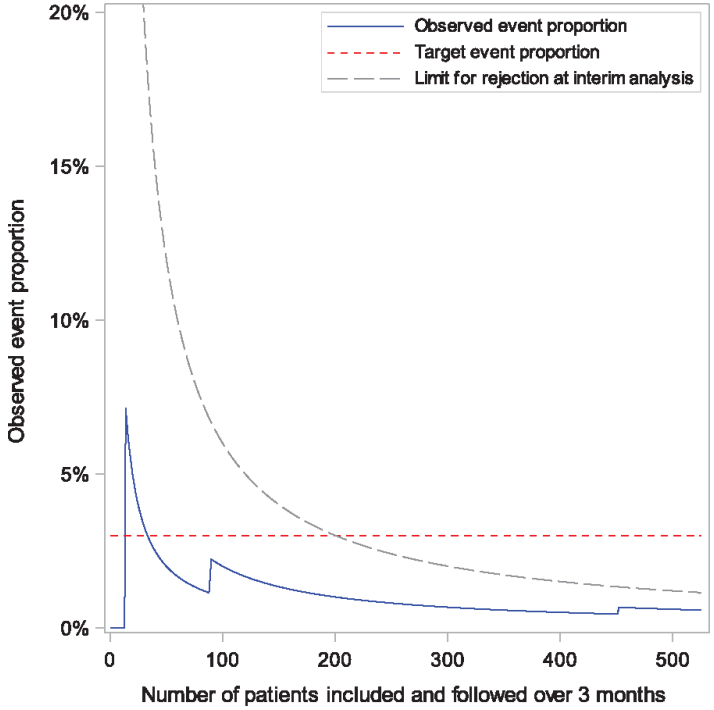
Flow diagram of the screening, selection, and enrolment process. PE, pulmonary embolism; VKA, vitamin K ...



European Heart Journal, ehz367, In press.

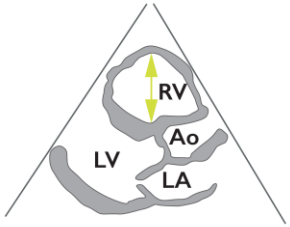
Early discharge?

Early stopping boundaries along subject-by-subject accounting of the event rate.

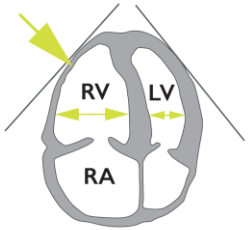


European Heart Journal, ehz367, In press.

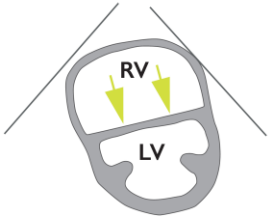
Echography: signs in favour



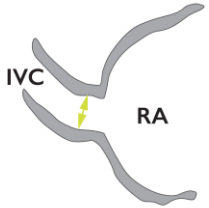
A. Enlarged right ventricle, parasternal long axis view



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

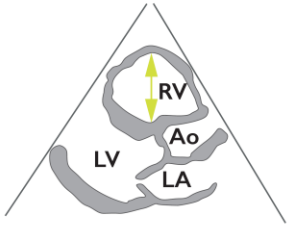


C. Flattened intraventricle septum (arrows) parasternal short axis view

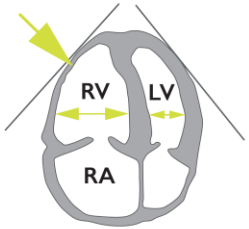


D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view

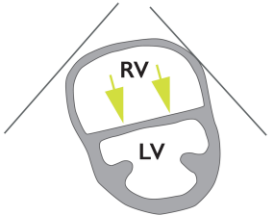
Echography: signs in favour



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



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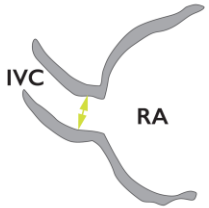

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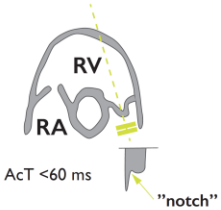
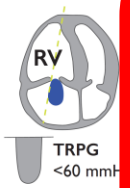
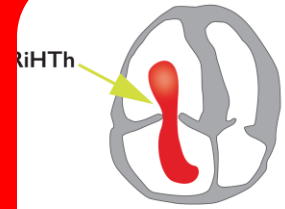
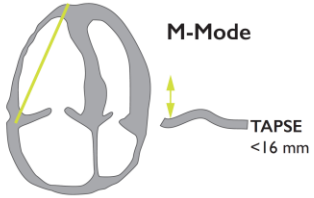




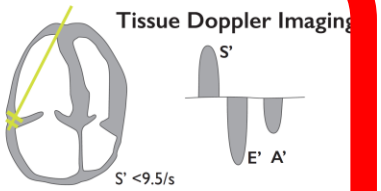
E. 60/60 sign: coexistence of acceleration time of pulmonary ejectio <60 ms and midsystolic "notch" with mildy elevated (<60 mmHg) peak systol gradient at the tricuspic valve



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)

Transfer to ICCU

- **echocardiography confirmation**
  - **right cavities :**
    - **dilated (41mm in medium ventricle)**
    - **moderately hypokinetic (TAPSE at 15mm and S wave at 9cm/s).**
    - **pressures were estimated at 55mmHg with a dilatation of the inferior vena cava.**
    - **The left ventricular function was preserved**
    - **no significant left valvulopathy and the pericardium was dry. The**
- **hypothesis of a pulmonary embolism**
  - **impossible to confirm because of the contraindication for the pulmonary angioscanner (predialysis real function and unstable hemodynamics)**
  - **pulmonary scintigraphy of ventilation perfusion?**

PE: evaluation of severity at a glance!

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

http://www.mdcalc.com/pulmonary-embolism-severity-index-pesi/

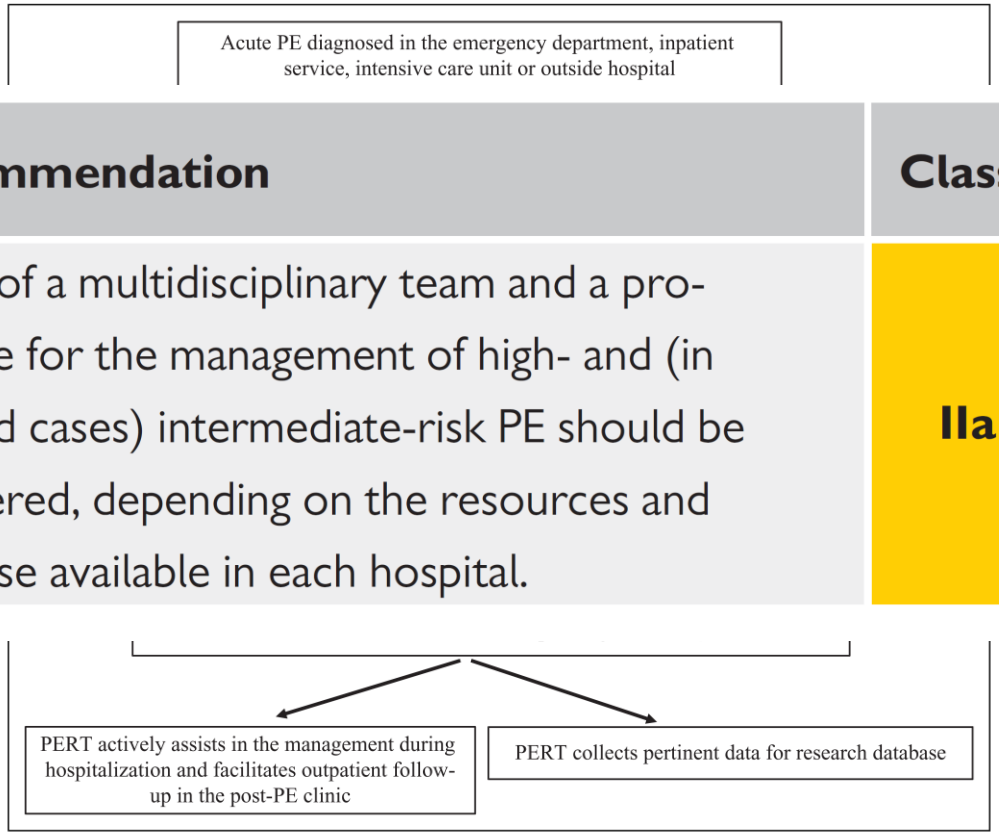
ESC 2014

ICCU: **PESI score estimated at 178 (class V).**

- **The patient presented no major contraindication of thrombolysis but several minor:**
  - **age> 75 years,**
  - **stroke**
- **After:**
  - **team discussion**
  - **dialogue with the patient,**
  - **the family**
  - **GP, thrombolysis was decided (acteplace, 100 mg over 2 hours).**
- **Only a moderate epistaxis**
- **The** **early oral anti**

How to decide rescue thrombolysis?

PE reponse teams



Recommendation	Class[a]	Level[b]
Set-up of a multidisciplinary team and a pro-gramme 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

Porrt
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PE-ESC guidelines 2019: thrombolysis?

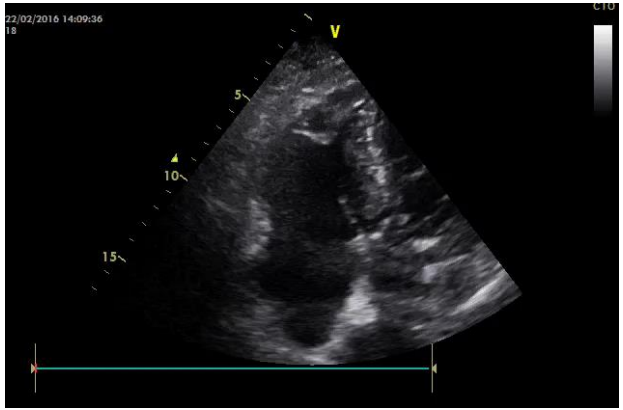
Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute**
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]	History of haemorrhagic stroke or stroke of unknown origin
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Ischaemic stroke 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

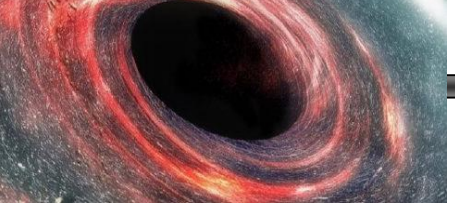
BP = blood pressure; IU = international units; rtPA, recombinant tissue-type plasminogen activator.

[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.

Outcomes

- Echography
  - Thrombus disappears quickly
  - TAPSE 14 mm ; onde S 8cm/s
- Epistaxis
- Discharge one week later at home

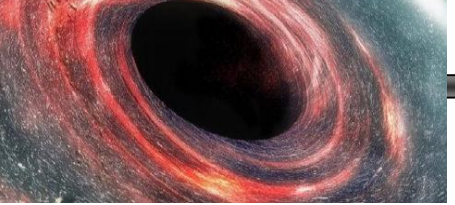




Gaps in knowledge

Diagnosis

- The optimal method to adjust (based on the patient's age or in combination with clinical probability) the D-dimer threshold, permitting the exclusion of PE while reducing the number of unnecessary imaging tests to a minimum, remains to be determined.
- The diagnostic value and clinical significance of isolated subsegmental contrast-filling defects in the modern CTPA era remain controversial.
- No robust data exist to guide the decision on whether to treat incidental PE with anticoagulants compared with a strategy of watchful waiting.
- For patients presenting with non-traumatic chest pain, the benefits vs. risks of 'triple rule-out' (for coronary artery disease, PE, and aortic dissection) CT angiography need further evaluation before such an approach can be routinely recommended.



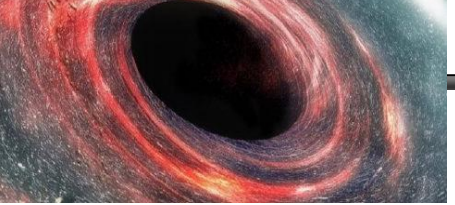
Assessment of pulmonary embolism severity and the risk of early death

- The optimal, clinically most relevant combination (and cut-off levels) of clinical and biochemical predictors of early PE-related death remain to be determined, particularly with regard to identifying possible candidates for reperfusion treatment among patients with intermediate-risk PE.
- The need for assessment of the RV status in addition to clinical parameters, to classify a patient with acute symptomatic PE as being at low vs. intermediate risk, needs to be confirmed by further prospective management (cohort) studies.

Gaps in knowledge

Treatment in the acute phase

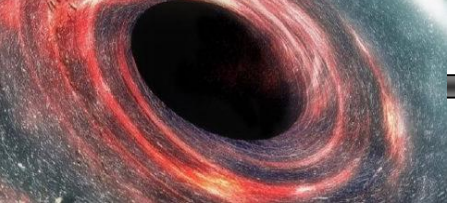
- The clinical benefits vs. risks of reduced-dose thrombolysis and catheter-based reperfusion modalities in patients with intermedia-te-high-risk PE should be evaluated in prospective randomized trials.
- The place of ECMO in the management of acute high-risk PE awaits support by additional evidence from prospective manage-ment (cohort) studies.
- The optimal anticoagulant drug(s) and regimen in patients with renal insufficiency and CrCl <30 mL/min remain unclear.
- The criteria for selecting patients for early discharge and outpatient treatment of PE, and particularly the need for assessment of the RV status with imaging methods and/or laboratory markers in addition to calculating a clinical score, need to be further validated in prospective cohort studies.



Gaps in knowledge

Chronic treatment and prevention of recurrence

- The clinical value and the possible therapeutic implications of models or scores assessing the risk of VTE recurrence, and the risk of bleeding under anticoagulation, need to be revisited in the NOAC era.
- The effectiveness of extended treatment with a reduced dose, or apixaban or rivaroxaban, should be confirmed in patients with a high risk of recurrent PE.
- The evidence supporting the efficacy and safety of NOACs for the treatment of PE in patients with cancer needs to be extended by further studies.
- In patients with cancer, the anticoagulant regimen and dose after the first 6 months should be clarified and prospectively tested.
- The optimal time for discontinuing anticoagulant treatment after an episode of acute PE in patients with cancer is yet to be determined.



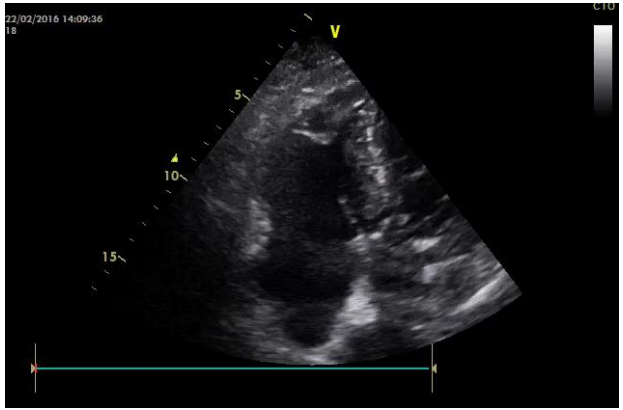
Long-term sequelae of pulmonary embolism

- The optimal follow-up strategy, including the spectrum of diagnostic tests that may be necessary, in patients with persisting symptoms and functional limitation after acute PE needs to be defined and prospectively validated.
- In the absence of persisting symptoms or functional limitation after acute PE, the criteria for identifying patients whose risk of developing CTEPH may be sufficiently high to justify further diagnostic workup require further elaboration and validation in prospective cohort studies.

Duration?

- One y later, as everything is OK, the GP proposes to stop the NOAC

- Agree?/Disagree?



Conclusions

- **Thrombolysis is indicated in severe PE**
- **Thrombolysis is indicated in selected patients admitted for intermediate-risk PE**
- **Place of low-doses protocols? Other regimens?**
- **Alternative managments?**
- **More trials are needed.**

Current trials registered on low doses of thrombolysis

Country	N	Begin	NCT	Remark
China	460	2009	***NCT01531829***	LWH *vs* LWH+half dose thrombolysis
USA	158	Soon	***NCT03581877***	*vs* **Catheter Acoustic Directed Thrombolysis for Submassive PE**
Italy	130	2021	***NCT02604238***	LWH *vs* LWH+half dose thrombolysis

Source: *Clinicaltrials*.gov
Serching terms: low dose | Interventional Studies | Pulmonary Embolism and Thrombosis
2019/01/10

Conclusions

- **Thrombolysis is indicated in severe PE**
- **Thrombolysis is indicated in selected patients admitted for intermediate-risk PE**
- **Place of low-doses protocols? Other regimens?**
- **Alternative managments?**
- **More trials are needed.**

Diagnosis	
A 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	
Assessment of 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
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

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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
PE in cancer	
Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with the exception of patients with gastrointestinal cancer.	IIa
PE in pregnancy	
Amniotic fluid embolism should be considered in a pregnant or post-partum woman, with unexplained haemodynamic instability or respiratory deterioration, and disseminated intravascular coagulation.	IIa

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Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE.	IIa
NOACs are not recommended during pregnancy or lactation.	III
Post-PE care and long-term sequelae	
Routine clinical evaluation is recommended 3–6 months after acute PE.	I
An integrated model of care is recommended after acute PE to ensure optimal transition from hospital to ambulatory care.	I
It is recommended that symptomatic patients with mismatched perfusion defects on a V/Q scan >3 months after acute PE are referred to a pulmonary hypertension/CTEPH expert centre, taking into account the results of echocardiography, natriuretic peptide, and/or cardiopulmonary exercise testing.	I

NEW

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NEW

Current trials registered on low doses of thrombolysis

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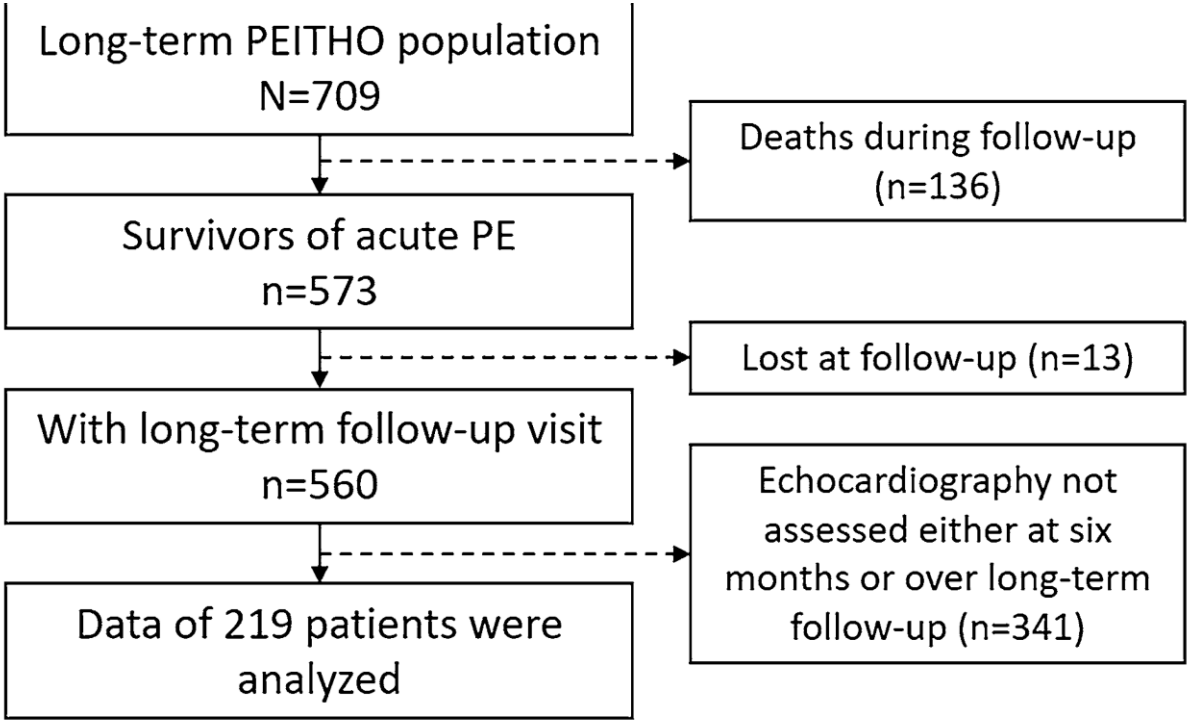
PEITHO: outcomes according to echographic results

Incomplete echocardiographic recovery at 6 months predicts long-term sequelae after intermediate-risk pulmonary embolism. A post-hoc analysis of the Pulmonary Embolism Thrombolysis (PEITHO) trial



Barco S, et al.
Clin Res Cardiol. 2018. *In press.*

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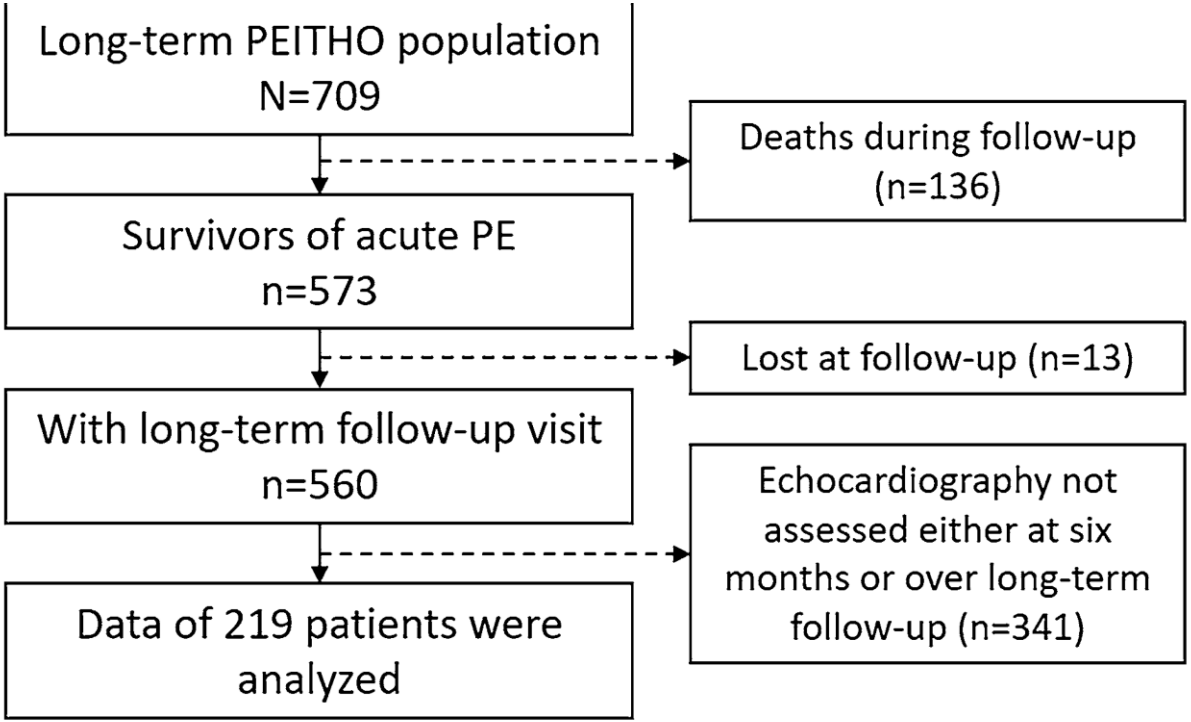

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Factors associated with pulmonary hypertension

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age ≤ 65 years	0.36	0.15–0.89	-	-
Male sex	0.47	0.21–1.08	-	-
Chronic heart failure	3.81	0.89–16.89	7.72	1.28–46.65
Active cancer	4.08	0.92–18.16	-	-
Prior venous thromboembolism	1.10	0.44–2.76	-	-
Unprovoked pulmonary embolism	0.99	0.37–2.61	-	-
Tenecteplase treatment	1.19	0.54–2.62	-	-
NYHA II, III or IV (assessed at 6 months)	3.20	1.33–7.71	-	-
Incomplete or absent recovery of echo parameters (assessed at 6 months)	4.77	1.80-12.63	7.14	2.15–23.78

Barco S, et al.
***Clin Res Cardiol*. 2018. *In press*.**

IVC filters are rarely of interest

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Recommendations	Class[a]	Level[b]
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