

제129차
대한결핵 및 호흡기학회
춘계학술대회
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Pulmonary Embolism Update 2020

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최원일

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- ▶ Long-term Sequelae of Pulmonary Embolism

Epidemiology

Epidemiology: 폐색전증의 빈도가 증가

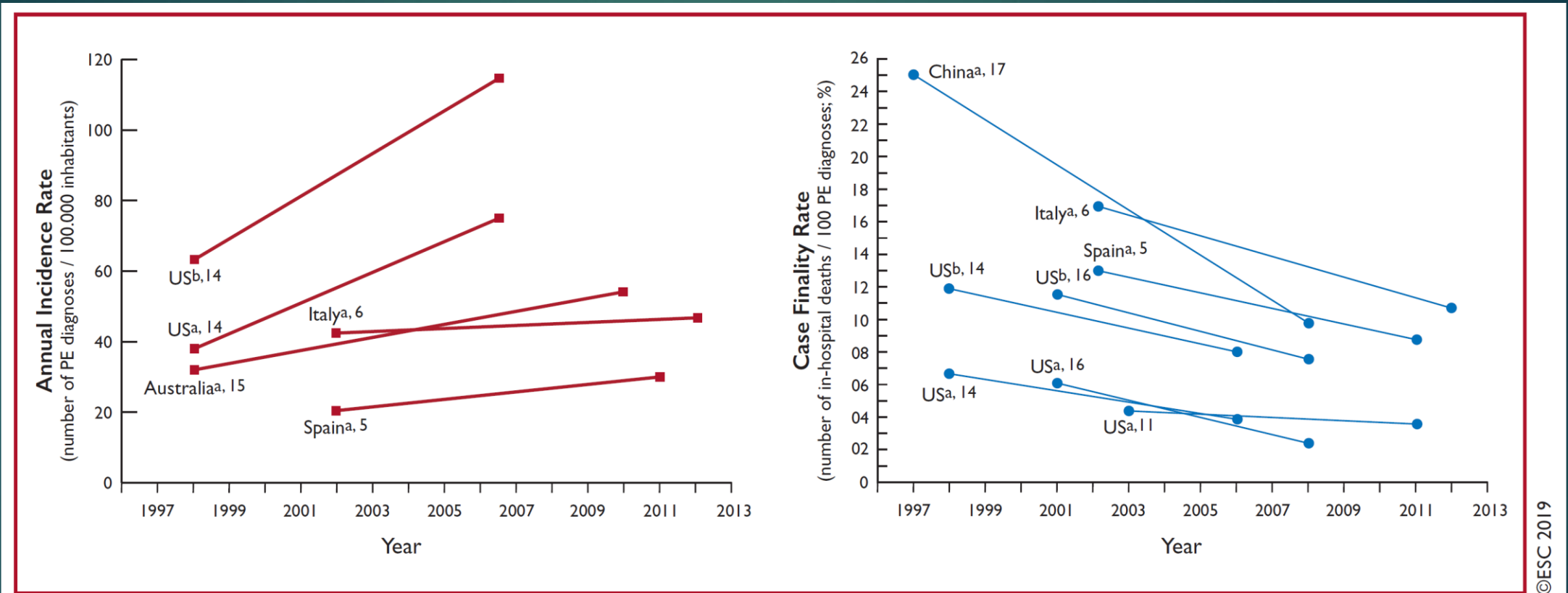
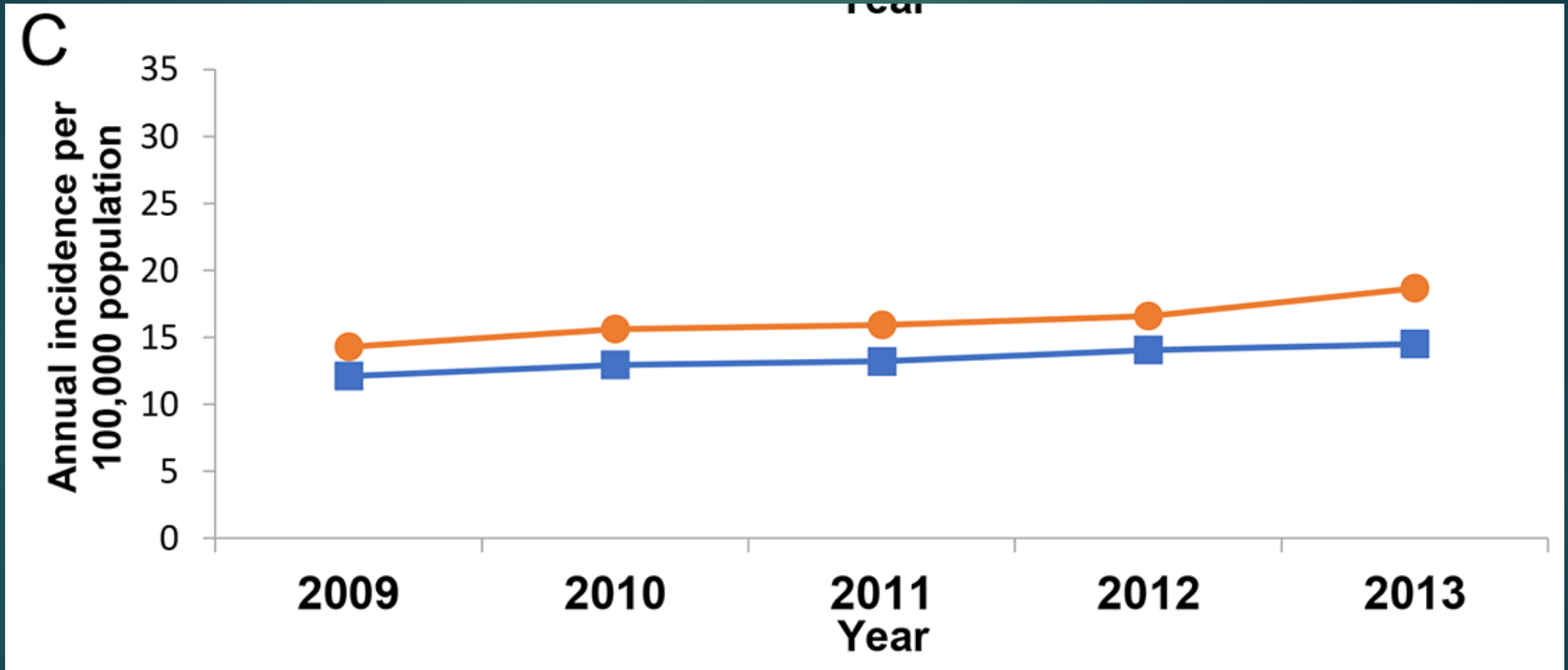


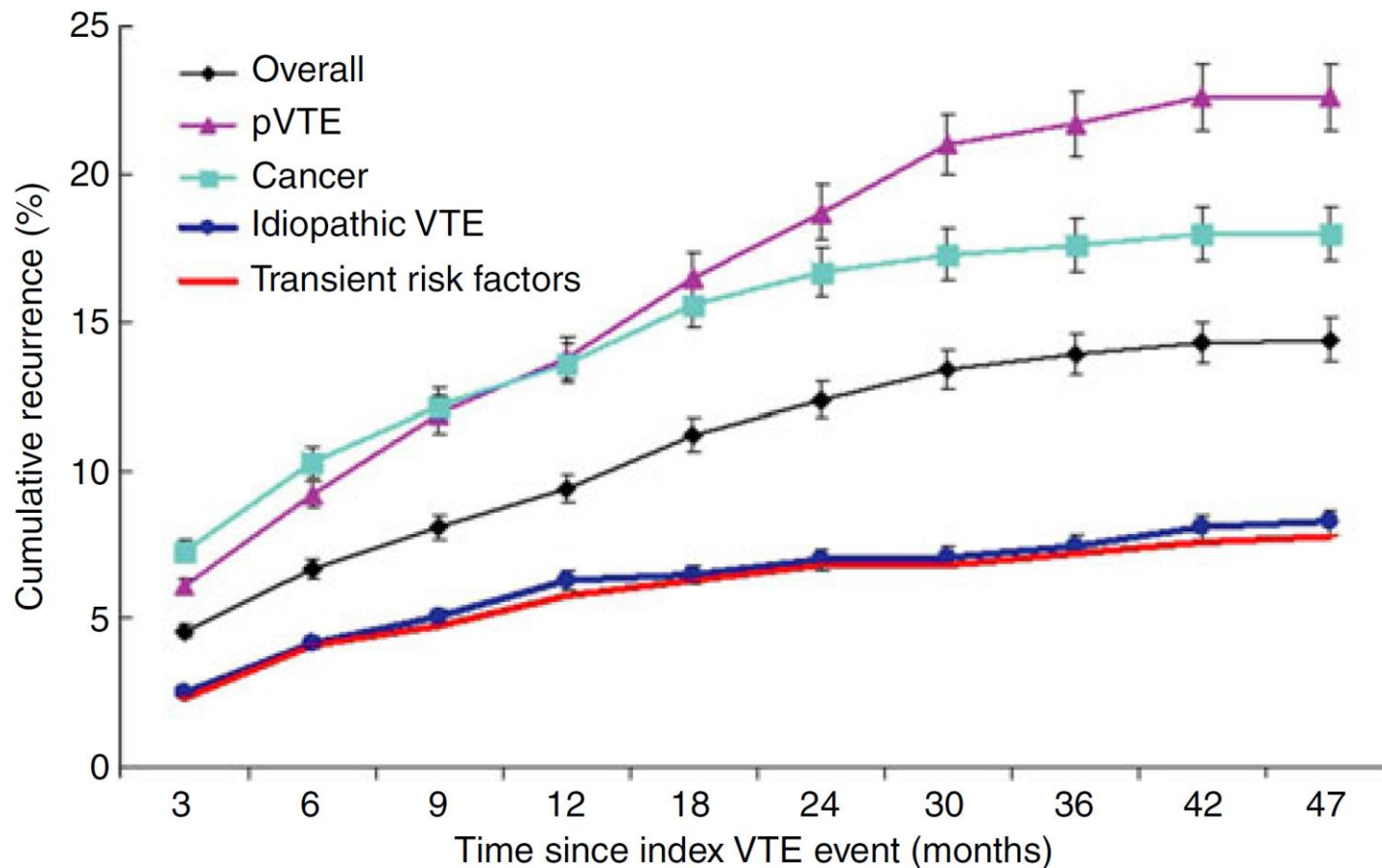
Figure 1 Trends in annual incidence rates (left panel) and case fatality rates (right panel) of pulmonary embolism around the world, based on data retrieved from various references.^{5,6,11,14–17} Reproduced with permission from JACC 2016;67:976-90. PE = pulmonary embolism; US = United States.

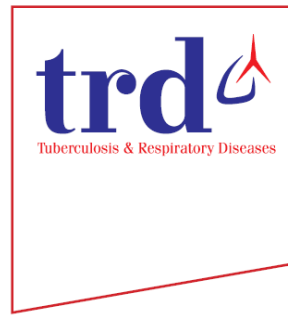
국내 폐색전증의 빈도



ORIGINAL ARTICLE

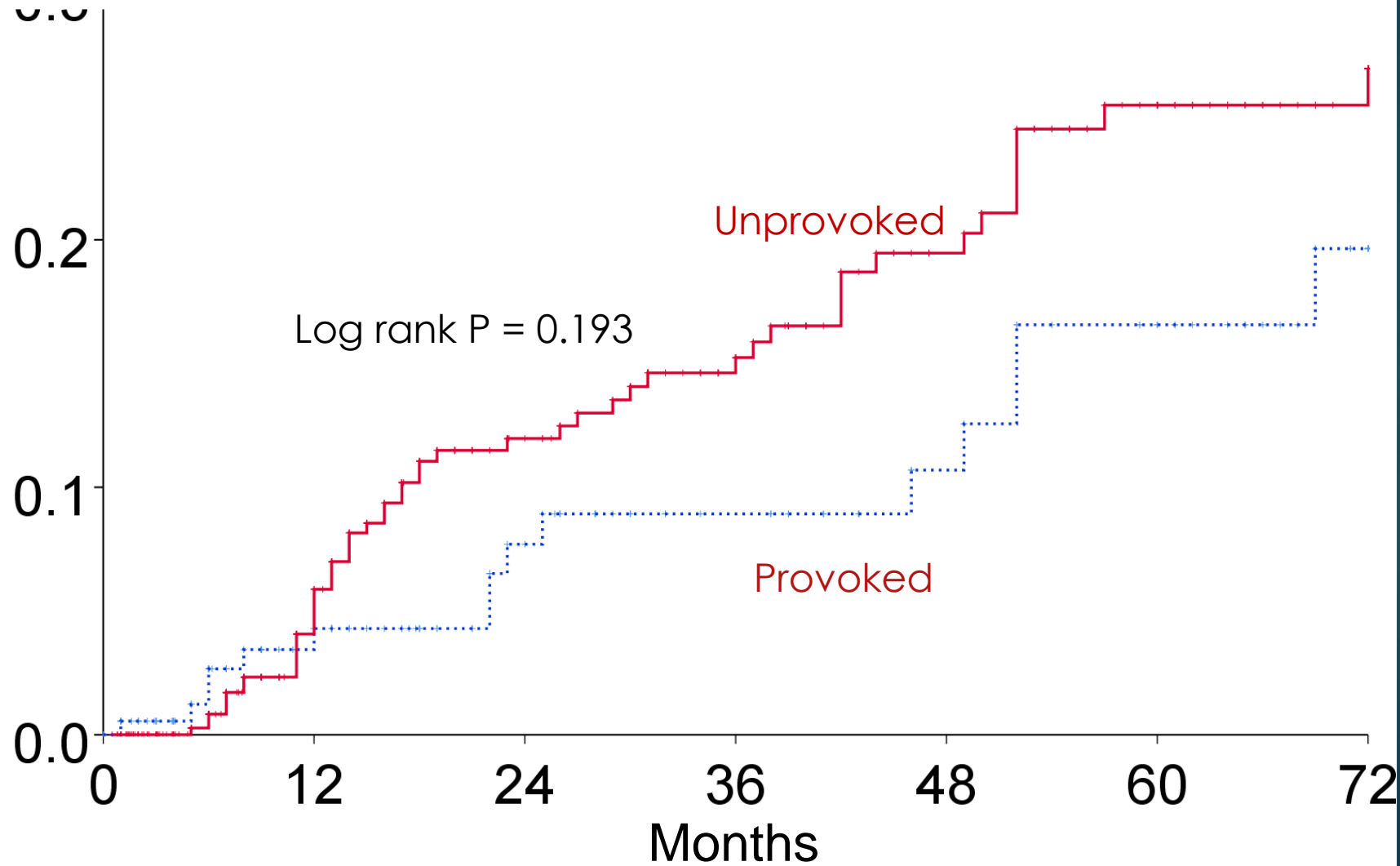
Incidence and cumulative recurrence rates of venous thromboembolism in the Taiwanese population





Incidence and Risk Factors of Recurrent Venous Thromboembolism after Pulmonary Embolism

Cumulative Incidence



PE Risk Factors

Provoked

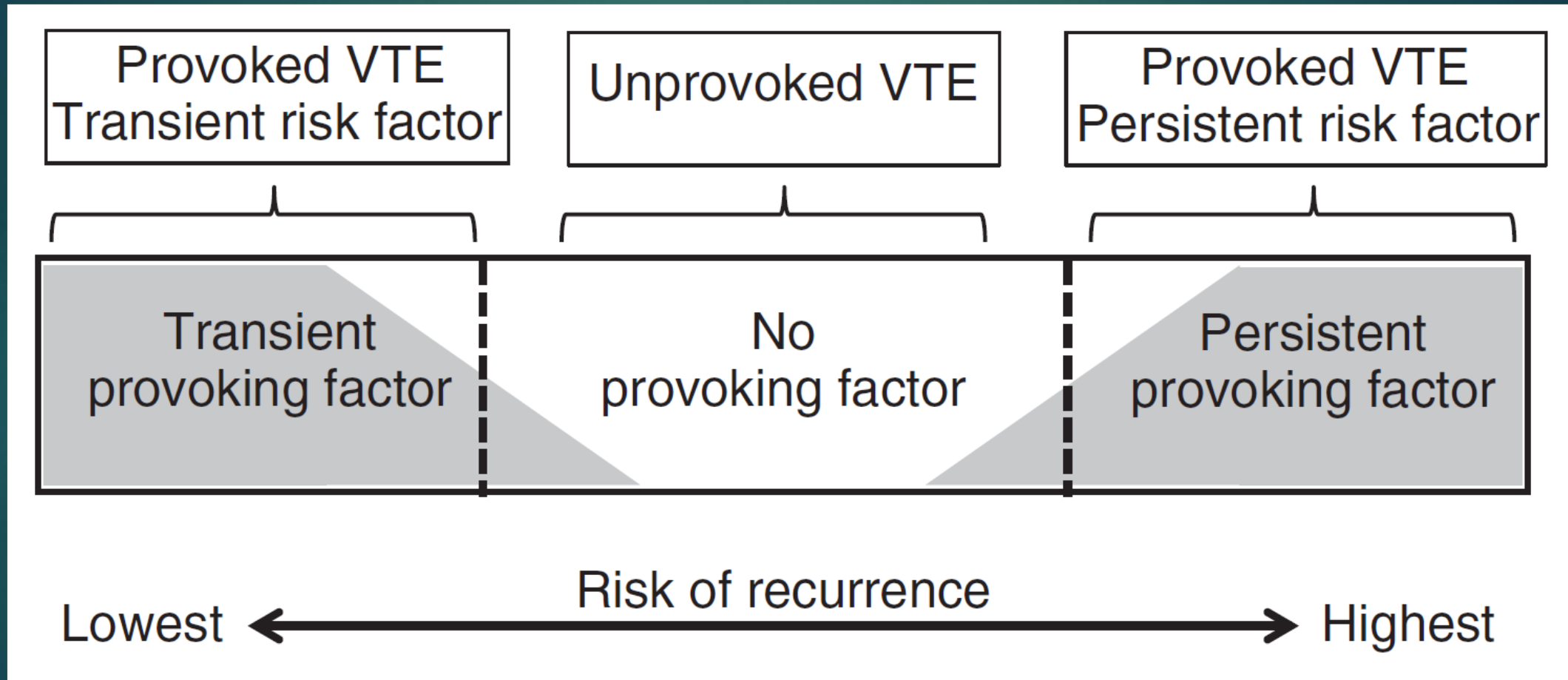
Patient with an antecedent (within 3 months) and transient major clinical risk factor for venous thromboembolism (VTE)

- Surgery, trauma, significant immobility, pregnancy or puerperium
- Hormonal therapy (oral contraceptive or hormone replacement therapy)

Unprovoked

- No antecedent major clinical risk factor for VTE
- Active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient

Conceptual framework for provoked and unprovoked venous thromboembolism



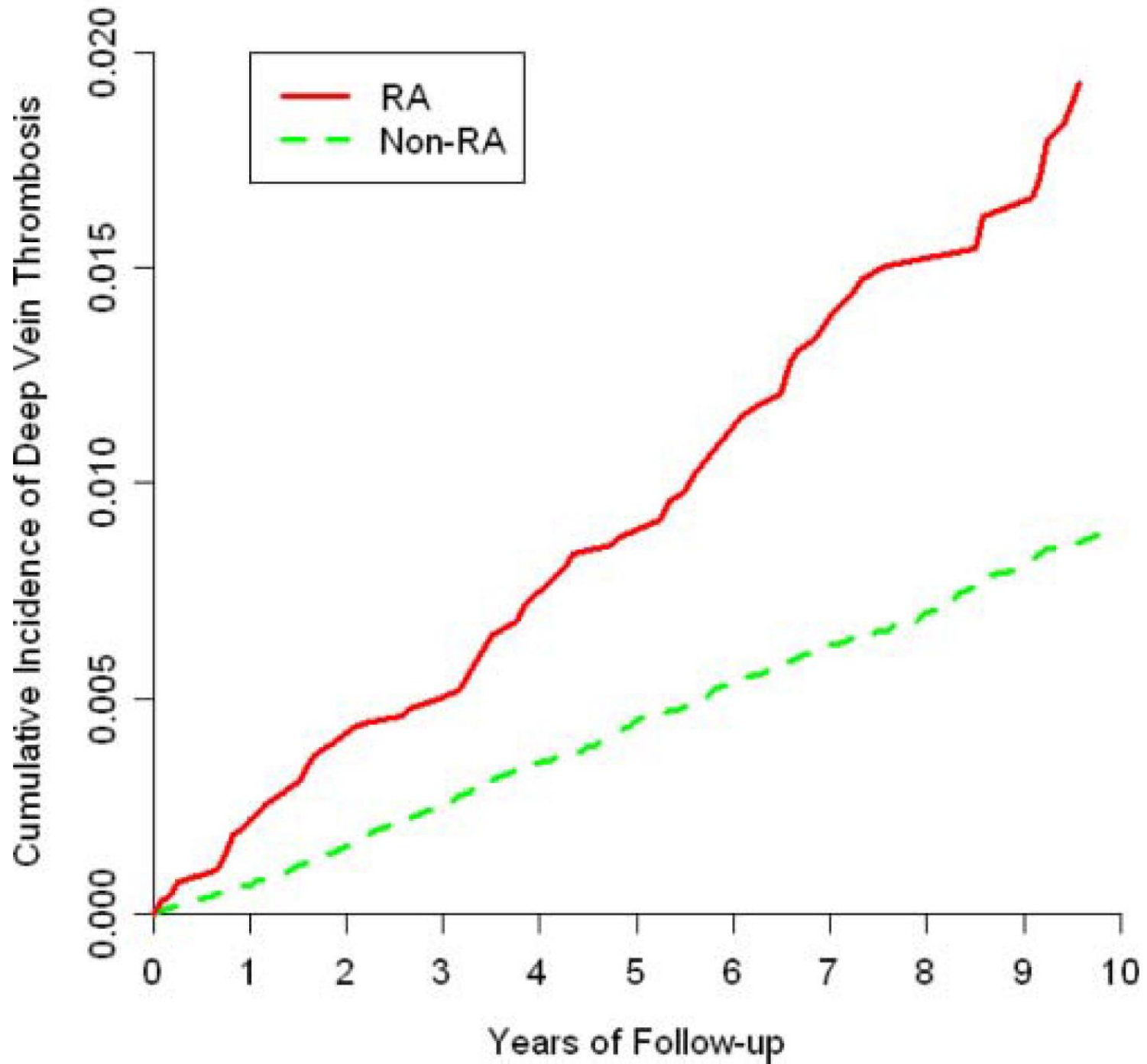
Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

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)	<ul style="list-style-type: none">• 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
High (>8% per year)		<ul style="list-style-type: none">• Active cancer• One or more previous episodes of VTE in the absence of a major transient or reversible factor• Antiphospholipid antibody syndrome

Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting

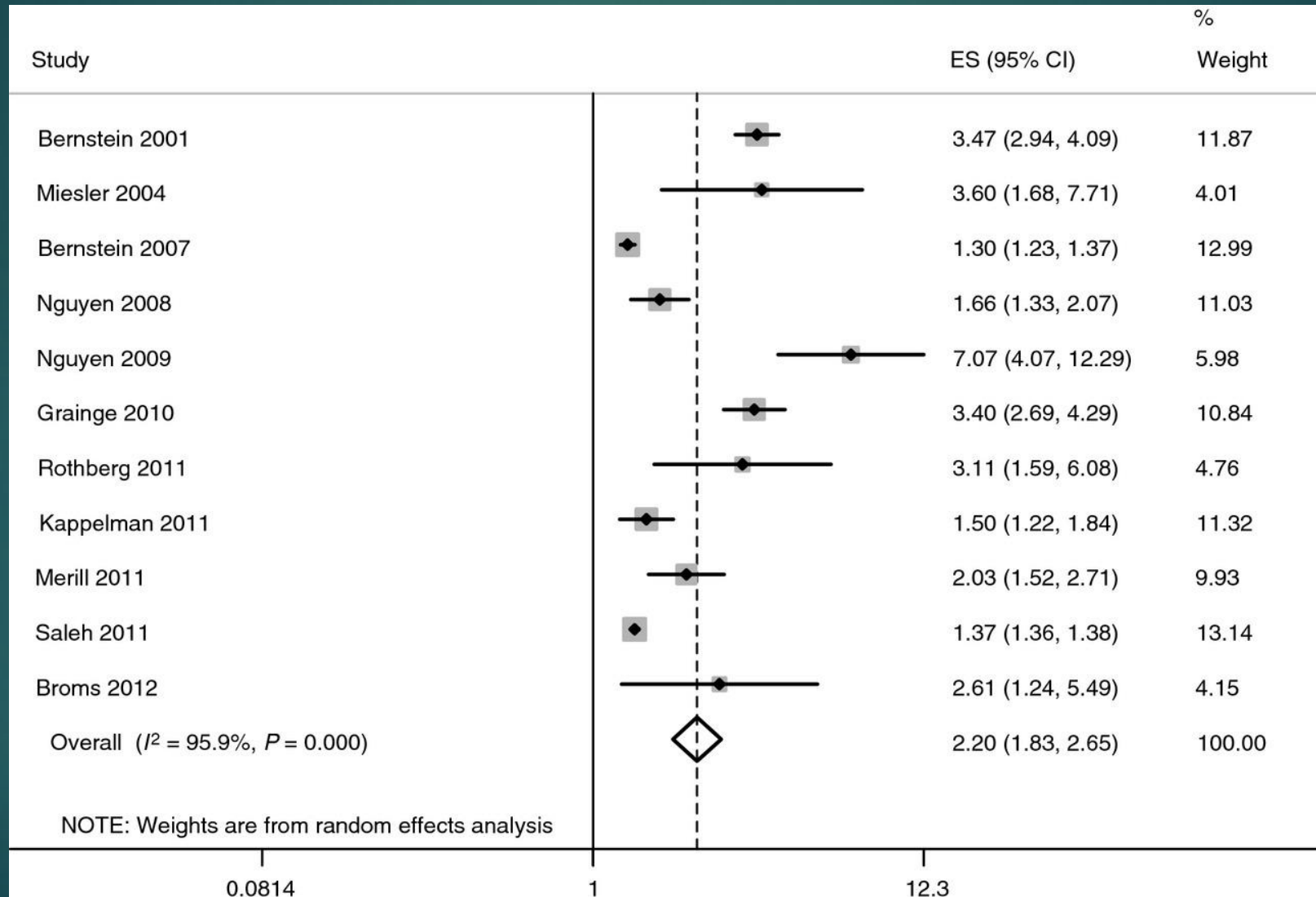
Liam Smeeth, Claire Cook, Sara Thomas, Andrew J Hall, Richard Hubbard, Patrick Vallance

Findings The risks of DVT and PE were significantly raised, and were highest in the first two weeks, after urinary tract infection. The incidence ratio for DVT was 2·10 (95% CI 1·56–2·82), and that for PE 2·11 (1·38–3·23). The risk gradually fell over the subsequent months, returning to the baseline value after 1 year. The risk of DVT was also higher after respiratory tract infection, but possible diagnostic misclassification precluded a reliable estimate of the risk of PE after respiratory infection.



[Ann Rheum Dis.](#) 2013 Jul;72(7):1182-7.

Meta-analysis: the risk of venous thromboembolism in patients with **inflammatory bowel disease**



Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term



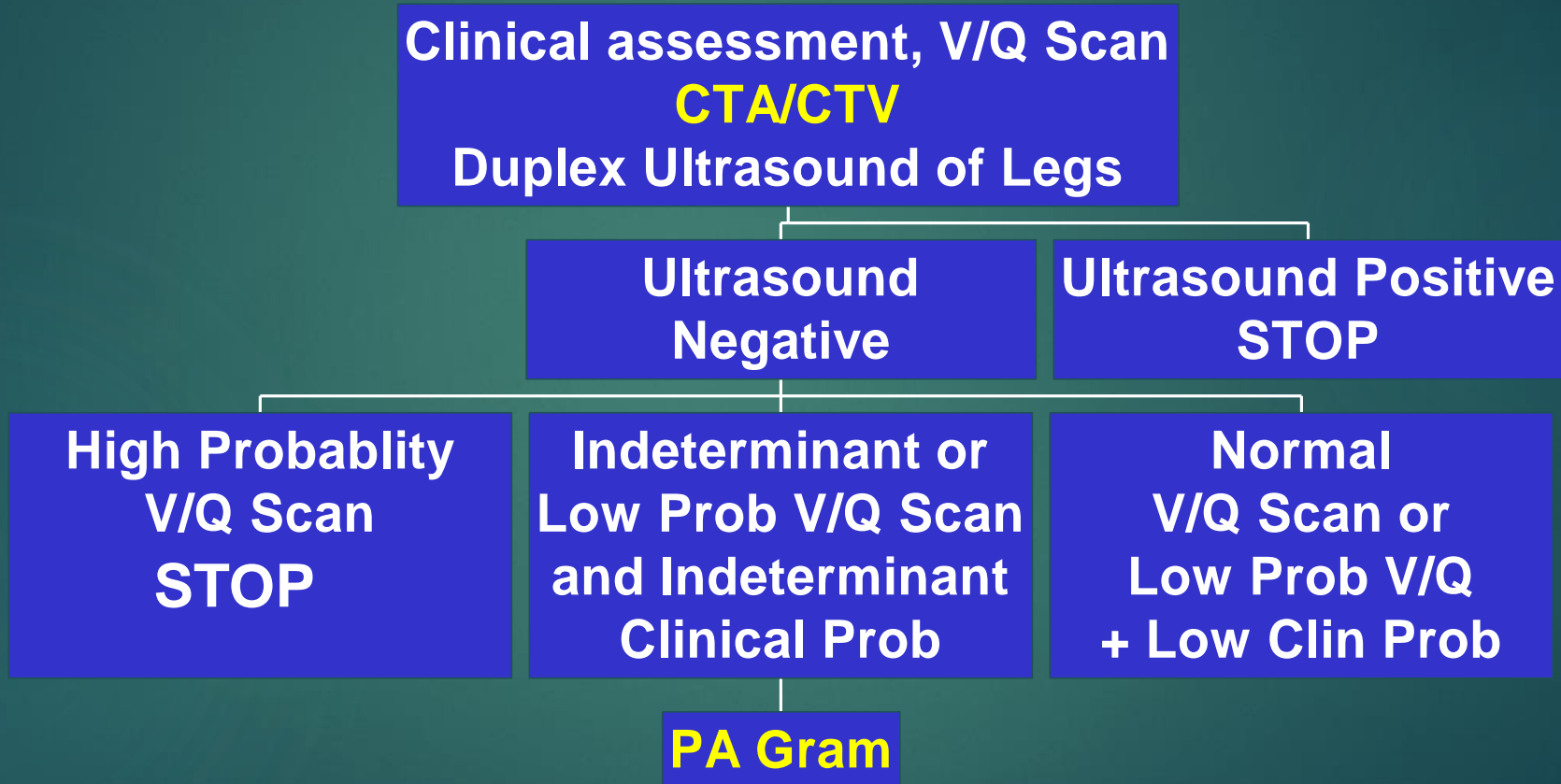
Estimated risk for long-term recurrence ^a	Risk factor category for index PE ^b	Examples ^b
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤ 10 -fold increased risk for first (index) VTE	<ul style="list-style-type: none"> • Minor surgery (general anaesthesia for <30 min) • 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	<ul style="list-style-type: none"> • Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	



Diagnosis of Pulmonary Embolism Update

PIOPED II Protocol

Multi-slice CTA/CTV



CHEST CTA vs CTAV

CTA % CTAV %

Do not perform CT venography as an adjunct to CTPA.
Class III, ESC 2019

NPV(truth/test)

95

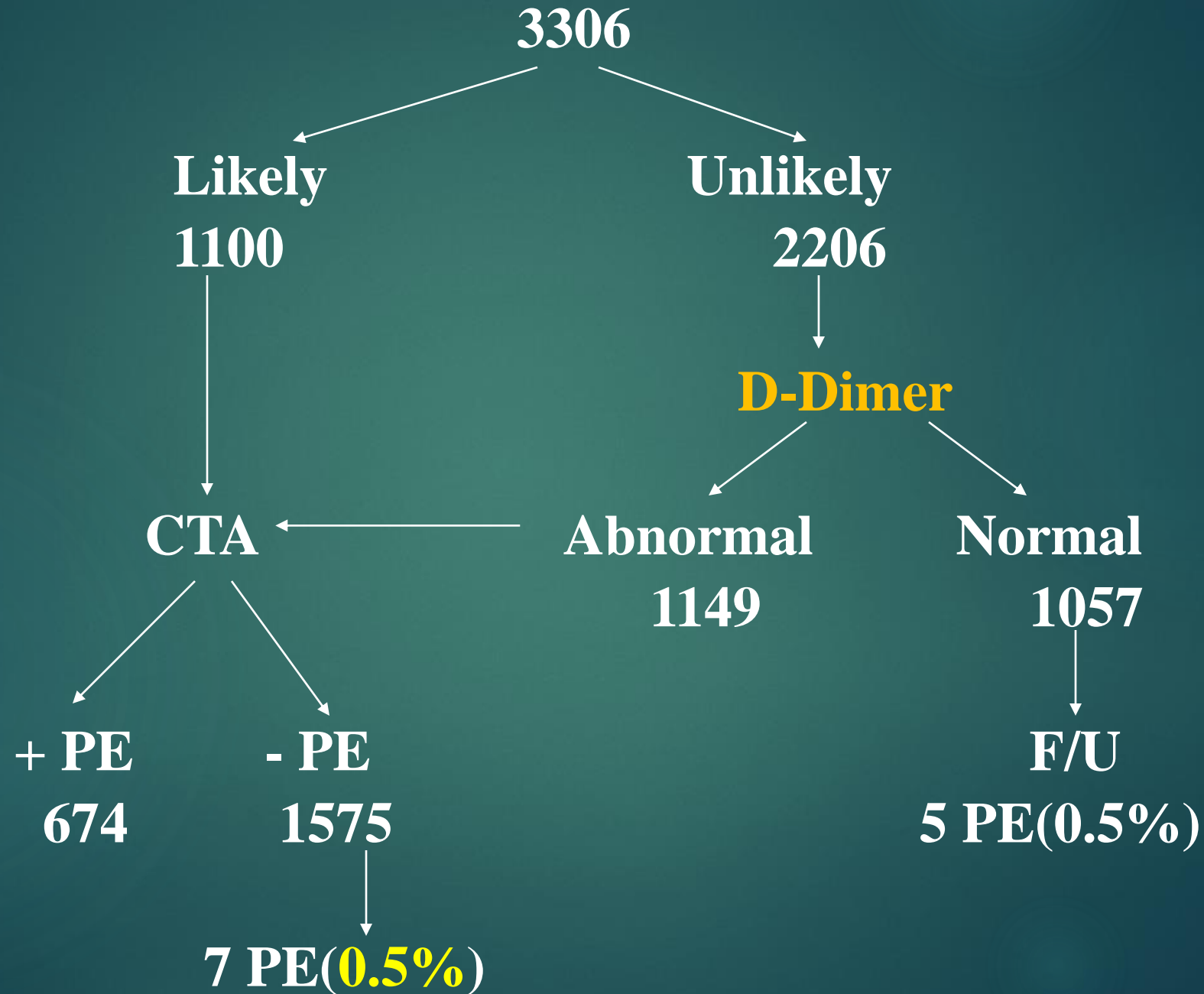
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PIOPED II, N Engl J Med, June, 2006

PIOPED II demonstrated the previously unrecognized problem that **14%**(25/175) of CTA read as positive for PE were in truth negative!

1. Unnecessary anticoagulation with bleeding risk.
2. Lifelong stigma of having a PE
3. A major public health cost

Clinical Assessment for PE (Christopher, NEJM)



Age-adjusted D-dimer cut-off in suspected PE

Derivation set

N=1721

Prevalence of PE:24%

**Age-adjusted
Cut-off value:
Age \geq 20 ($\mu\text{g/L}$ FEU)
Above 50 years**

(1 FEU=2 x DDU)

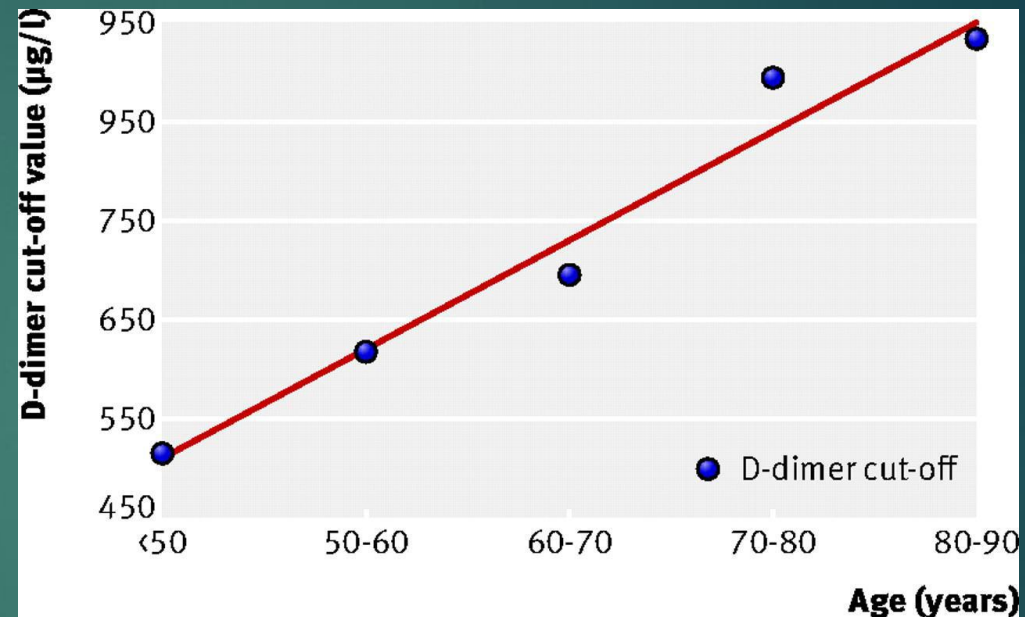
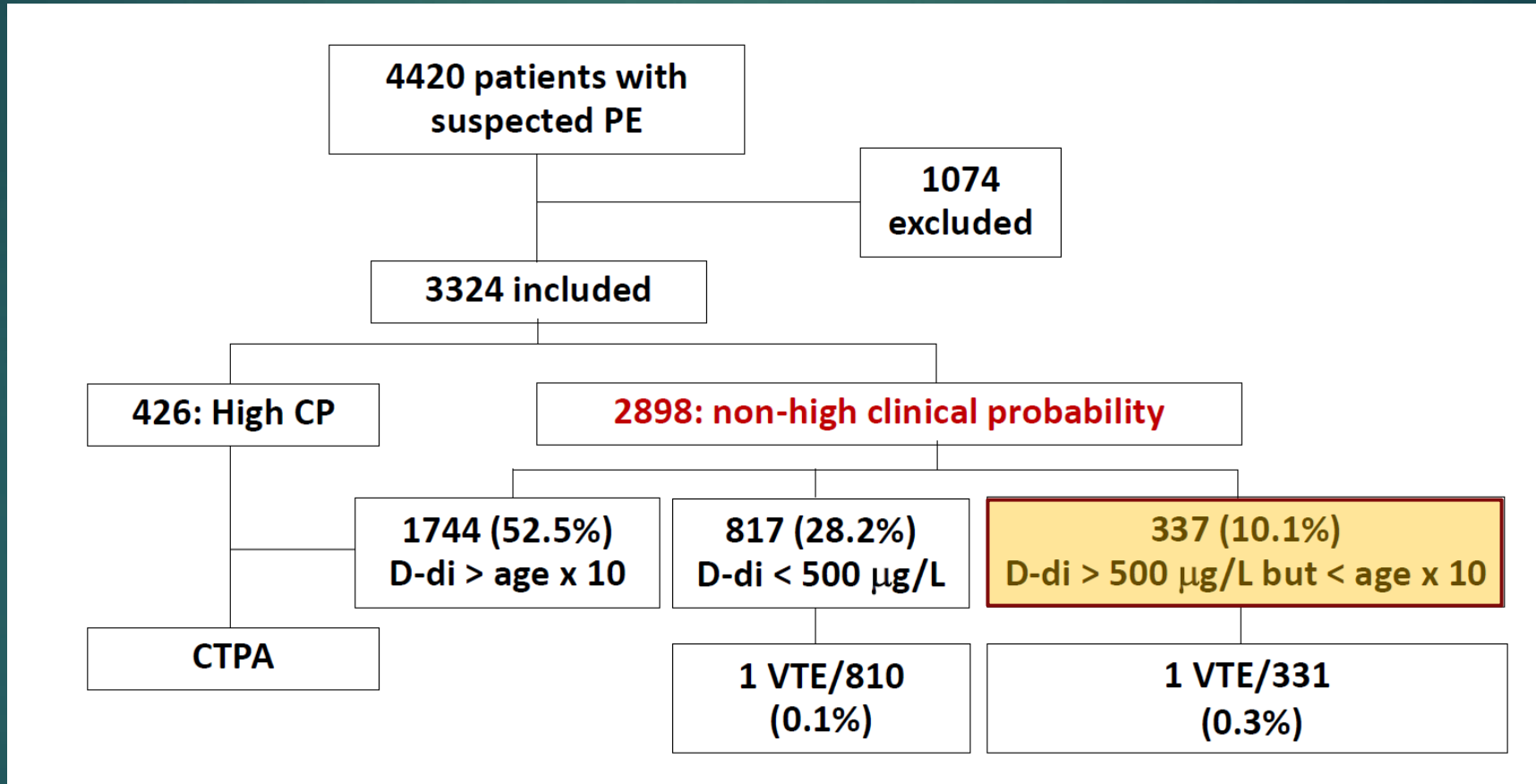


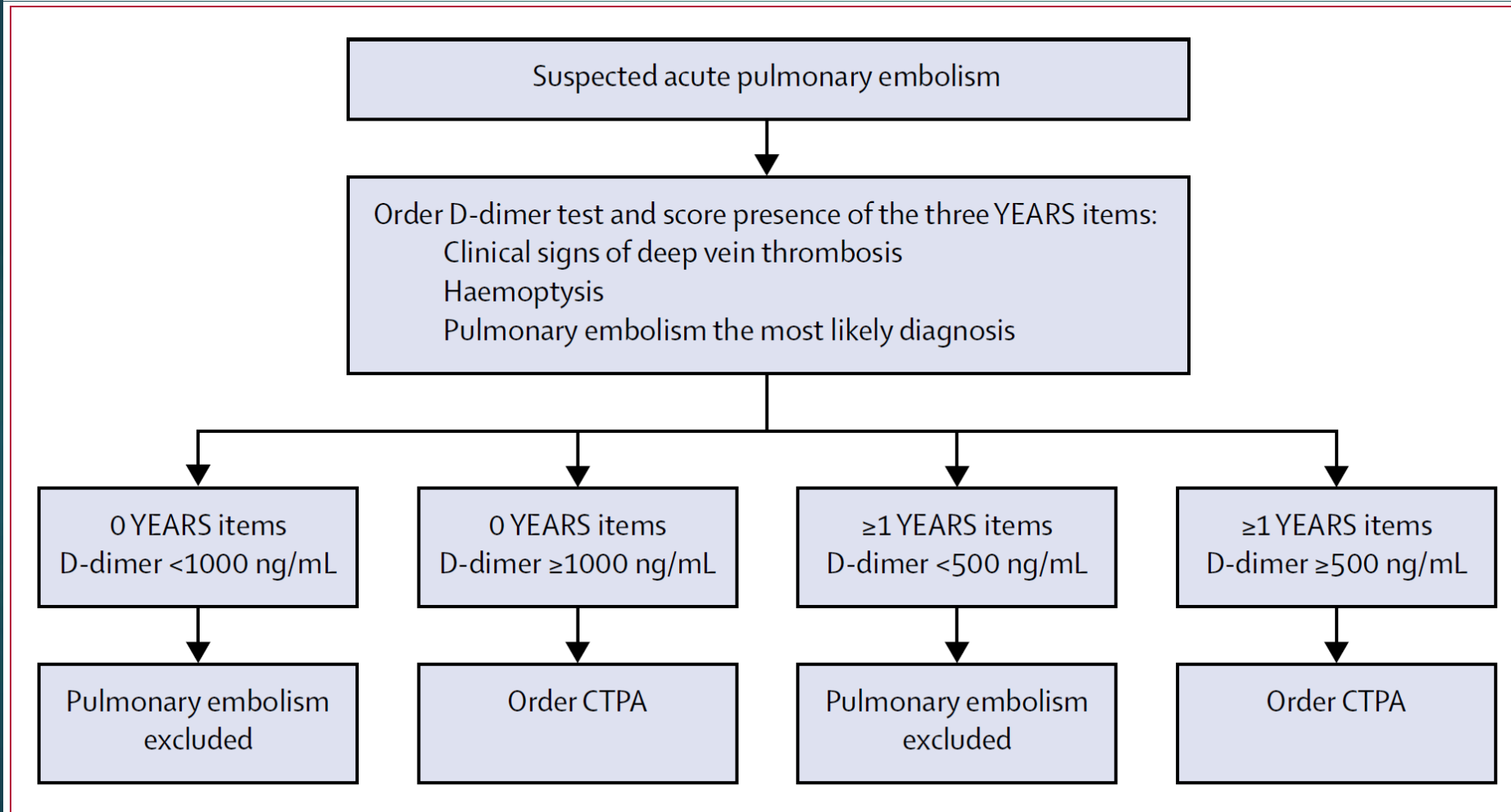
Fig1) Optimal cut-off values for D-dimer test for pulmonary embolism by age in patients with an unlikely clinical probability of pulmonary embolism (sensitivity set at 100%)

BMJ 2010; 340: c1475

ADJUST PE: Study Design and Results



Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study



ORIGINAL ARTICLE

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability

Clive Kearon, M.B., Ph.D., Kerstin de Wit, M.B., Sameer Parpia, Ph.D.,
Sam Schulman, M.D., Ph.D., Marc Afilalo, M.D., Andrew Hirsch, M.D.,
Frederick A. Spencer, M.D., Sangita Sharma, M.D., Frédérick D'Aragon, M.D.,
Jean-François Deshaies, M.D., Gregoire Le Gal, M.D., Ph.D.,
Alejandro Lazo-Langner, M.D., Cynthia Wu, M.D., Lisa Rudd-Scott, R.N.,
Shannon M. Bates, M.D., and Jim A. Julian, M.Math.,
for the PEGeD Study Investigators*

Table 1. Model for Determining the Clinical Probability of Pulmonary Embolism, According to the Wells Score.*

Clinical Feature	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate >100 beats/min	1.5
Immobilization for ≥ 3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

* Data are from Wells et al.²⁴ The condition of patients is scored according to the following criteria: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. DVT denotes deep venous thrombosis, and ECG electrocardiography.



D-dimer

Clinical Low probability
Well's score < 2



D-dimer < 1000 ng/ml

Clinical intermediate
probability
Well's score 2-6



D-dimer < 500 ng/ml



Ruled out PE without further testing

Table 3. Number of D-Dimer Tests and Chest Imaging Examinations with the PEGeD Strategy as Compared with Other Diagnostic Strategies.*

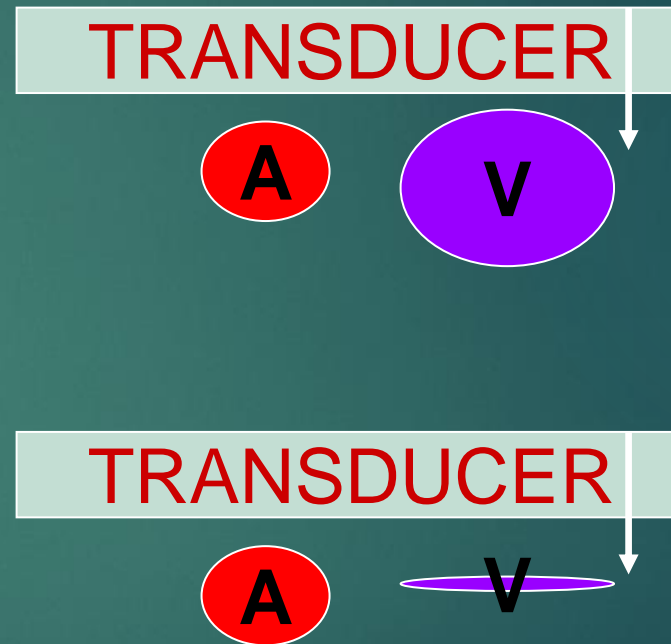
Diagnostic Strategy	Low C-PTP (N = 1752)		Moderate C-PTP (N = 218)		High C-PTP (N = 47)		All Patients (N = 2017)	
	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†
PEGeD	1752	467	218	178	0	47	1970	692
Standard‡	1752	782	0	218	0	47	1752	1047
Difference: PEGeD – standard	0	-315	218	-40	—	0	218	-355
Age-adjusted§	1752	654	218	164	0	47	1970	865
Difference: PEGeD – age-adjusted	0	-187	0	14	—	0	0	-173
YEARS¶	1752	520	218	176	47	37	2017	733
Difference: PEGeD – YEARS	0	-53	0	2	-47	10	-47	-41

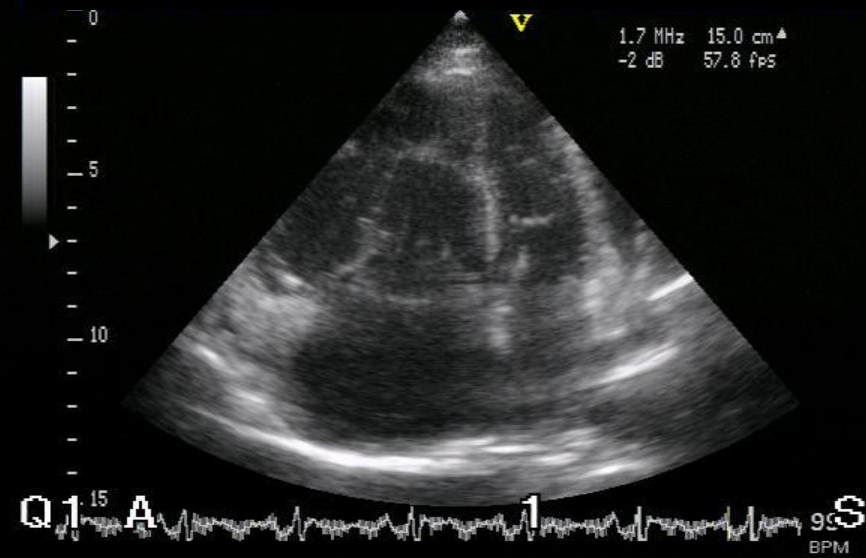
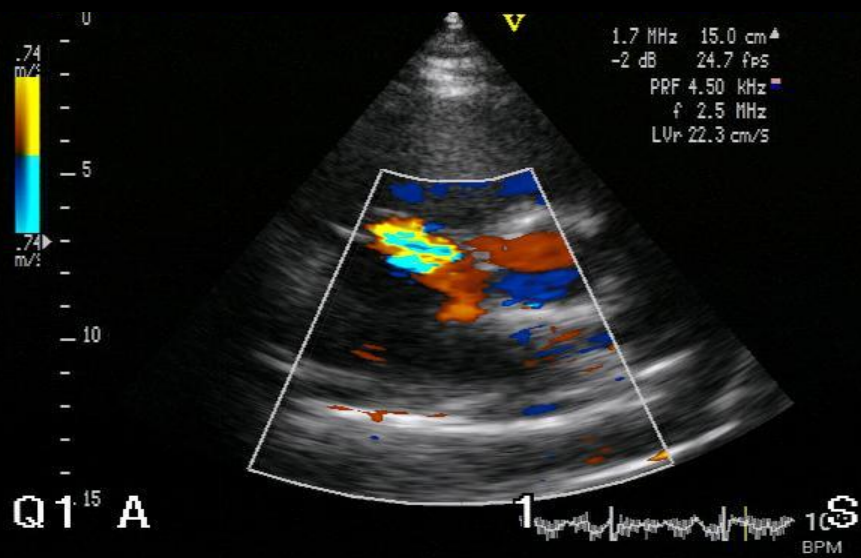
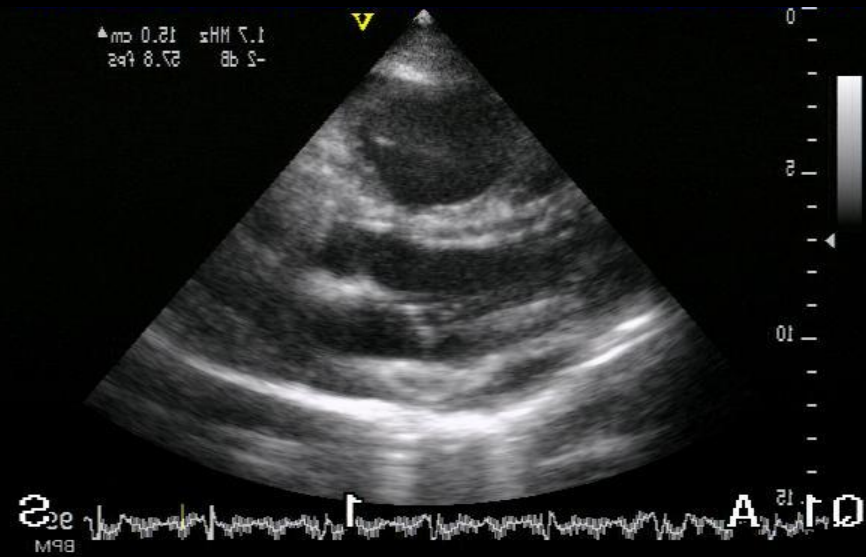
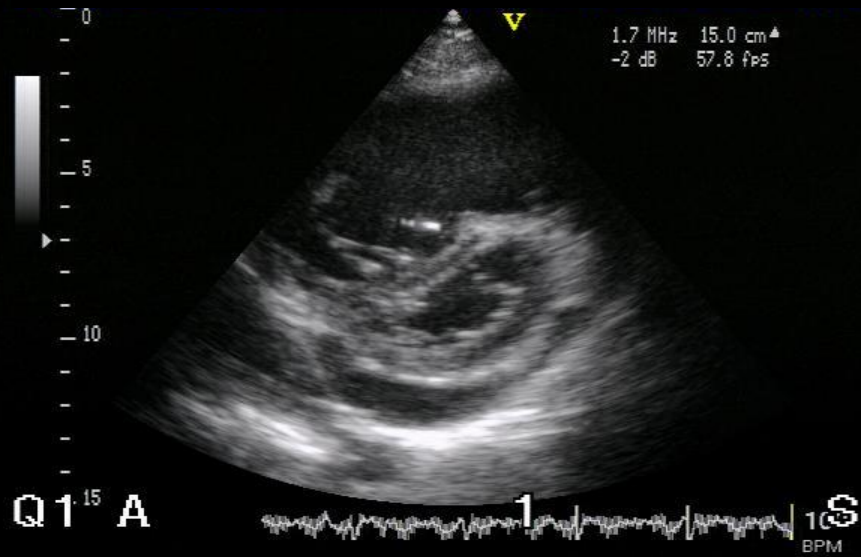
Diagnosis of Acute PE in Hemodynamically Unstable

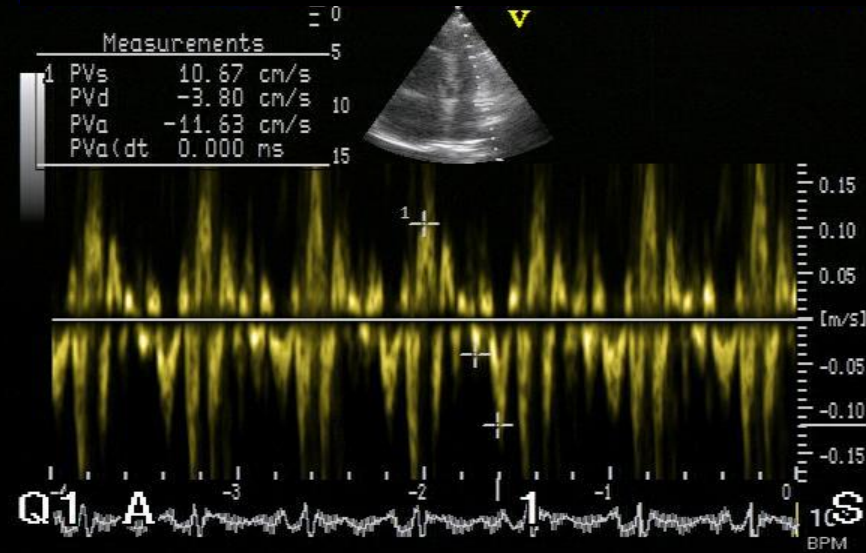
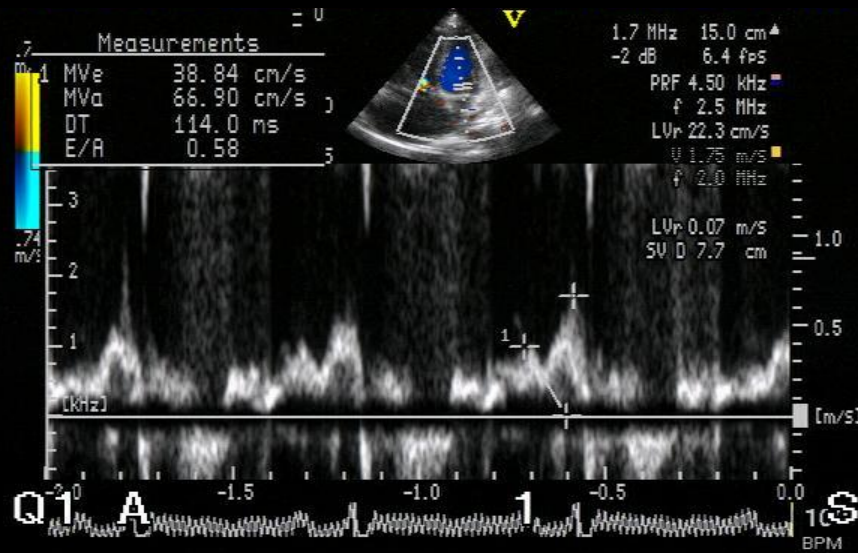
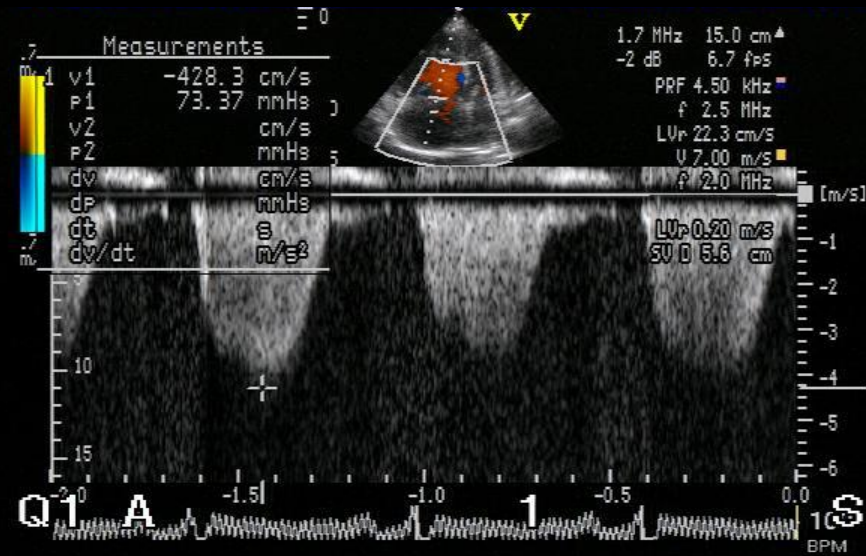
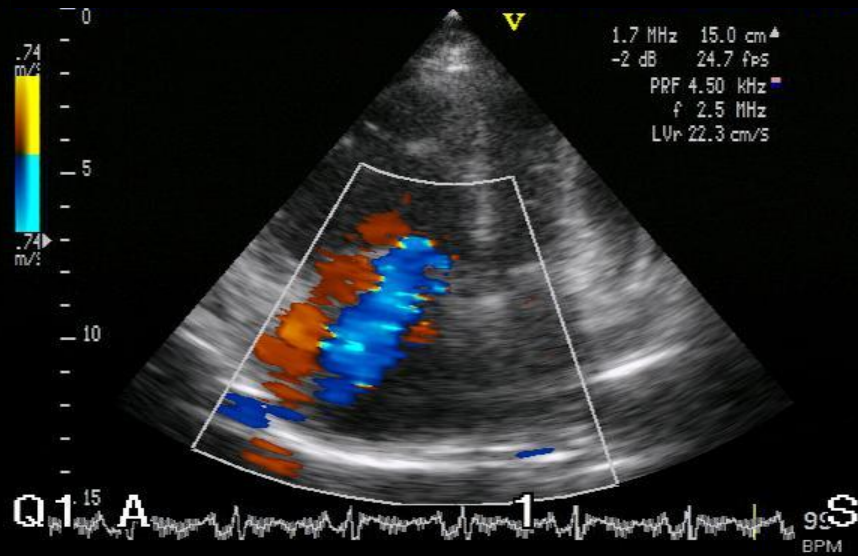
- ▶ Lower extremity compression USG
 - ▶ does not diagnose PE, it is sufficient for the diagnosis of deep venous thrombosis (DVT), which is sufficient to initiate treatment.
- ▶ Echocardiography
 - ▶ the presence of **new** right ventricular strain or direct visualization of thrombus within the heart

Deep Venous Thrombosis: Ultrasound

- ▶ Positive Exam
 - ▶ Vein enlarged
 - ▶ Hypo-echoic
 - ▶ Non-compressible
- ▶ Negative Exam
 - ▶ Vein collapses
 - ▶ If artery collapses, too much pressure

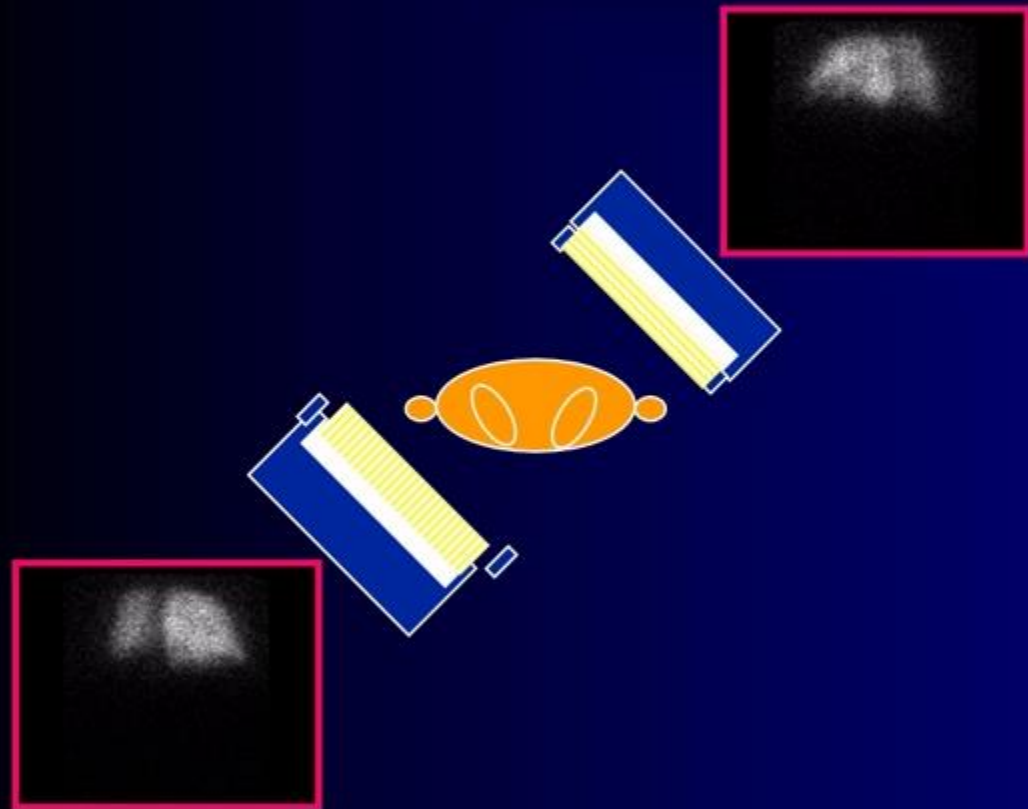




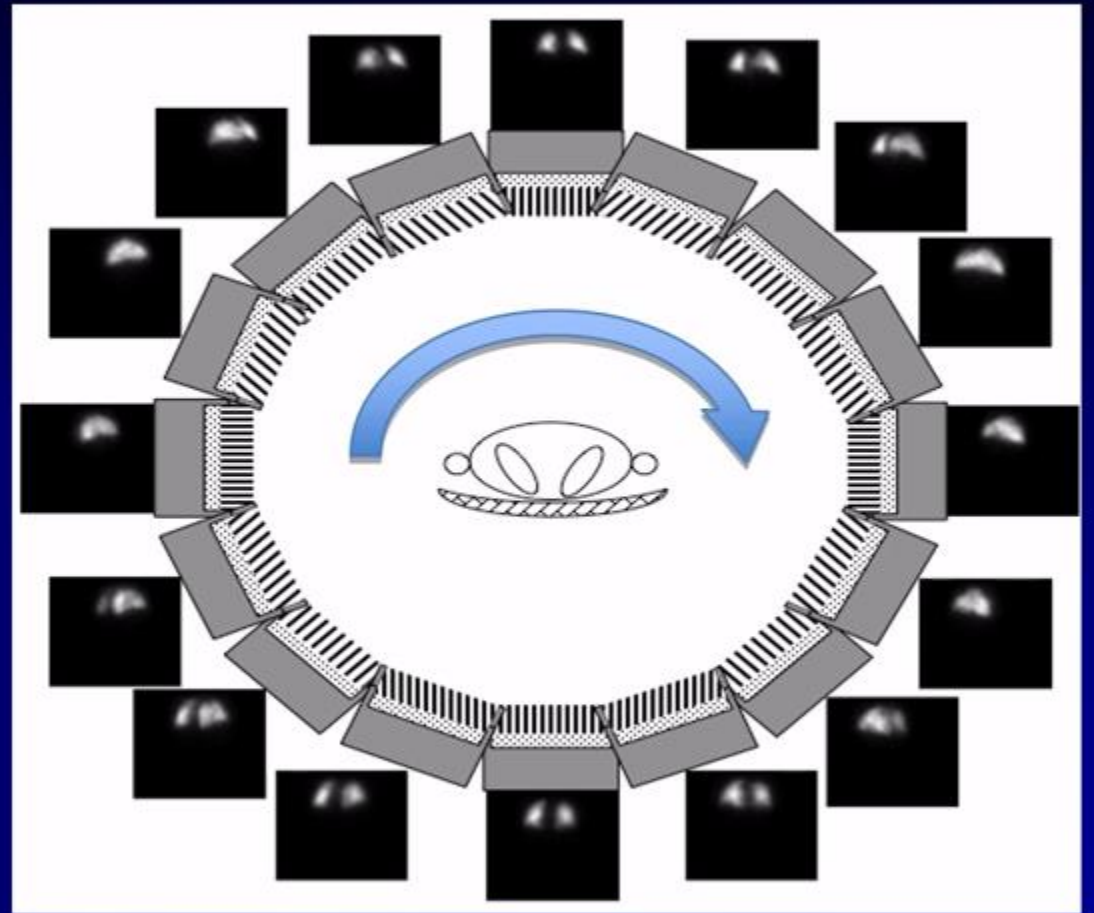


V/Q SPECT

Tomographic acquisition



Planar V/Q scan



Tomographic acquisition



Assessment of pulmonary embolism severity and the risk of early death

Pulmonary Embolism Severity Index

	Points assigned
Age	+1 per year
Male sex	+10
Cancer*	+30
Heart failure	+10
Chronic lung disease	+10
Pulse ≥ 110 beats per min	+20
Systolic blood pressure < 100 mm Hg	+30
Respiratory rate ≥ 30 breaths per min	+20
Temperature $< 36^{\circ}\text{C}$	+20
Altered mental status†	+60
Arterial oxygen saturation $< 90\%$ ‡	+20

Overall point score for a patient is obtained by summing the patient's age in years with the points for every applicable predictor. A score of < 66 is risk class I, 66–85 is risk class II, 86–105 is risk class III, 106–125 is risk class IV, and > 125 is risk class V. *History of cancer or active cancer. †Disorientation, lethargy, stupor, or coma. ‡With or without the administration of supplemental oxygen.

Table 1: Pulmonary embolism severity index

- ▶ Class I, < 66
- ▶ Class II, 66–85
- ▶ Class III, 86–105
- ▶ Class IV, 106–125
- ▶ Class V, > 125

Pulmonary Embolism Severity Index

- ▶ Class I, <66
 - ▶ Class II, 66-85
 - ▶ Class III, 86-105
 - ▶ Class IV, 106-125
 - ▶ Class V, >125
- Safely treatment in an outpatient clinic**

RV function assessment in low-risk patients

- ▶ In the 2019 ESC guideline, the selection of low-risk patients with PE who qualify **for home treatment** is based on the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI), **combined with the mandatory absence of RV dysfunction on transthoracic echocardiography or CTPA**

Is it necessary right ventricular (RV) dysfunction measurement in normotensive patients with PE to identify low-risk patients eligible for home treatment?

Table 2. Adverse Outcomes in Patients with Acute Pulmonary Embolism Treated Out-of-Hospital Stratified by RV/LV Ratio

	RV/LV ratio > 1.0 (n = 224)	RV/LV ratio ≤ 1.0 (n = 527)	OR (95% CI)
1. All-cause mortality within 3 mo	5 (2.2%)	5 (0.9%)	2.4 (0.68–8.3)
2. Recurrent VTE within 3 mo	1 (0.5%)	7 (1.3%)	0.33 (0.04–2.7)
3. Total adverse events	6 (2.7%)	12 (2.3%)	1.2 (0.44–3.2)

Definition of abbreviations: CI = confidence interval; LV = left ventricular; OR = odds ratio; RV = right ventricular; VTE = venous thromboembolism.

Assessment of pulmonary embolism severity and the risk of early death

Table 8 Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	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

PEITHO – inclusion criteria

Troponin Positive:

Troponin I (ng/ml)

Centaur, Bayer > 0.6

Axsym, Abbott > 0.6

Troponin T (ng/ml)

Elecsys, Roche > 0.04

PEITHO – inclusion criteria

ECHO: RV Dysfunction

At least 1 of the following:

- 1) RV dilation (RVED > 30 mm, or RVED/ LVED > 0.9)
(apical or subcostal 4-CH view, parasternal short-axis view)
- 2) Hypokinesis of RV free wall
(any view)
- 3) Tricuspid systolic velocity > 2.6 m/s
(apical 4-CH view, parasternal short-axis view)

HAEMODYNAMIC INSTABILITY?

NO

Perform troponin test^f

Troponin positive
+ RV dysfunction:
**INTERMEDIATE-
HIGH RISK^b**

Troponin negative:
**INTERMEDIATE-
LOW RISK^b**

Reperfusion
treatment
haemodynamic
support

Monitoring;
consider rescue
reperfusion,
if deterioration

HOSPITALIZE

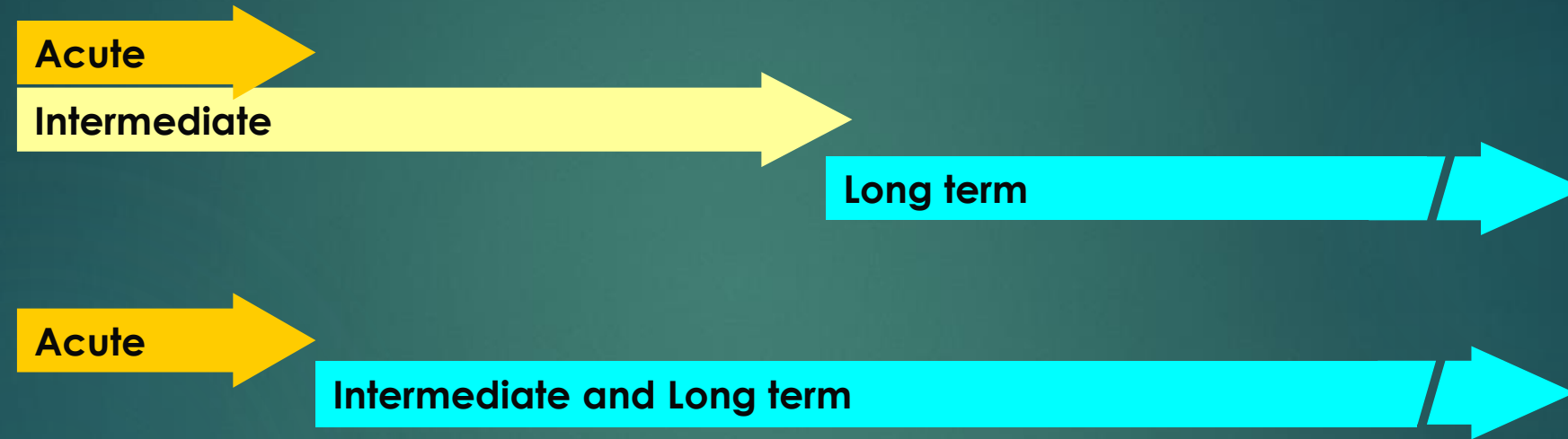
Anticoagulation

Anticoagulation Initiation

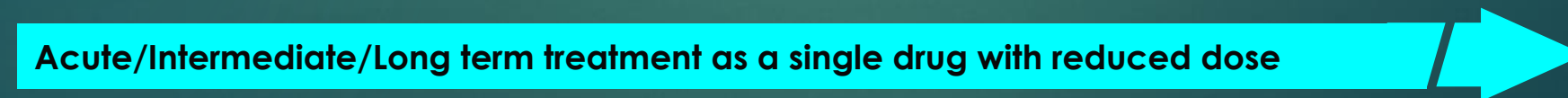
- ▶ In patients with high or intermediate clinical probability of PE anticoagulation should be initiated while awaiting the results of diagnostic tests.
- ▶ LMWH, UFH, DOACs

Rivaroxaban/Apixaban for treatment of PE

Phases of the disease



Rivaroxaban/Apixaban treatment for PE



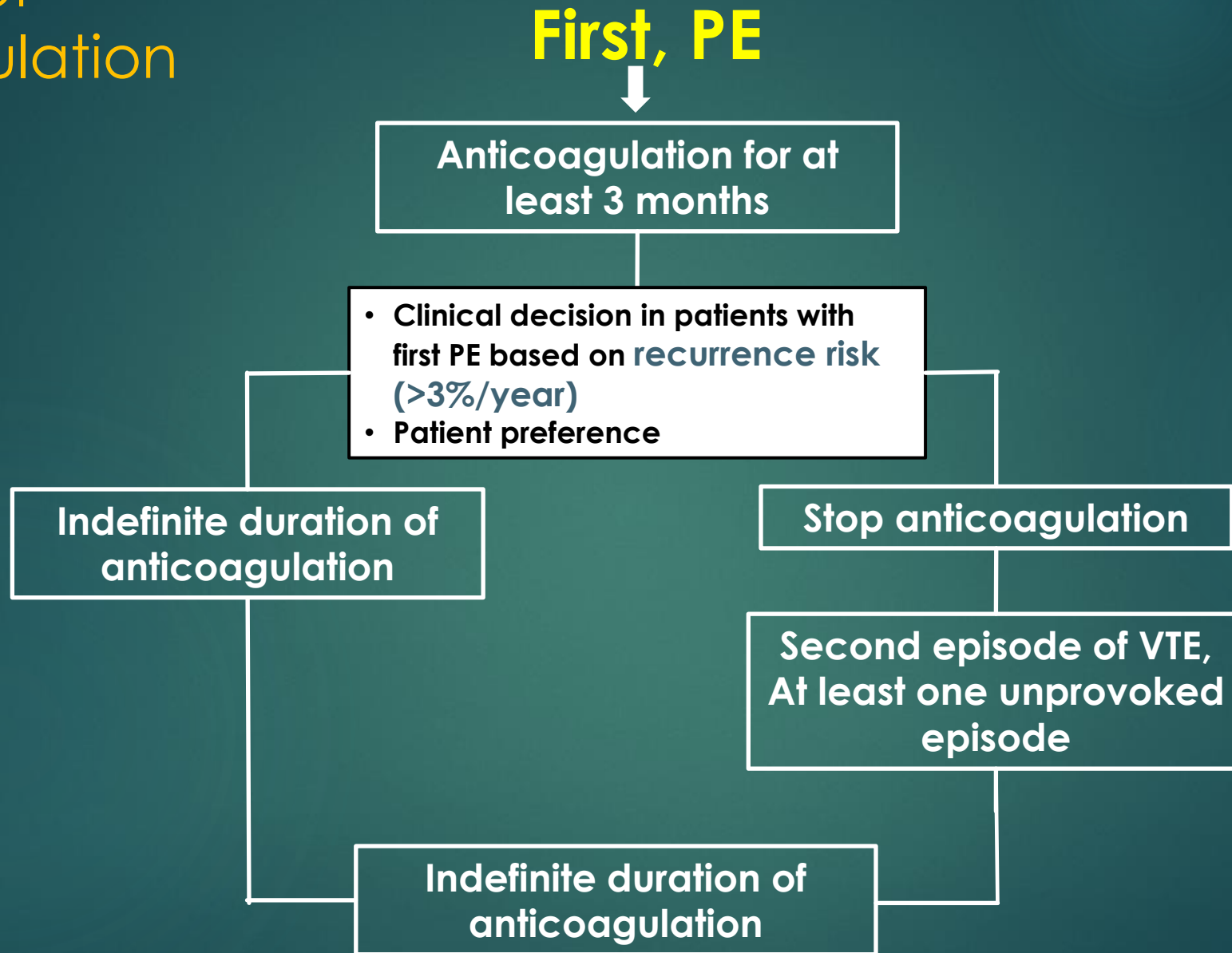
DOACs for treatment of PE

- ▶ Cochrane meta-analysis of 11 randomized trials-major bleeds are fewer in DVT:
 - Thrombin inhibitors: odds ratio 0.68; 95% CI, 0.47-0.98
 - Xa inhibitors: odds ratio 0.57;95% CI,0.43- 0.76
- ▶ No difference in PE for recurrence, mortality or major bleeds
 - ▶ Rivaroxaban alone¹
 - ▶ Apixaban alone²
- ▶ ESC 2019 and ACCP 2016 suggest DOACs rather than VKA

¹*N Engl J Med.* 2012;366(14):1287-1297.

²*N Engl J Med.* 2013;369(9):799-808.

Duration of Anticoagulation



Duration of Anticoagulation



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
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



Percutaneous catheter-directed treatment



Intravenous thrombolysis

Thrombolytics contraindicated

Thrombolytic failure

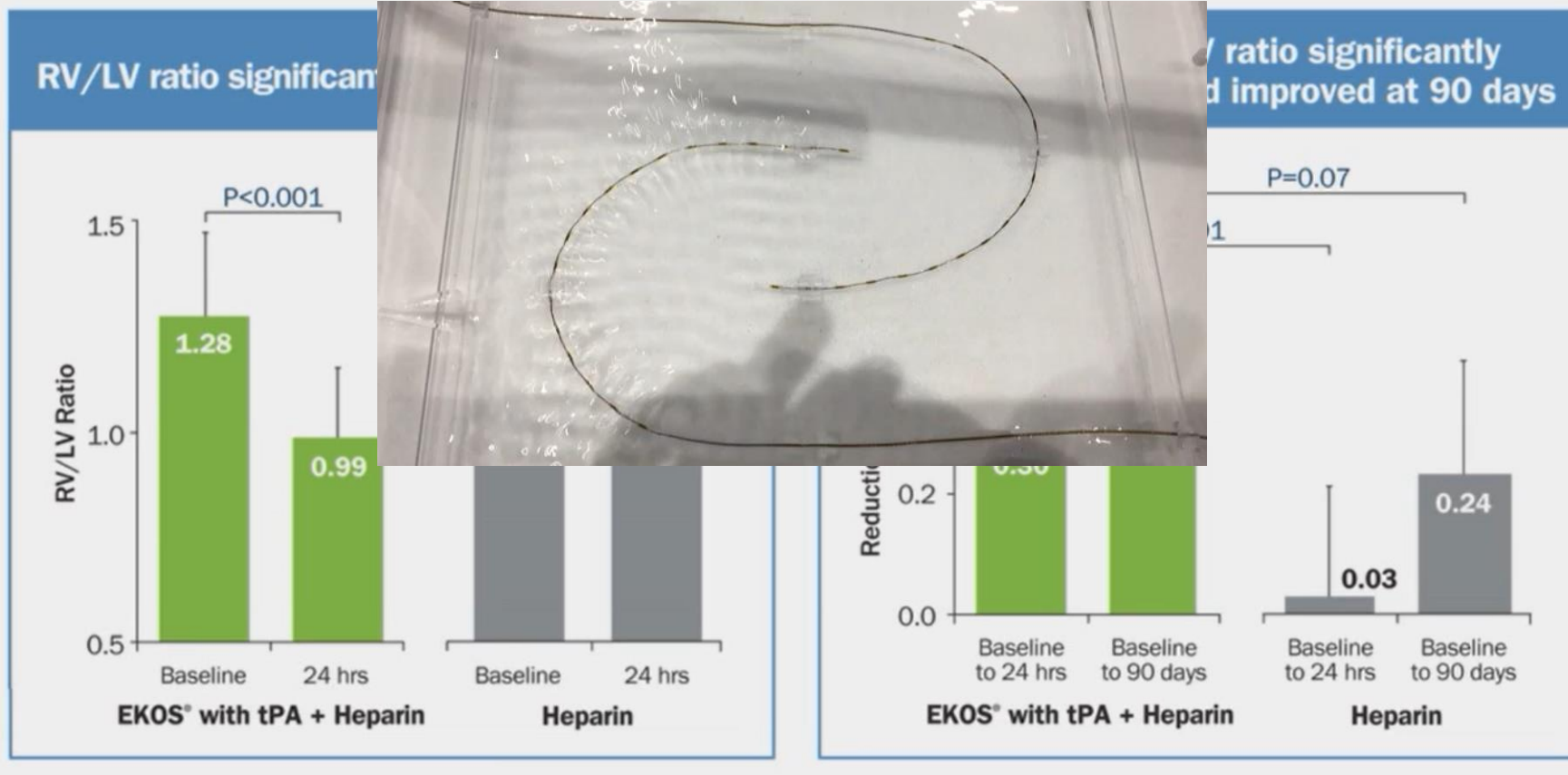
Alternative to thrombolysis preferred

Rescue

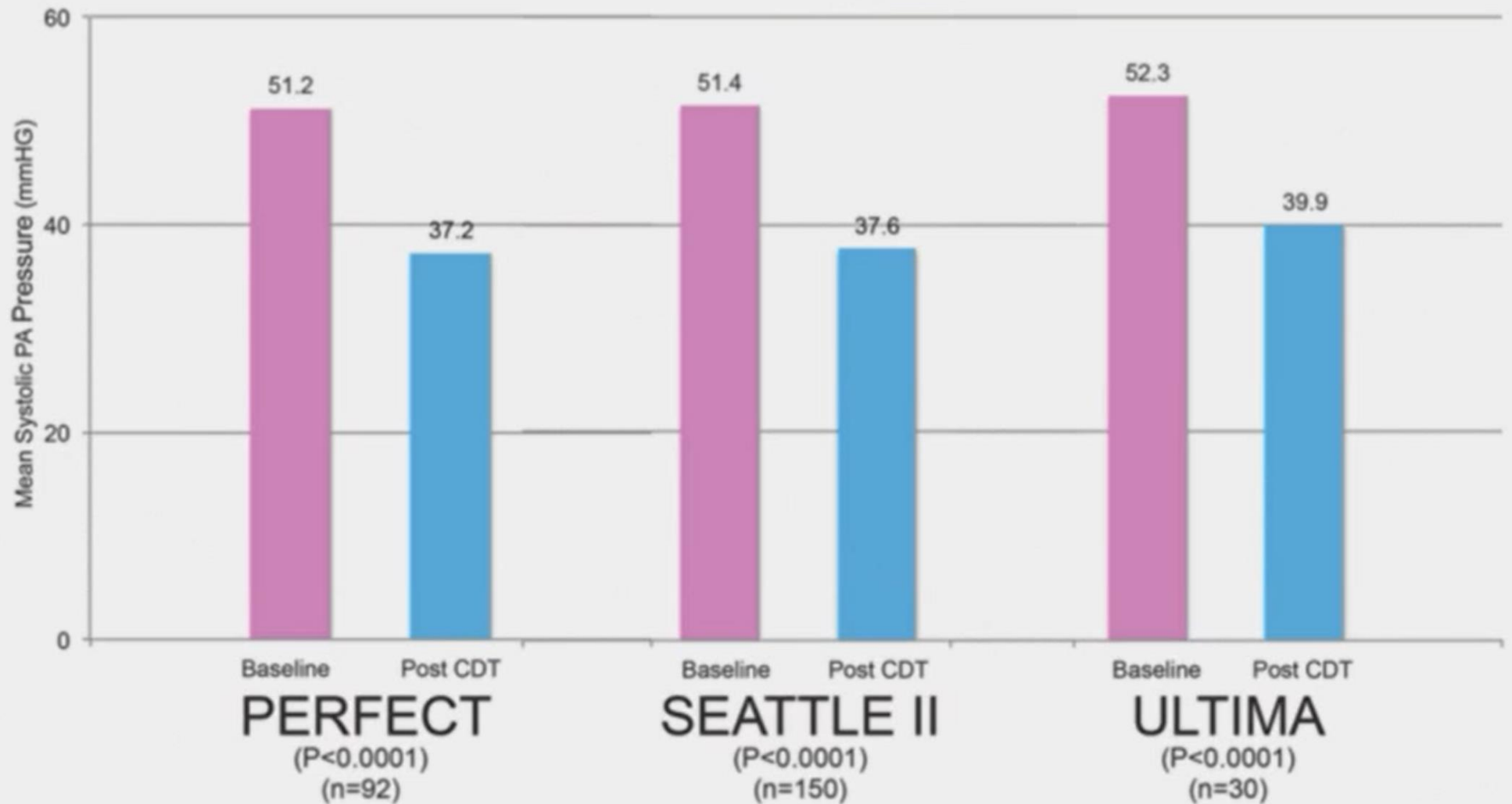
Surgical Embolectomy

Catheter Directed Therapy

ULTIMA – CDT reduced RV/LV ratio to a greater extent than heparin at 24 hours*



PA pressure reduction



860 patient meta-analysis: reinforces efficacy and small but present bleeding risk of CDT

TABLE II. Meta-Analysis Characteristics and Outcomes

Study	Sample size	Massive PE <i>n</i> (%)	Total dose of tPA (mg)	Catheter type	Mortality with sub-massive PE	Mortality with massive PE	ICH	Major bleeding or vascular injury ^a	Fatal bleeding, fatal vascular injury, or ICH
Current Cohort	137	16 (12)	17 ^b	USAT (84%), S-CDT (16%)	0	5	2	13	3
Chamsuddin et al. [10]	10	10 (100)	21.8	USAT	0	0	0	0	0
Lin et al. group 1 [11]	11	11 (100)	17.2	USAT	0	1	0	0	0
Lin et al. group 2 [11]	14	14 (100)	25.4	S-CDT	0	2	0	3	0
Engelhardt et al. [12]	24	5 (20.8)	33.5	USAT	0	0	0	4	0
Kennedy et al. [13]	60	12 (20)	35.1	USAT	0	3	0	0	0
Dumantepe et al. [14]	22	8 (36.4)	21 ^b	USAT	0	1	0	0	0
ULTIMA [5]	30	0 (0)	20.8	USAT	0	0	0	0	0
Quintana et al. [15]	10	2 (20)	18 ^b	USAT	0	0	0	0	0
Bagla et al. [16]	45	0 (0)	24	USAT	0	0	0	1	0
Engelberger et al. [17]	52	14 (26.9)	21	USAT	0	2	0	1	0
Mccabe et al. [18]	53	0 (0)	24.6	USAT	0	0	1	2	1
Nykamp et al. [19]	45	13 (28.9)	30.5	USAT	0	0	0	0	0
PERFECT [6]	100	28 (28)	28	USAT (36%), S-CDT (64%)	2	4	0	0	0
SEATTLE II [7]	150	31 (20.7)	23.7	USAT	2	1	0	13	0
Liang et al. [20]	69	10 (14.5)	NA	USAT (52%), S-CDT (39%)	1	1	0	2	0
Yoo et al. [21]	28	12 (42.9)	NA	USAT	0	4	0	1	0
Total	860	186 (21.6)	24.2		5 (0.74%)	24 (12.9%)	3 (0.35%)	40 (4.65%)	4 (0.47%)

6.6 Recommendations for acute-phase treatment of high-risk pulmonary embolism^a

Recommendations	Class ^b	Level ^c
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
Systemic thrombolytic therapy is recommended for high-risk PE. ²⁸²	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^{d 281}	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^d	IIa	C

Inferior Vena Cava Filter

Survival Effects of Inferior Vena Cava Filter in Patients With Acute Symptomatic Venous Thromboembolism and a Significant Bleeding Risk



Prospective Cohort RIETE data base

40,142 pts → 371 had filter for known bleeding risk

Matched 344 filter vs. 344 w/o filter

PE Mortality : 1.7% vs. 4.9% $p = .03$

Recurrent VTE 6.1% vs. .06% $p < .001$

Original Investigation

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism

A Randomized Clinical Trial

Finding:

3 months Filter- 3% No Filter- 1.5% $p = 0.5$

6 months Filter - 3.5% No Filter- 2.0%

No difference: Bleed, **Mortality**, DVT

Original Investigation | Cardiology

Association of Inferior Vena Cava Filter Placement for Venous Thromboembolic Disease and a Contraindication to Anticoagulation With 30-Day Mortality

- ▶ **IVC filter placement was associated with a significantly increased hazard ratio of 30-day mortality (1.18; 95%CI, 1.13-1.22; $P < .001$).**
- ▶ When the propensity score was included in the Cox model, IVC filter placement remained associated with an increased hazard ratio of 30-day mortality (1.18; 95%CI, 1.13-1.22; $P < .001$).

6.9 Recommendations for inferior vena cava filters

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



Long-term sequelae of pulmonary embolism

DIAGNOSIS OF ACUTE PE

Anticoagulate

FOLLOW-UP AT 3–6 MONTHS^a

Dyspnoea and/or functional limitation^b?

Yes

No

TTE:
Determine probability of PH^c

≥1 present:
may consider TTE

ASSESS:
Risk factors for CTEPH^d

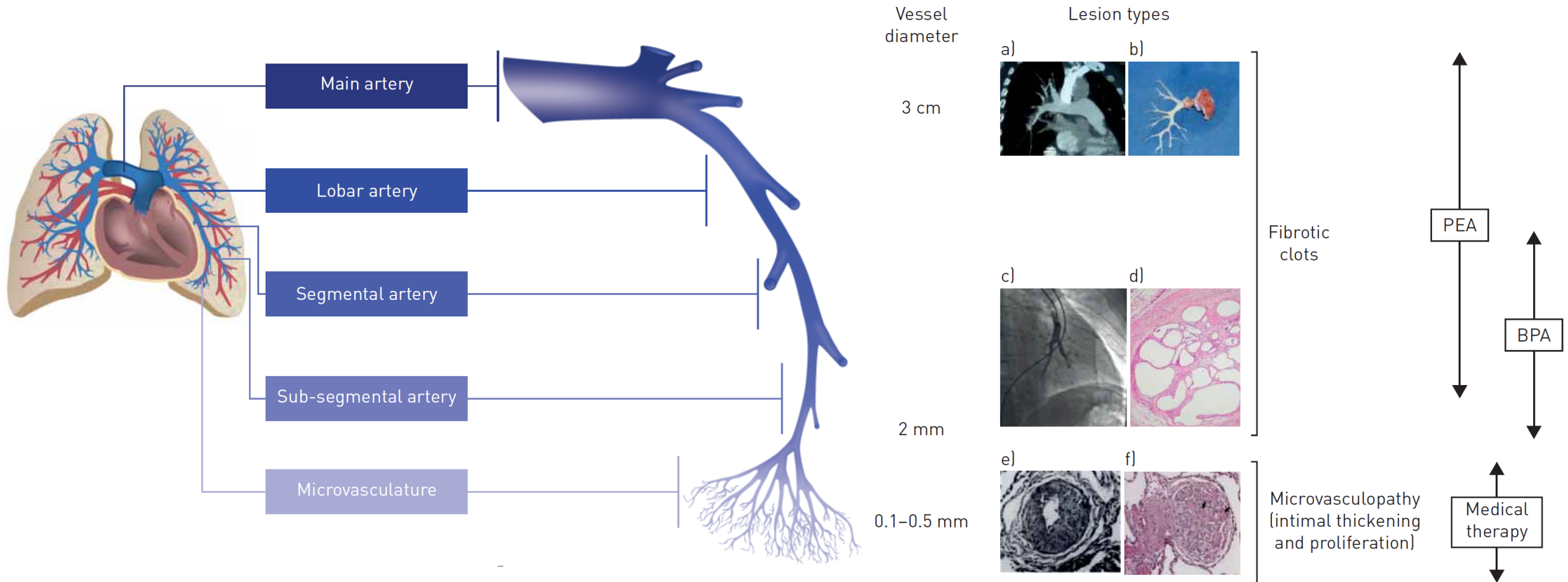
V/Q SCAN:
Mismatched perfusion defects?

Yes

Refer to PH/CTEPH expert
centre for further diagnostic
work-up

ESC 2019

Chronic thromboembolic pulmonary hypertension management



Summary

- ▶ **Epidemiology**
 - ▶ Increasing incidence of PE
 - ▶ 5-Yr recurrence rate of VTE after PE was about 21% in Korea
- ▶ **Classification of the Risk Factors**
 - ▶ Re-classified PE risk factors based on the recurrence rate
- ▶ **Diagnosis of Pulmonary Embolism**
 - ▶ Adjusted D-dimer and clinical probability may reduce CTPA exam
 - ▶ V/Q SPECT
- ▶ **Assessment of Pulmonary Embolism Severity and the Risk of Early Death**
 - ▶ RV evaluation by TTE
 - ▶ Intermediate low risk of early death
 - ▶ Intermediate high: both RV dysfunction and positive troponin → close observation and consider reperfusion, if deterioration

Summary

▶ Anticoagulation

- ▶ Extended anticoagulation except major transient/reversible risk factors

▶ Percutaneous Catheter-directed Treatment

- ▶ Growing area in intermediate-high risk PE patients
- ▶ High-risk PE, thrombolysis is contraindicated or failed

▶ Inferior Vena Cava Filter

- ▶ Conflicts results
- ▶ The rooms for filter indication is going to reduced

▶ Long-term Sequelae of Pulmonary Embolism

- ▶ PEA/BPA/Medical therapy

경청해 주셔서 감사합니다