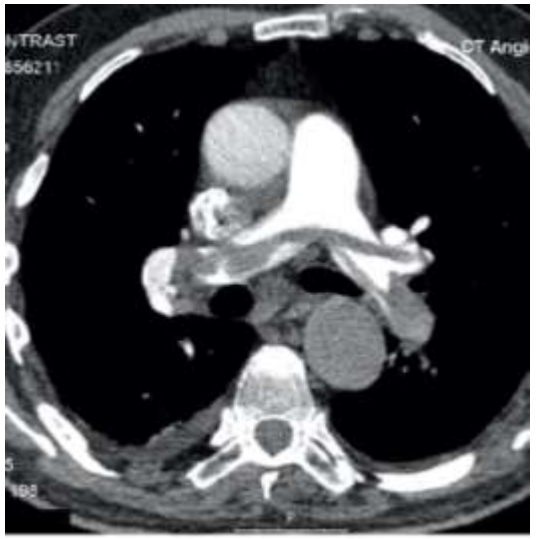


MANAGEMENT OF PULMONARY THROMBOEMBOLISM

ALAN S

ROADMAP:

- CLINICAL VIGNETTE
- EVALUATION AND ASSESSMENT OF CLINICAL PROBABILITY
- UTILITY OF D-DIMER
- UTILITY OF RADIOLOGICAL INVESTIGATIONS
- MANAGEMENT
- TREATMENT OPTIONS – PHARMACOLOGICAL AND CATHETER BASED MODALITIES
- SPECIAL SITUATIONS: CANCER/PREGNANCY
- CONCLUSION

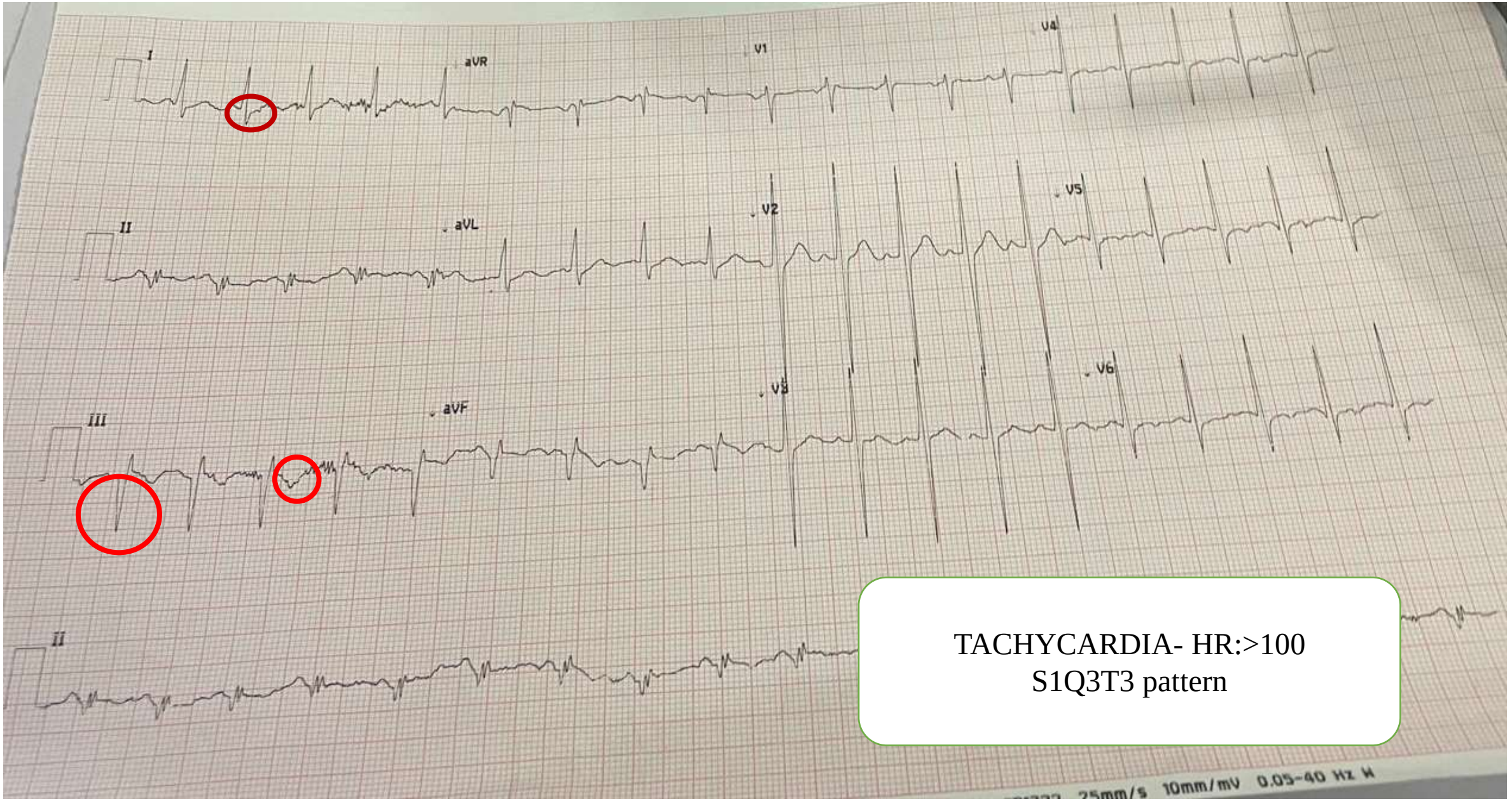
CASE VIGNETTE:

A lictions, present to
orks at an IT
isodes, fever,
102/80mmHg)

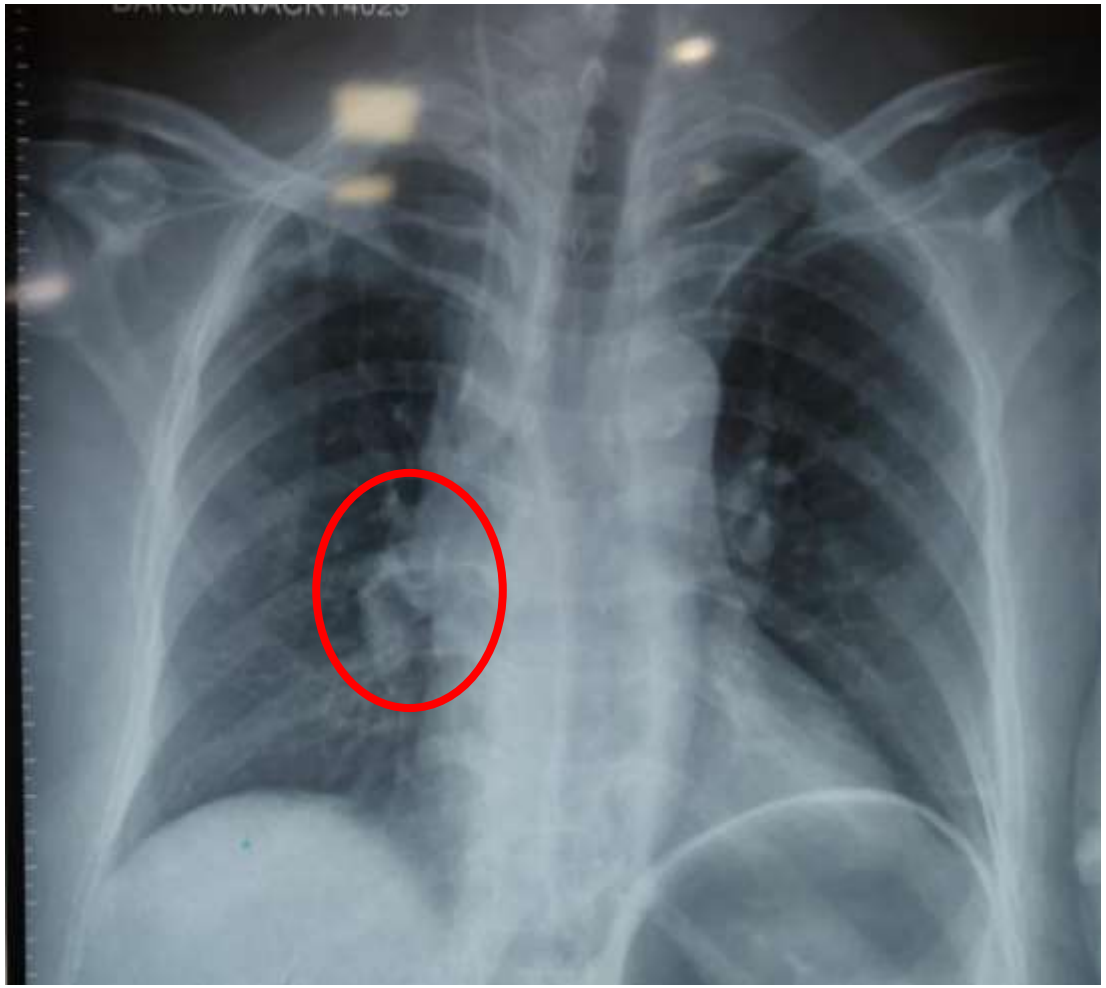
D/D

- PULMONARY THROMBOEMBOLISM
- PERICARDITIS
- PLEURISY (Viral Syndrome /Costochondritis / Musculoskeletal)
- PNEUMOTHORAX
- ACUTE CORONARY SYNDROME
- ANXIETY

HOW TO APPROACH???



TACHYCARDIA- HR:>100
S1Q3T3 pattern



FINDINGS?

PALLA SIGN

ASSESSMENT OF CLINICAL PROBABILITY

- Clinical judgement includes signs, symptoms, ECG, chest radiographs

  Main disadvantage- lacks standardization

- Prediction rules

  a. Wells score

  b. Geneva rule

Konstantinides SV et al. Eur Heart J 2020;41(4):543

Wells score

Items	Clinical decision rule points	
	Original version[1]	Simplified version[2]
Previous PE or DVT	1.5	1
Heart rate >100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alterative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Revised Geneva Rule

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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

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Comparison of the Wells score with the revised Geneva score for assessing suspected pulmonary embolism: a systematic review and meta-analysis

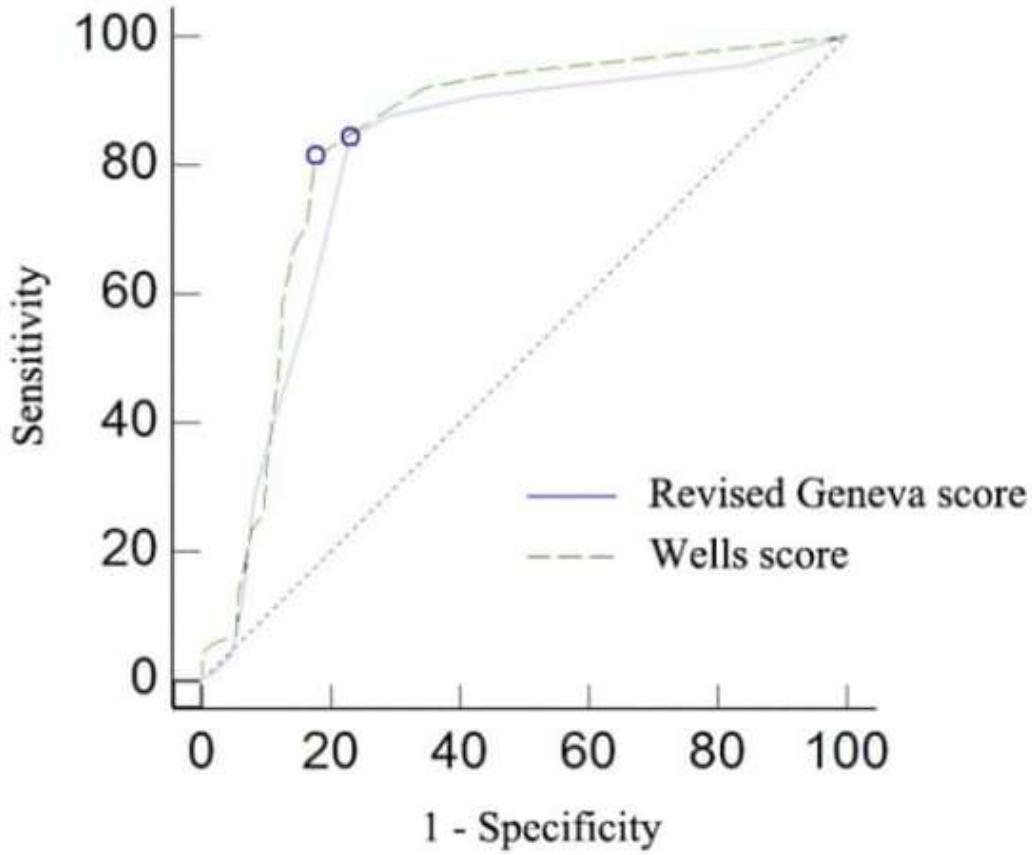
	Sensitivity	Specificity
Wells score	63.8 to 79.3 %	48.8 to 90 %
Revised Geneva score	55.3 to 73.6 %	51.2 to 89 %

Wells score was more effective than the revised Geneva score in determining PE in suspected patients

Shen JH et al. J Thromb Thrombolysis. 2016;41(3):482

- Wells score more accurate than the revised Geneva score for assessing the pretest probability of PE in hospitalized patients

- Revised Geneva score more appropriate for screening tool in ED



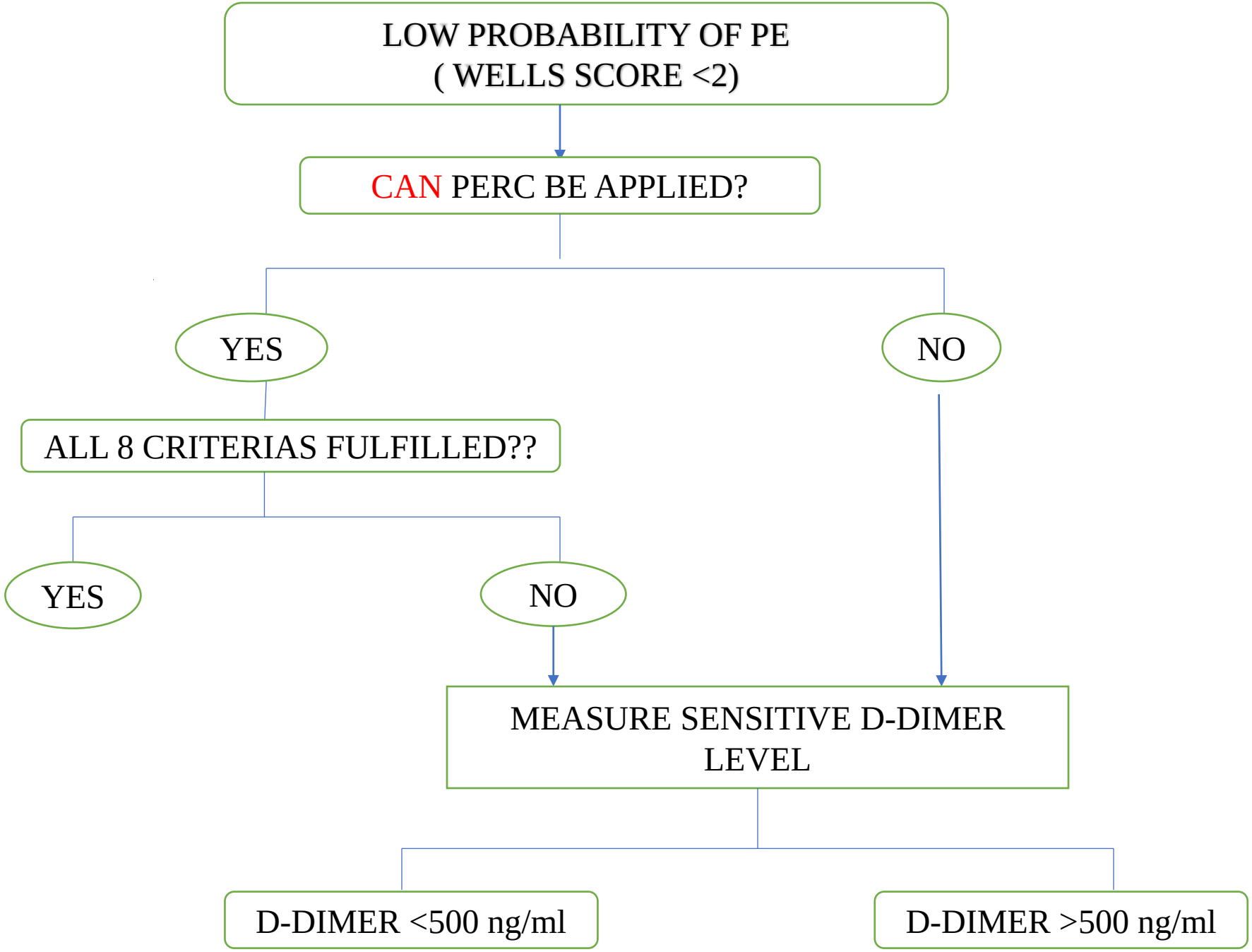
Ma Y et al. Eur J Intern Med. 2016;36:e18

INDEX PATIENT:

Items	Clinical decision rule points	
	Original version[1]	Simplified version[2]
Previous PE or DVT	1.5	1
Heart rate >100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alterative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

INTERMEDIATE

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

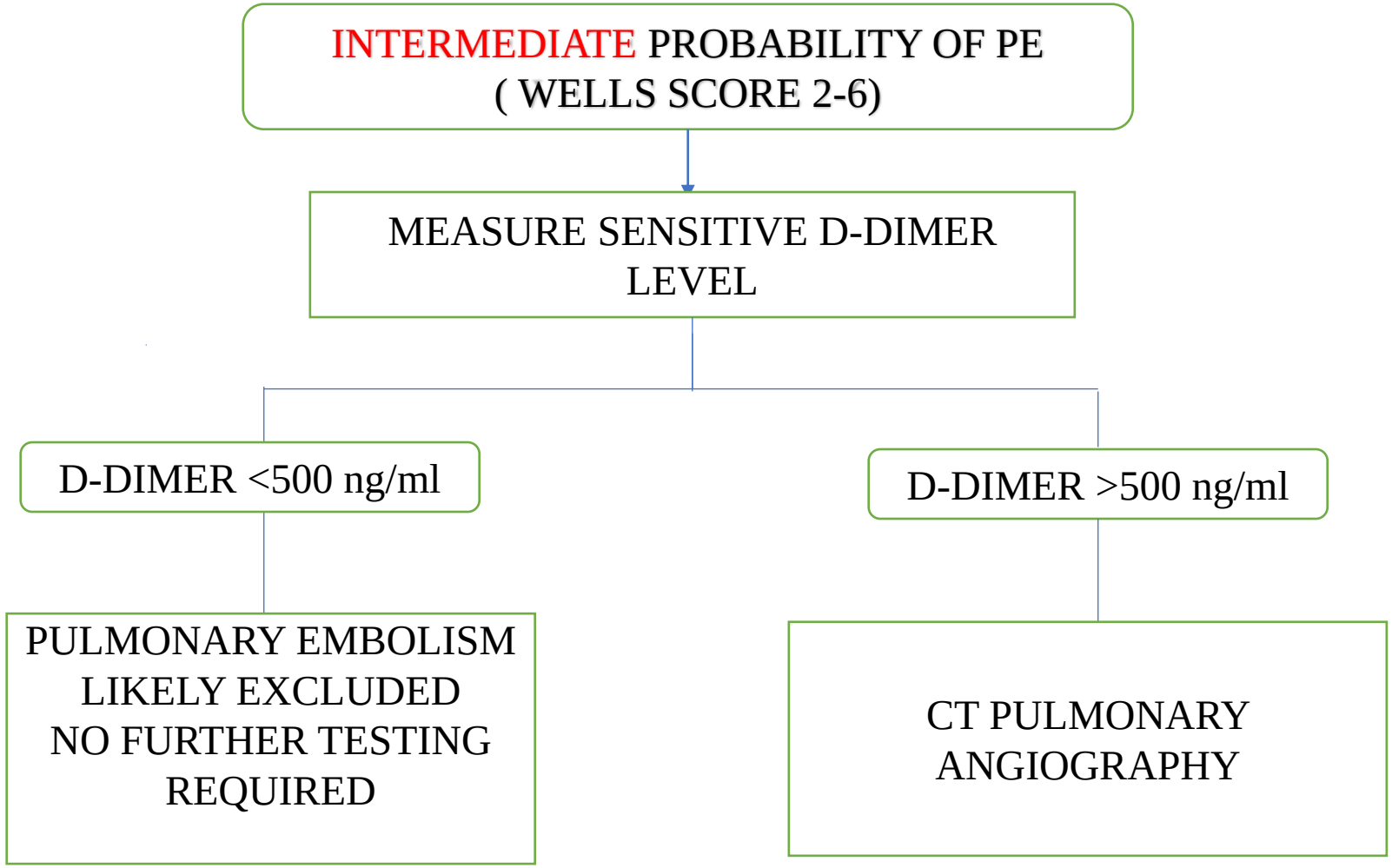

LOW PROBABILITY OF PE
(WELLS SCORE <2)
CAN PERC BE APPLIED?
YES
NO
ALL 8 CRITERIAS FULFILLED??
YES
NO
MEASURE SENSITIVE D-DIMER LEVEL
D-DIMER <500 ng/ml
D-DIMER >500 ng/ml

PULMONARY EMBOLISM RULE OUT CRITERIA (PERC)

- Age <50y
- HR <100/MIN
- Oxyhaemoglobin saturation >94%
- No haemoptysis
- No oestrogen use
- No prior DVT or PE
- No unilateral limb swelling
- No surgery/trauma requiring hospitalization within prior 4 weeks

Only valid in low clinical probability

Konstantinides SV et al. Eur Heart J. 2020;41(4):543


INTERMEDIATE PROBABILITY OF PE
(WELLS SCORE 2-6)
MEASURE SENSITIVE D-DIMER LEVEL
D-DIMER <500 ng/ml
D-DIMER >500 ng/ml
PULMONARY EMBOLISM LIKELY EXCLUDED NO FURTHER TESTING REQUIRED
CT PULMONARY ANGIOGRAPHY

INDEX PATIENT

Values	**Result**
CKMB	<1ng/ml
MYO	17.6ng/ml
TnI	0.06ng/ml
BNP	1800
DDIM	3000
Raised D-Dimer and BNP	

D- dimer testing

- Highly sensitive D dimer assay (ELISA)
- Sensitivity >95 %
- Specificity 35 – 40 %
- Normal D-dimer excludes acute PE with either a low or a moderate pre-test probability (rule out)
- Not useful for confirmation of PE

Immuno fluorescence method used in SOB kits

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Original Investigation

March 19, 2014

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism

The ADJUST-PE Study

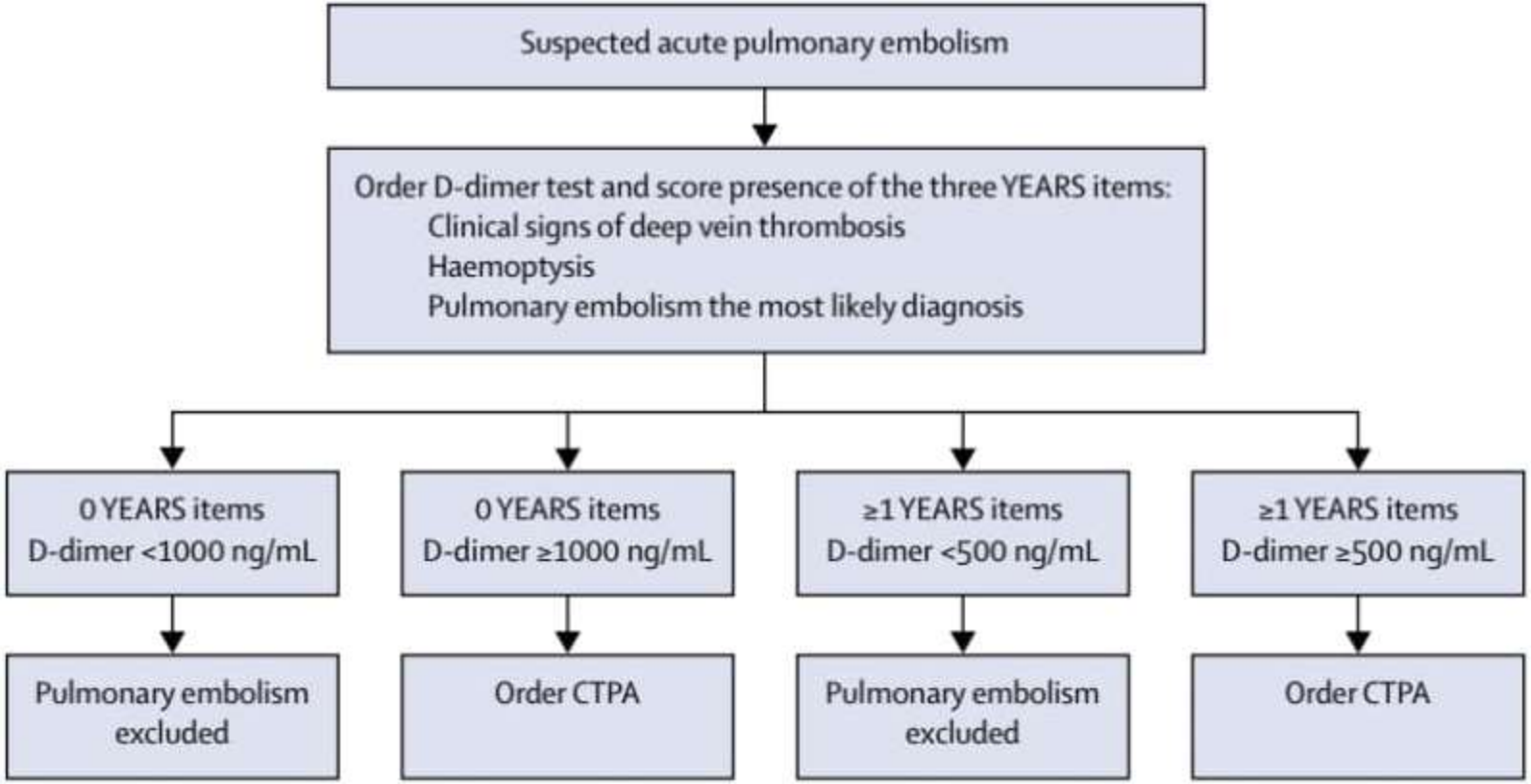
Marc Righini, MD[1]; Josien Van Es, MD, PhD[2]; Paul L. Den Exter, MD[3]; et al

- Multi-center multi-national prospective in 19 centers
- Outpatients with clinically suspected PTE: 3346
- Intervention: Age adjusted D-dimer score:(Patient's age x10) μg/l as new cut-off
- Primary outcome: Failure rate of diagnostic strategy during 3month follow-up
- Outcome: Larger number of patients >75yrs age could be ruled out with age adjusted D-dimer
- (6.4% using 500ug/L vs 29.7% using age adjusted variable could be excluded)

Righini M et al. JAMA. 2014.19;311(11):1117

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

*Tom van der Hulle, Whitney Y Cheung, Stephanie Kooij, Ludo F M Beenen, Thomas van Bemmel, Josien van Es, Laura M Faber, Germa M Hazelaar, Christian Heringhaus, Herman Hofstee, Marcel M C Hovens, Karin A H Kaasjager, Rick C J van Klink, Marieke J H A Kruip, Rinske F Loeffen, Albert T A Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Liselotte M van der Pol, Suzanne Schol-Gelok, Marije ten Wolde, Frederikus A Klok, Menno V Huisman, for the YEARS study group**

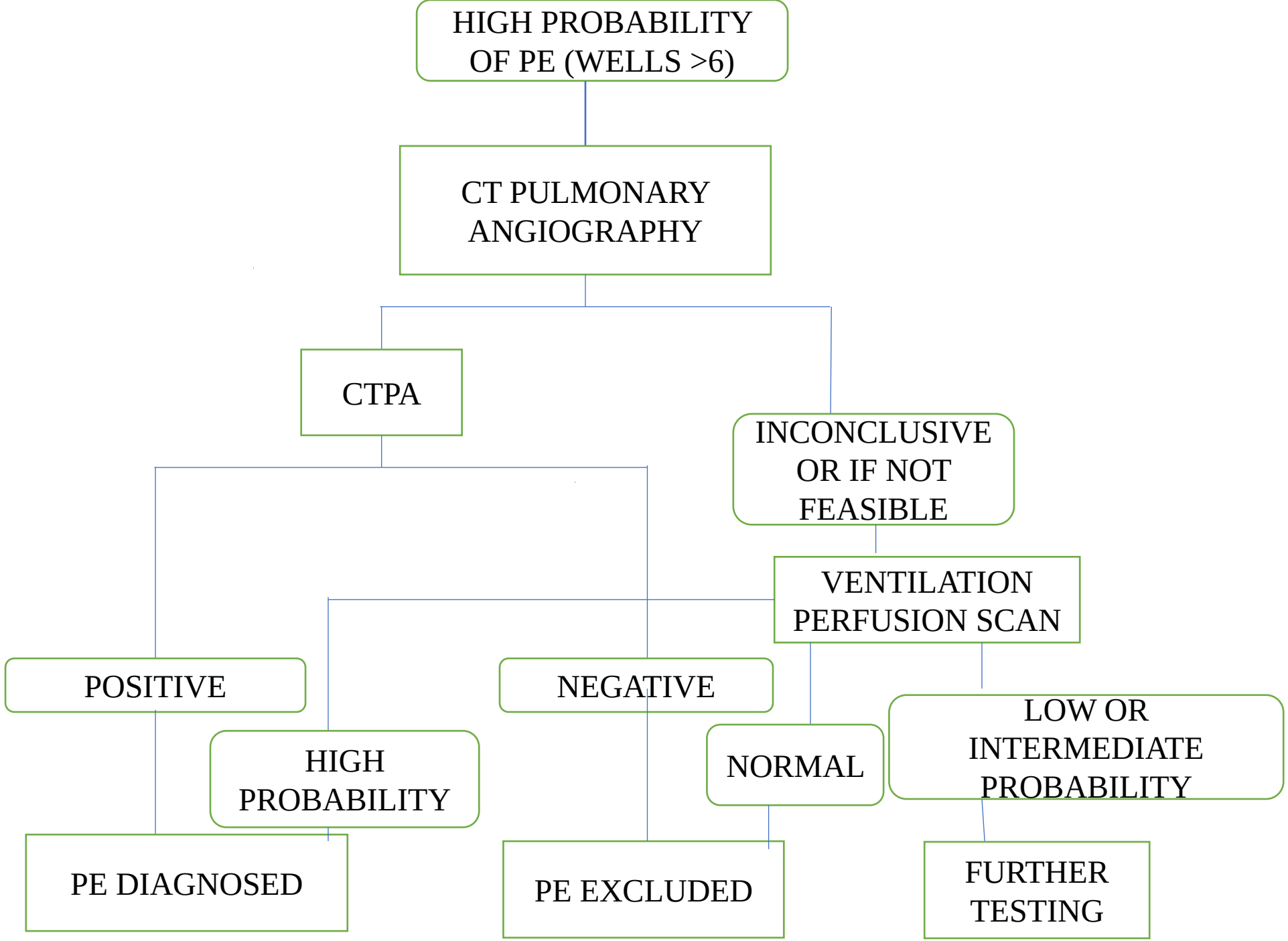


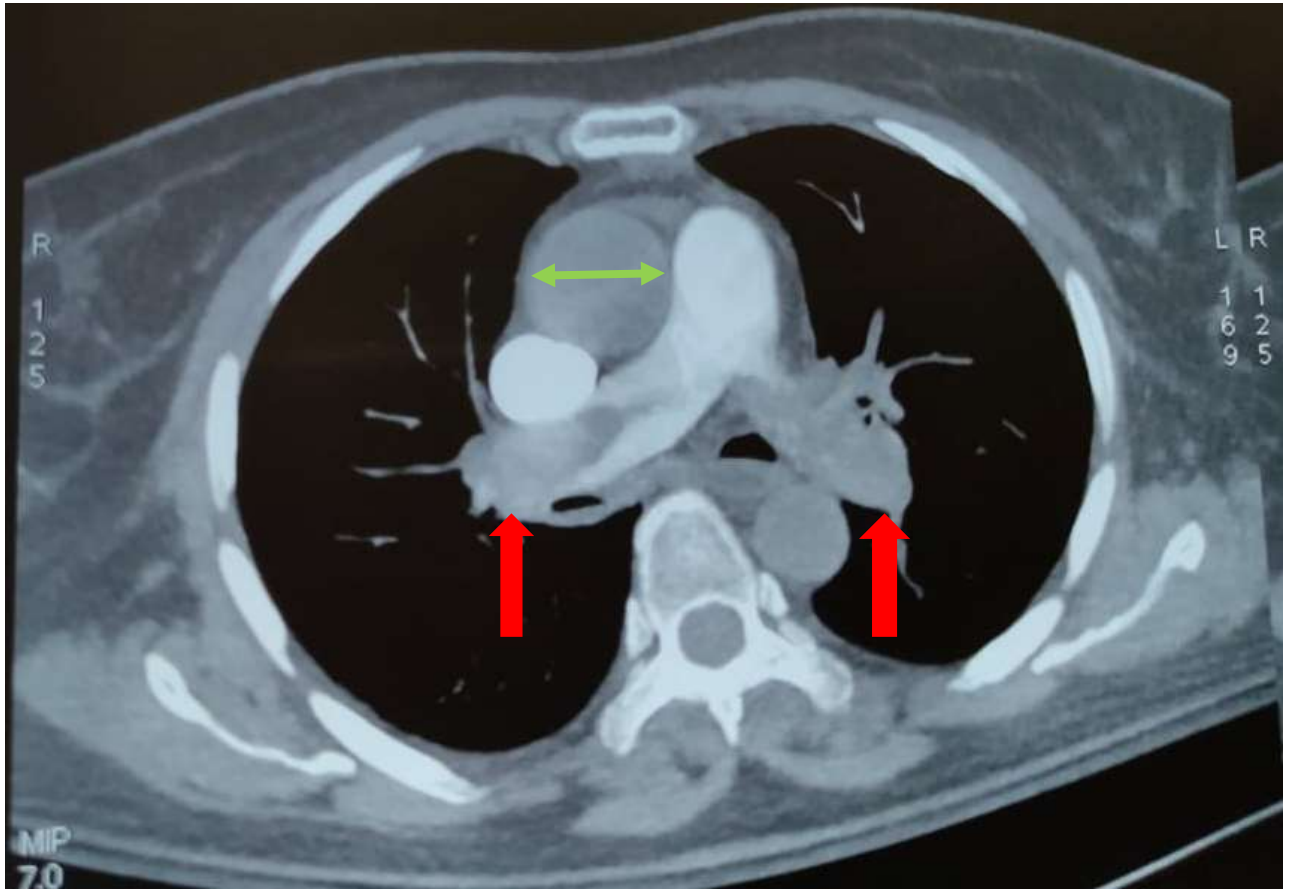
Van der Hulle T et al. Lancet. 2017,15;390(10091):289-297

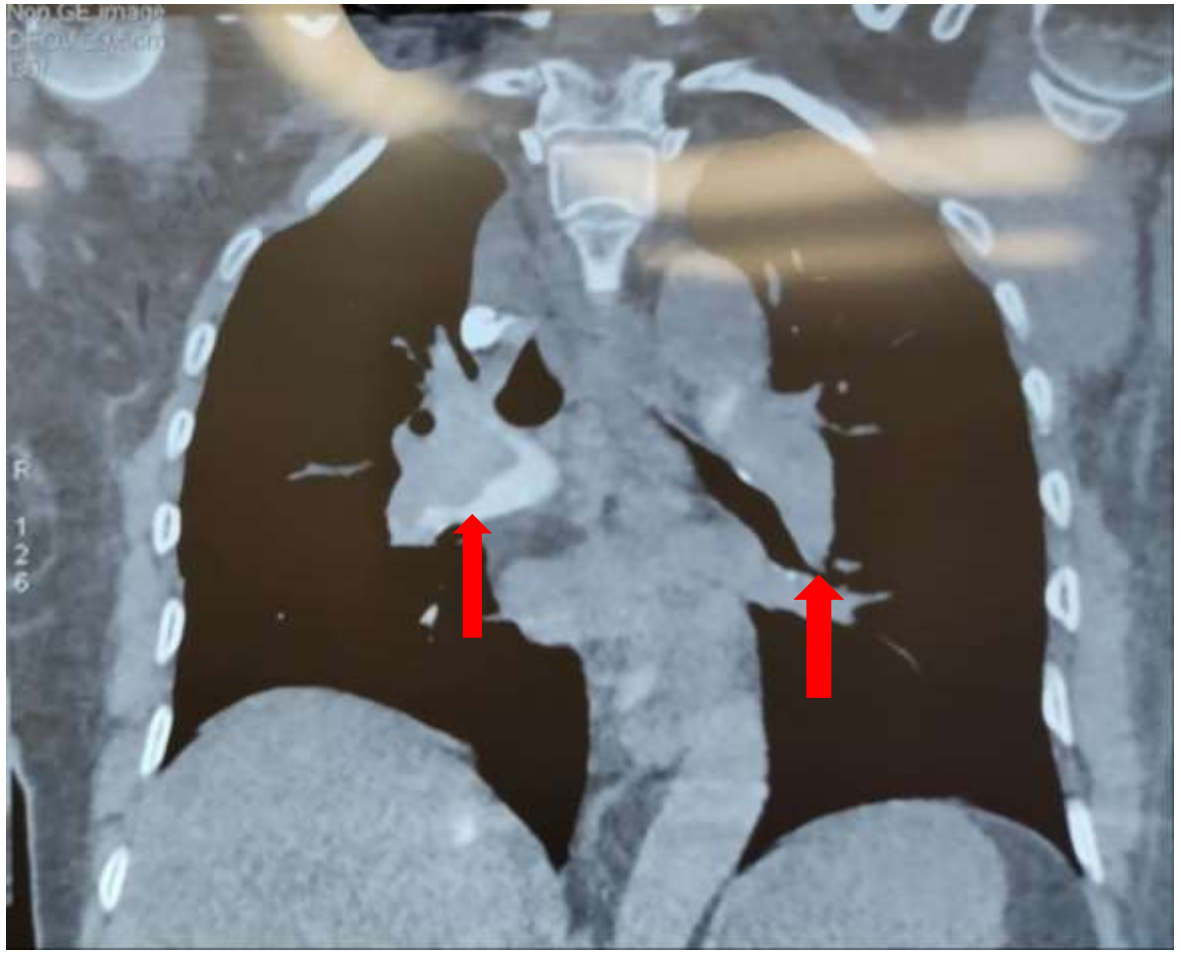
D-dimer cut-offs adapted to clinical probability

- CTPA was avoided in 48% of the included patients using this algorithm, compared to 34% if the Wells rule and a fixed D-dimer threshold of 500 ng/mL would have been applied

Van der Hulle T et al. Lancet. 2017,15;390(10091):289-297


HIGH PROBABILITY OF PE (WELLS >6)
CT PULMONARY ANGIOGRAPHY
CTPA
INCONCLUSIVE OR IF NOT FEASIBLE
VENTILATION PERFUSION SCAN
POSITIVE
NEGATIVE
HIGH PROBABILITY
NORMAL
LOW OR INTERMEDIATE PROBABILITY
PE DIAGNOSED
PE EXCLUDED
FURTHER TESTING





INDEX PATIENT

CT PULMONARY ANGIOGRAPHY

- **FIRST CHOICE DIAGNOSTIC IMAGING MODALITY**

  SENSITIVITY AND SPECIFICITY OF >90% IN LOW AND INTERMEDIATE

  SENSITIVITY INCREASE >96% IN HIGH RISK GROUP

- Contraindicated in patients with history of moderate to severe iodinated contrast allergy or renal insufficiency (eGFR <30 ml/min per 1.73m^2)

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multidetector Computed Tomography for Acute Pulmonary Embolism

Paul D. Stein, M.D., Sarah E. Fowler, Ph.D., Lawrence R. Goodman, M.D., Alexander Gottschalk, M.D., et al. for the PIOPED II Investigators*

June 1, 2006
N Engl J Med 2006; 354:2317-2327
DOI: 10.1056/NEJMoa052367

➢Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II - sensitivity 83% specificity 96%

PRE-TEST PROBABILITY	NPV	PPV
Low	89%	58%
Intermediate	96%	92%
High	60%	96%

CTPA

Advantages

- Excellent accuracy
- Low rate of inconclusive results (3-5%)
- May provide alternative diagnosis if PE excluded
- Short acquisition time

Disadvantages

- Radiation exposure
- Exposure to iodine contrast
- Risks in pregnant and breastfeedingwomen
- C/I in renal failure
- Clinical relevance of CTPA diagnosis of subsegmental PE unknown.

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Imaging Modality	Strengths	Weakness
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
Pulmonary Angiography	Historical Gold Standard	➢ Invasive procedure ➢ Not readily available in all centres
Compression USG	>90% sensitivity and >95% specificity for proximal DVT High PPV for PE if proximal positive CUS Useful in cases with CT contraindication-Pregnancy	1/3 cases of PE with neg CUS Operator variability Upper limb DVT occasionally missed Neg CUS doesn't rule out PE

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

ECHOCARDIOGRAPHY

- ❖ Risk stratification
- ❖ Thrombus demonstration: RV/PA
- ❖ RV strain or pressure overload (sensitivity and specificity – 53% and 61%)
- ❖ Rule out mimics:
- Pericardial tamponade
- Acute valvular dysfunction
- Severe global or regional LV dysfunction
- Aortic dissection

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

RISK STRATIFICATION AND ASSESSMENT

Pulmonary Embolism Severity Index (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%)

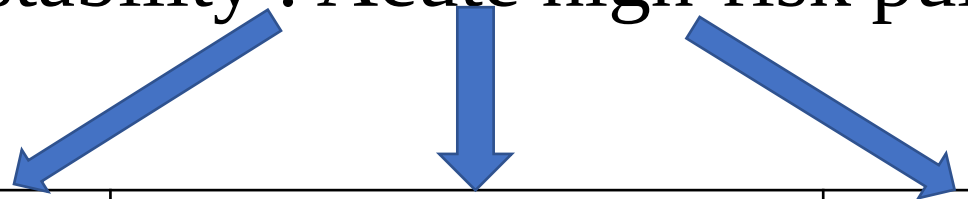
Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Classification of Severity

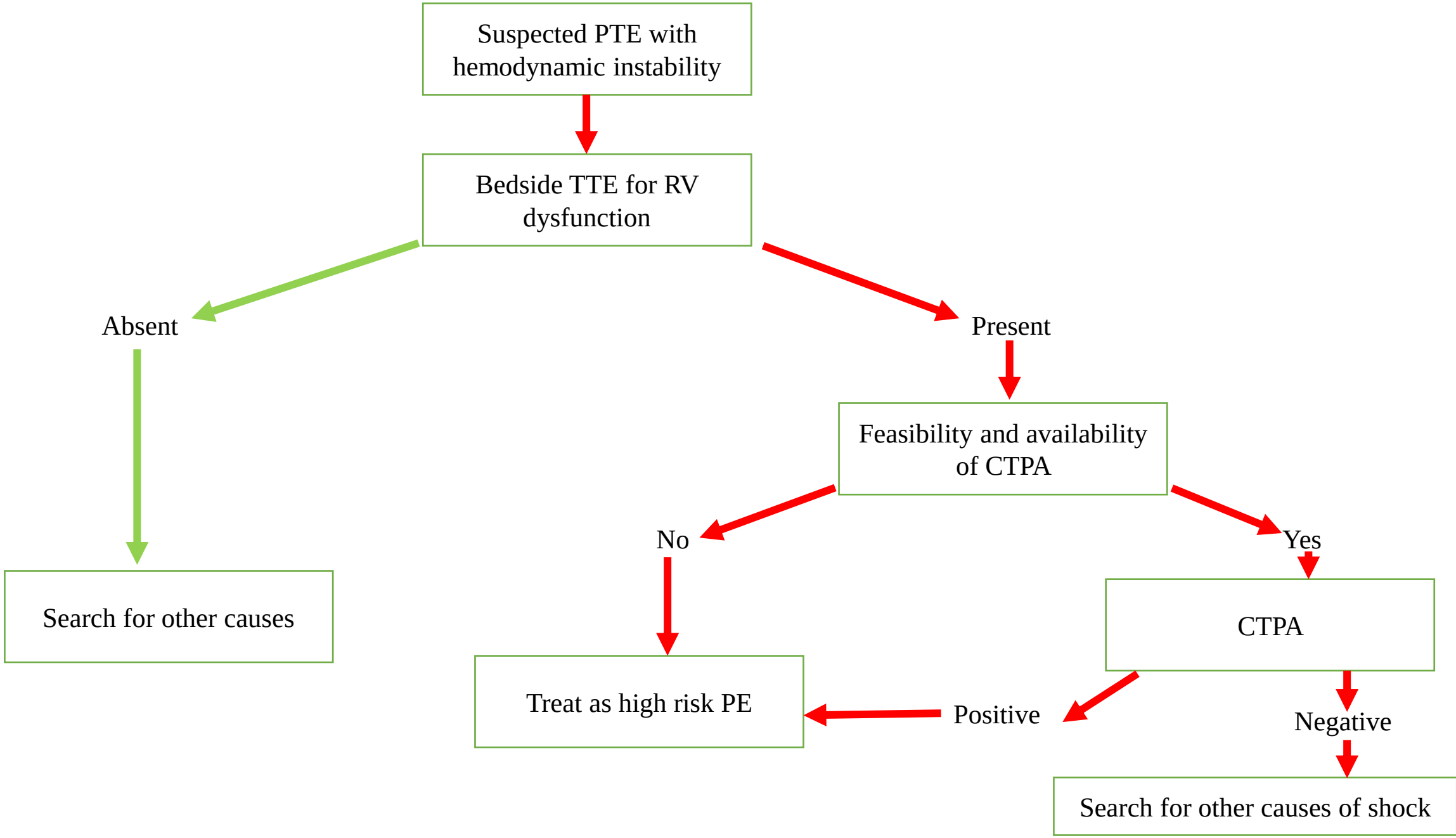
Early mortality risk		**Indicators of risk**			
		Hemodynamic instability	PESI III or IV or sPESI ≥1	RV dysfunction on CTPA or TTE	Elevated troponin levels
High (15-65)%		+	+	+	+
Intermediate(5-15%)	High	-	+	+	+
	Low	-	+	One or none positive	
Low (<1%)		-	-	-	-

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Hemodynamic instability : Acute high-risk pulmonary embolism



Cardiac Arrest	Obstructive Shock	Persistent Hypotension
Need for Cardio-pulmonary 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, hypovolemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	



Konstantinides SV et al. Eur Heart J. 2020;41(4):543

INDEX PATIENT:

Dx: Intermediate High Risk PTE

- Started on Inj UFH subcutaneous dosing(333U/kg f/b 250U/kg BD)
- IV fluid-500ml over 1hr
- Oxygen supplementation
- Close monitoring of vitals

Treatment of Acute PE

4 PILLARS

- Hemodynamic and respiratory support
- Anticoagulation
- Reperfusion treatment
- Vena cava filters

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Hemodynamic and respiratory support

- **Oxygen therapy and ventilation**

- Target ≥ 90%
- Severe hypoxemia, hemodynamic collapse or respiratory failure – intubation with mechanical ventilation
- Coexistent right heart failure: Prone for hypotension following intubation
- (NIV/HFNC > IMV)

- **Pharmacological treatment of RVF**

- Small volume of fluids :(500-1000ml); Improves cardiac index
- Vasopressors – Nonresponsive to IVF
- Norepinephrine – Most frequently used as its effective and less likely to cause tachycardia
- Dobutamine –Increase myocardial contractility

  Systemic hypotension which worsen hypotension at low doses

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Anticoagulation

- Parenteral anticoagulation- LMWH/UFH/Fondaparinux

- NOACs-
  a. Direct thrombin inhibitors: Dabigatran

  b. Oral Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

DEFINITION

- INITIAL ANTICOAGULATION: Administered immediately following VTE
- ANTI-COAGULATION FOLLOWING INITIAL PHASE: Typically administered for finite time period
- EXTENDED ANTICOAGULATION: Beyond typical 3months with scheduled stop date
- INDEFINITE ANTICOAGULATION: Beyond 3months but without scheduled stop date

Drug	Dosing	Advantages
UFH	Subcutaneous: (333units/kg f/b 250units/kg every 12hrs) IV: Weight Based (80 units/kg f/b 18 units/kg/hr) Non-weight Based (bolus 5000 units followed by 1000units/hr infusion and subsequent fixed dose adjustments q6 hrly	Can be given in: ➢Severe renal failure (CrCl < 30ml/min)/ Obesity ➢Primary Reperfusion treatment imminent
LMWH	ENOXAPARIN – 1mg/kg BD (preferred); alternatively 1.5mg/kg OD can be used DALTEPARIN – 200 units/kg OD	➢ Duration is longer ➢ Fixed dosing is feasible as anti Xa activity correlates well with body weight ➢ Laboratory monitoring is not necessary ➢ Lower risk of HIT and can be used as outpatient therapy ➢ Fewer thrombotic complications, improved thrombus regression, reduced rates of haemorrhage

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

NOACs

Large phase III clinical trials comparing VKAs with NOACs for acute VTE

- Non inferiority trials
- Recurrent VTE occurred in 2.0% of NOAC recipients compared with 2.2% in VKA recipients (RR 0.9)
- Lower risk of bleeding in NOAC (1.1%) as compared to VKA(1.7%) (RR 0.6)

van Es N et al. Blood 2014;124(12):1968

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

December 23, 2010
N Engl J Med 2010; 363:2499-2510
DOI: 10.1056/NEJMoa1007903

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

April 5, 2012
N Engl J Med 2012; 366:1287-1297
DOI: 10.1056/NEJMoa1113572

TRIAL	DOSAGE	COMPARATOR	OUTCOME
EINSTEIN-DVT	15mg BD for 21days f/b 20mg OD	ENOXAPARIN/VKA (3-6months)	NON-INFERIOR SIMILAR BLEEDING RISK
EINSTEIN-PE	Same	ENOXAPARIN/VKA	NON-INFERIOR SIMILAR BLEEDING RISK
EINSTEIN-Ext STUDY	Same	PLACEBO	SUPERIOR TO PLACEBO HIGHER BLEEDING RISK
EINSTEIN CHOICE STUDY	10mg OD/20mg OD post 6-12months anticoagulation	ASPIRIN 100mg OD	REDUCED VTE RECURRENCE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., et al., for the RE-COVER Study Group*

December 10, 2009
N Engl J Med 2009; 361:2342-2352
DOI: 10.1056/NEJMoa0906598

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism

Sam Schulman, M.D., Ph.D., Clive Kearon, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Sebastian Schellong, M.D., et al., for the RE-MEDY and the RE-SONATE Trials Investigators*

February 21, 2013
N Engl J Med 2013; 368:709-718
DOI: 10.1056/NEJMoa1113697

TRIAL	DOSE	COMPARATOR	OUTCOME
RECOVER	150mg BD	(Post 9days heparin) Warfarin/6months	NON INFERIOR EQUAL BLEEDING RISK
RECOVER-II	150mg BD	(Post 9.5 days heparin) Warfarin/6months	NON INFERIOR LESSER BLEEDING RISK
RESONATE	150mg BD	(Post 12 months of approved anticoagulation) PLACEBO	LOWER RECURRENT VTE HIGHER BLEEDING
RE-MEDY	150mg BD	(Post 3 months of approved anticoagulation) Warfarin	NON INFERIOR LESSER BLEEDING RISK

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., et al., for the AMPLIFY Investigators*

August 29, 2013
N Engl J Med 2013; 369:799-808
DOI: 10.1056/NEJMoa1302507

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., et al., for the AMPLIFY-EXT Investigators*

February 21, 2013
N Engl J Med 2013; 368:699-708
DOI: 10.1056/NEJMoa1207541

TRIAL	DOSE	COMPARATOR	OUTCOME
AMPLIFY	10mg BD for 7days f/b 5mg BD	ENOXAPARIN(bridge)f/b WARFARIN 6months	NON INFERIOR LESSER BLEEDING RISK
AMPLIFY-EXT	2.5mg BD 5mg BD	PLACEBO	BOTH DOSES NON-INFERIOR SIMILAR BLEEDING RISK

Drug	Target	Peak effect (hours)	Half Life (hours)	Renal clearance (%)	Protein binding (%)	Renal/Hepatic Monitoring	Dosing
Dabigatran	Factor IIa	1.5	14-17	>80	35	Renal	• CrCl>30: 150mg BD • CrCl<30: C/I
Apixaban	Factor Xa	3	8-14	25	85	Renal/Hepatic	• CrCl>50: 5mg BD • CrCl 30-50: 2.5mg BD CrCl <30: C/I
Rivaroxaban	Factor Xa	2-3	7-11	33	90	Renal/Hepatic	• CrCl>50: 20mg OD • CrCl 30-50: 15mg OD • CrCl <30: C/I

Noseworthy PA et al. Chest. 2016;150(6):1302

NOACs AVOIDED

- Severe renal failure
- Pregnancy and lactation
- APLA syndrome
- Mechanical heart valves
- Along with drugs that are strong inhibitors or inducers of P- glycoprotein and/or CYP3A4

van Es N et al. Blood. 2014 ;124(12):1968

Switching Warfarin to NOAC	
Dabigatran	Stop Warfarin, Monitor INR/PT; Start when INR<2
Apixaban	Stop Warfarin, Monitor INR/PT; Start when INR<2
Edoxaban	Stop Warfarin, Monitor INR/PT; Start when INR<2.5
Rivaroxaban	Stop Warfarin, Monitor INR/PT; Start when INR<3
Switching One NOAC to other	
Any NOAC	Start second NOAC when next dose of first NOAC due
LMWH Bridge	
Edoxaban/Dabigatran	Overlap between 5-11 days of treatment
Switching NOAC to Warfarin	
Dabigatran	• Overlap Dabigatran with warfarin until INR therapeutic on Warfarin(ASH) • Overlap with Warfarin for 3days(normal RFT)/2days(CrCl 30-50)/1day(15-30)
Apixaban	• Overlap Apixaban with Warfarin until INR therapeutic and INR testing before next Apixaban dose • Discontinue Apixaban/Parenteral AC bridge with Warfarin
Rivaroxaban	• Overlap Rivaroxaban with Warfarin until INR therapeutic and INR testing before next Apixaban dose • Discontinue Rivaroxaban/Parenteral AC bridge with Warfarin

Witt DM et al. Blood Adv. 2018;2(22):3257

INDEX PATIENT:

After 2hrs:
BP: 84/60
500ml NS given over 30 min
Oxygen supplementation- VM:0.28 SpO2: 94%
Repeat BP: 88/66

Nor-Adrenaline started-(8/50) @ 10mcg/min
BP: 90/66

HEMODYNAMIC INSTABILITY

THROMBOLYSIS IN PTE

- Faster improvement : Pulmonary obstruction/Pulmonary artery pressure/Pulmonary vascular resistance
- Greatest benefit within the first 48h, but useful for 6-14days
- Associated with a significant reduction of overall mortality in patients with PE (especially high risk PE)
- Persistent RV dysfunction, clinical instability: Unsuccessful thrombolysis
- Associated with an increase in severe bleeding and intracranial haemorrhage

Marti C et al. Eur Heart J. 2015 ;36(10):605

Molecule	Regimen	Contraindications to fibrinolysis
Alteplase	100 mg over 2 h (**Preferable**)	**Absolute** ➢ History of haemorrhagic stroke or stroke of unknown origin ➢ Ischaemic stroke in previous 6 month ➢ Central nervous system neoplasm ➢ Major trauma, surgery, or head injury in previous 3 weeks ➢ Active bleeding **Relative** ➢ TIA in previous 6 months ➢ Oral anticoagulation ➢ Pregnancy or first post-partum week ➢ Traumatic resuscitation ➢ Refractory hypertension (systolic BP >180 mmHg) ➢ Advanced liver disease ➢ Active peptic ulcer
	0.6 mg/kg over 15 min (maximum dose 50mg)	
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12-24 h	

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

- Anticoagulation discontinued immediately before and during thrombolytic therapy
- Minor bleeding: Often seen; Not an indication to stop
- Vitals/Hemoglobin monitoring if bleed noted
- Signs of major bleed: Hemodynamic compromise/Mental status/Hb fall/Need for transfusion/Copious bleeding- STOP THROMBOLYTICS
- Paucity regarding reversal- Cryoprecipitate/FFP/Protamine sulfate: Experience not evidence based
- Re-initiation of anticoagulation after 24hrs, particularly long acting
- IV UFH restarted without bolus, preferably after aPTT is less than twice its upper limit of normal

Ucar EY et al. Lung. 2015;193:121

Intermediate-Risk Pulmonary Embolism

PEITHO trial

- Multicenter double blind placebo controlled RCT: 1006 patients were included
- Compared Tenecteplase plus heparin with placebo plus heparin in normotensive patients with intermediate-risk pulmonary embolism
- Prevented hemodynamic decompensation and collapse (2.6% vs 5.6%)
- Increased risk of major haemorrhage (6.3% vs 1.2%) & stroke (2.4% vs 0.2%)

LOW DOSE THROMBOLYSIS

- Meta-analysis of five studies (440 patients), three of which compared low dose rt-PA (0.6 mg/kg, maximum 50mg or 50mg infusion 2h) with standard dose (100mg infusion 2h)

- No statistical differences in recurrent PE or all cause mortality between these two groups

- More major bleeding events in standard dose rt-PA group(OR 0.33, 95%CI 0.12-0.91; P=0.94, I(2)=0%)

Zhang Z et al. Thromb Res. 2014;133(3):357

Trial	Study Design	Patient	Intervention	Comparator	Outcome
MOPPET	Prospective randomized single center open study		Low dose Alteplase + Heparin	Heparin	Outcome: PHTN at 28months Pulmonary Hypertension in Control vs Thrombolysis group(57% vs 16%; p-value<0.001) Lesser duration of hospital stay in Thrombolysis group(2.2 vs 4.9; p-value<0.001) No bleeding in either group/ No significant mortality difference
TOPCOAT *Terminated prematurely*	Randomized double blind placebo controlled	Control: 43 Intervention: 40	Tenecteplase + Heparin	Heparin	Outcome: Composite outcome- Death/Circulatory shock/Intubation/major bleeding within 5days; Recurrent PE/poor functionsl capacity at 90day followup Adverse outcome significantly lower with intervention group (15% vs 37% p=0.017
MAPPET-3	Prospective randomized double blind placebo controlled	Control: 138 Intervention:118	Heparin+ Alteplase	Heparin	Outcome: In hospital death or clinical deterioration requiring escalation of treatment at end of hospital stay or on day 30 of randomization Rate of primary endpoint lower in intervention group(11% vs 25%, p-value: 0.006) Rate of recurrent PE/Bleeding incidence similar
TIPES	Randomized double blind placebo controlled	Control: 28 Intervention:23	Tenecteplase + Heparin	Heparin	Outcome: Reduction of RV dysfunction at 24hrs Reduction of right to left ventricle EDD ratio at 24hrs was 0.31 for Tenecteplase vs 0.10 for placebo(P=0.04)

CATHETER BASED THERAPIES

- Catheter-directed thrombolysis
- Ultrasound-assisted catheter-directed thrombolysis
- Rheolytic thrombectomy plus catheter-directed thrombolysis
- Combined techniques

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

CATHETER BASED THERAPIES

- INDICATIONS:

– failed systemic thrombolysis

– shock likely to cause death before systemic thrombolysis can take effect

– high risk of bleeding

- Decrease major bleeding including ICH
- Lower dose used- 24mg tissue plasminogen activator used
- Higher risk of
  - vascular access-related complications
  - contrast induced nephropathy
- Reserved for use in centres with appropriate expertise

Kearon C et al. Chest. 2016 ;149(2):315

SURGICAL EMBOLECTOMY

- INDICATIONS:
  - Hemodynamic instability in whom thrombolysis contra-indicated
  - Echocardiographic evidence of embolus within patent foramen ovale/right atrium/right ventricle
- Retrospective cohort (257 vs 1854 of thrombolytic therapy):
  - No difference between surgical/thrombolysis in 30 day mortality or 5yr survival
  - Bleeding risk and recurrent PE higher in thrombolysis group
- Combination of ECMO with surgical embolectomy in high risk patients
- Limited to large centers-experienced surgeon and cardiopulmonary bypass required

Lee T et al. J Thorac Cardiovasc Surg. 2018 ;155(3):1084

Vena Cava Filters

Classic Indications -

✓ Absolute contraindication to anticoagulant treatment

✓ Recurrent PTE despite adequate anticoagulation

✓ Failure of Anti-coagulation

Relative Indications-

- Iliocaval DVT or large, free-floating proximal DVT
- Difficulty establishing therapeutic anticoagulation
- Chronic PE treated with thromboendarterectomy
- Poor compliance with anticoagulation
- High risk of complication of anticoagulation (e.g., risk for frequent falls)

RETRIEVABLE FILTERS!!

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Original Investigation

FREE

April 28, 2015

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

A Randomized Clinical Trial

Patrick Mismetti, MD, PhD[1,2,3]; Silvy Laporte, MS, PhD[2,3]; Olivier Pellerin, MD, MSc[4,5]; et al

» Author Affiliations | Article Information

JAMA. 2015;313(16):1627-1635. doi:10.1001/jama.2015.3780

- Randomized, open-label, blinded end point trial
- Primary outcome: Symptomatic recurrent PE at 3months
- Secondary Outcomes: Recurrent PE at 6months/ Symptomatic DVT/Major Bleeding/Death at 3 and 6months/Filter complications
- Use of a retrievable inferior vena cava filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent pulmonary embolism at 3 months
- Does not support the use of this type of filter in patients who can be treated with anticoagulation.

OUTPATIENT ANTICOAGULATION

- Meta analysis of 13 studies(n=1657)
- No statistical significance in outpatient vs in-patient treatment in low risk PE
  - Rate of recurrent VTE (1.7 vs 1.2 %)
  - Mortality (1.9 vs 0.74 %)
  - Major bleeding events (0.97 vs 1 %)
- Home treatment or early discharge of selected low-risk patients with PE is as safe as inpatient treatment

Zondag W et al. Eur Respir J. 2013;42(1):134

OUTPATIENT ANTICOAGULATION

- Accepted parameters for selecting home treatment:

  a. Hestia criteria

  b. PESI

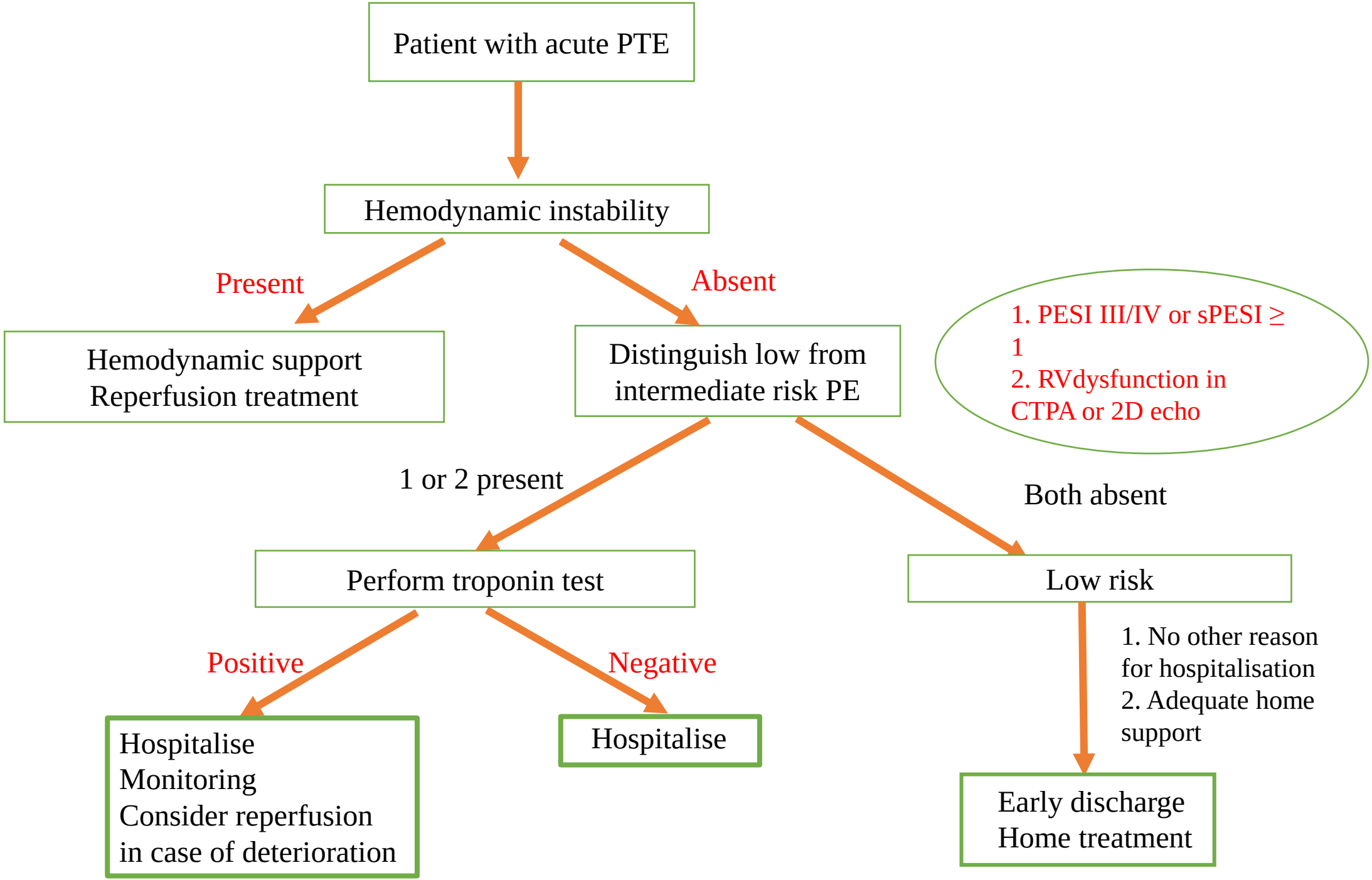
- No incremental value of NT- proBNP

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

OUTPATIENT ANTICOAGULATION

HESTIA RULE
HEMODYNAMICALLY STABLE ?
THROMBOLYSIS/EMBOLECTOMY NEEDED ?
HIGH RISK OF BLEEDING ?
NEED OF OXYGEN SUPPLEMENTATION ?
PULMONARY EMBOLISM DIAGNOSED DURING ANTICOAGULANT TREATMENT ?
IV PAIN MEDICATION > 24 HRS ?
MEDICAL OR SOCIAL REASON FOR TREATMENT IN HOSPITAL > 24HRS ?
Cr CLEARANCE < 30 ML/MIN ?
SEVERE LIVER IMPAIRMENT ?
PREGNANT ?
DOCUMENTED HIT ?

IF THE ANSWER TO ANY OF THESE QUESTIONS IS YES , THE PATIENT CAN'T BE TREATED AT HOME


Patient with acute PTE
Hemodynamic instability
Present
Absent
Hemodynamic support
Reperfusion treatment
Distinguish low from intermediate risk PE
1. PESI III/IV or sPESI ≥ 1
2. RVdysfunction in CTPA or 2D echo
1 or 2 present
Both absent
Perform troponin test
Low risk
Positive
Negative
1. No other reason for hospitalisation
2. Adequate home support
Hospitalise
Monitoring
Consider reperfusion in case of deterioration
Hospitalise
Early discharge
Home treatment

Chronic treatment and Prevention of recurrence

- Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE
- First PE/VTE secondary to major transient or reversible factors: 3months
- Indefinite duration: APLA/ Recurrent PE/Cancer until remission attained
- Anticoagulation beyond 3 months should be considered

a. First episode of PE and no identifiable risk factor.
b. PE associated with persistent risk factor other than APLA.
c. First episode of PE associated with a minor transient or reversible risk factor

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Chronic treatment and Prevention of recurrence

Estimated risk for long term recurrence	Risk factor category for index PE	Examples
Low (<3%/year)	Major transient or reversible risk factor associated with >10 fold increase risk	➢ Surgery with GA >30min ➢ Confined to hospital bed for ≥ 3 days ➢ Trauma with fractures
Intermediate (3-8%/ year)	Minor transient or reversible factors associated with ≤10-fold increased risk for (index) VTE	➢ Minor surgery ➢ Duration of hospital stay < 3 days ➢ Pregnancy or estrogen therapy ➢ Long haul flight
	Non malignant persistent risk factors	➢ IBD ➢ Active autoimmune disease
	No identifiable risk factor	
High (>8%/year)		➢ Active cancer ➢ >_1 episode in absence of a major transient or reversible factor ➢ APLA

Discontinuation of anticoagulation after 3 months is recommended

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

Research

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators

- Unprovoked PTE- no major risk factors/known thrombophilia: 371 patients
- Randomized Double blind trial; 14 French Centers
- 18months treatment and 24 months follow-up with Initial 6months treatment with VKA
- PRIMARY OUTCOME: 6/184 in Warfarin group(3.3%) vs 25/187 in Placebo group(13.5%)
- SECONDARY OUTCOME: 24 month follow-up- 33(20.8%)in Warfarin vs 42(24%) in placebo
- 18month additional treatment reduced composite outcome of recurrent venous thrombosis but benefit not maintained on discontinuation

Choice of Anticoagulation in Cancer

- Indefinite Anticoagulation unless treatment completed/cured/remission
- Meta analysis in 2015 identified 10 RCTs including 3242 cancer patients
- Compared the relative efficacy and safety of LMWH, VKA, and DOAC for the treatment of cancer-associated VTE
- LMWH emerged as significantly superior to VKA with respect to risk reduction of recurrent VTE.
- Recent CHEST 2021 update: Oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy

Konstantinides SV et al. Eur Heart J. 2020;41(4):543

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., et al., for the Hokusai VTE Cancer Investigators*

February 15, 2018
N Engl J Med 2018; 378:615-624
DOI: 10.1056/NEJMoa1711948

- Open label non-inferiority trial
- Oral Edoxaban vs Subcutaneous Dalteparin for 6-12months
- Primary Outcome: Composite of recurrent venous thromboembolism or major bleeding during 12 months
  - {67/522(Edoxaban) vs 71/524(Dalteparin)}
- Rate of major bleeding higher especially Upper GI bleed in patients with GI malignancy(6.9% vs 4%) but not statistically significant
- Non-inferior with respect to bleeding and recurrent thromboembolism

VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

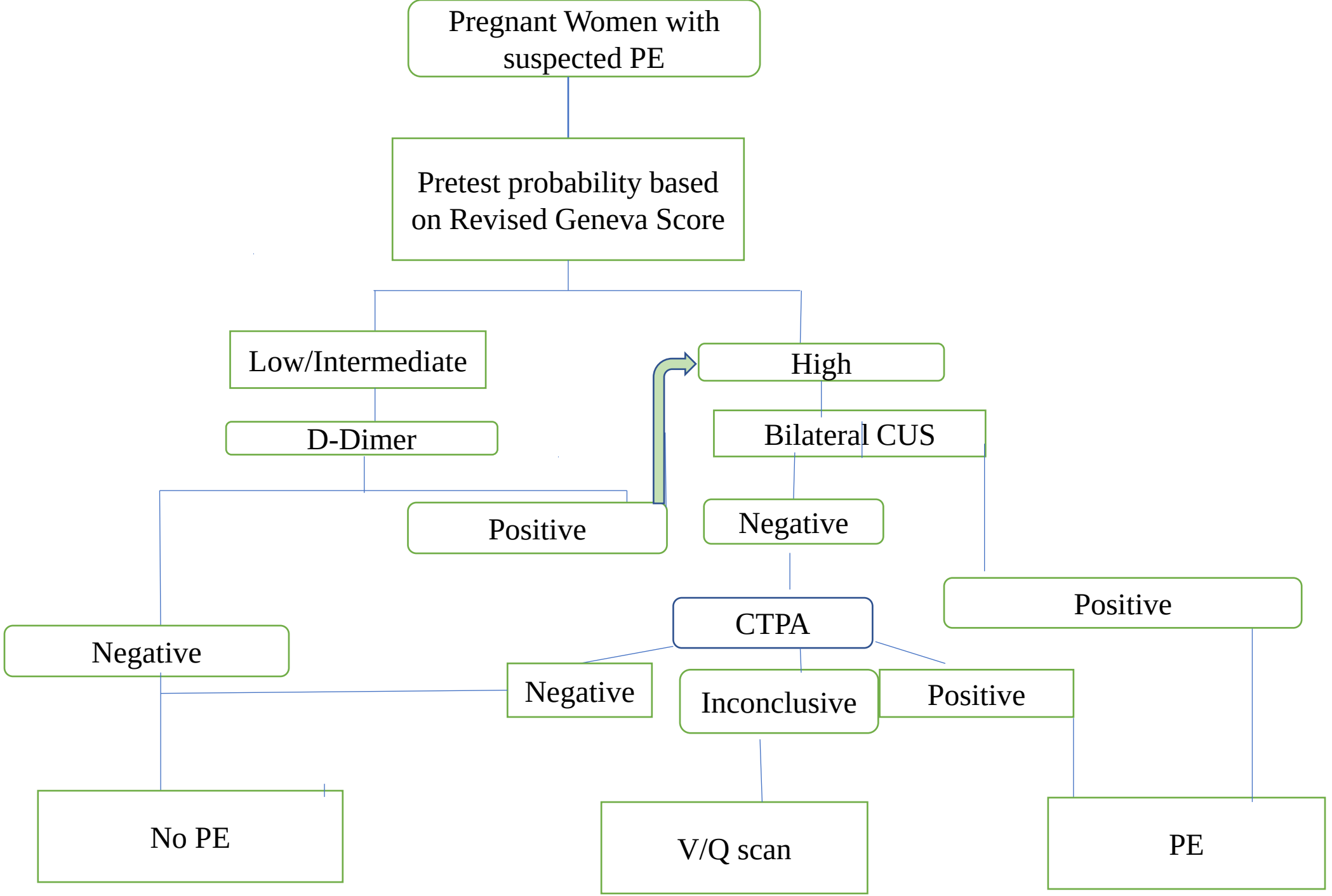
Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

- Multicenter randomized open label pilot trial
- Dalteparin vs Rivaroxaban for 6months
- VTE recurrence over 6months/ Safety assessment: Major bleeding and Clinically relevant nonmajor bleeding
- VTE recurrence rate was 11% (95% CI, 7% to 16%) with Dalteparin and 4% (95% CI, 2% to 9%) with rivaroxaban (hazard ratio [HR], 0.43; 95% CI, 0.19 to 0.99)
- Major bleeding was 4% (95% CI, 2% to 8%) for Dalteparin and 6% (95% CI, 3% to 11%) for rivaroxaban (HR, 1.83; 95% CI, 0.68 to 4.96).
- CRNMB were 4% (95% CI, 2% to 9%) and 13% (95% CI, 9% to 19%), respectively (HR, 3.76; 95% CI, 1.63 to 8.69).
- Rivaroxaban was associated with relatively low VTE recurrence but higher CRNMB compared with dalteparin.

PREGNANCY AND PTE

- CTPA/CXR: High clinical suspicion
- V/Q SPECT : Low fetal and maternal radiation exposure
- LMWH : Treatment of choice and advised for future pregnancies
- High Risk PE: Thrombolysis/Surgical Embolectomy
- Anticoagulant : Continued >6weeks after delivery with minimum overall 3months

Konstantinides SV et al. Eur Heart J. 2020;41(4):543


Pregnant Women with suspected PE
Pretest probability based on Revised Geneva Score
Low/Intermediate
High
D-Dimer
Bilateral CUS
Positive
Negative
Positive
CTPA
Negative
Negative
Inconclusive
Positive
No PE
V/Q scan
PE

INDEX PATIENT:

Thrombolysed with Alteplase 100mg

↓

BP after 4hrs: 112/72- Inotrope tapered

↓

Clexane introduced after 24hrs

↓

NOAC-Rivaroxaban introduced

Procoagulant workup negative

↓

Maintained on AC for 3months/ No dyspnea or functional limitation

↓

Advised for Future LMWH in pregnancies.

SUMMARY:

- Unexplained hypoxemia in presence of normal CXR should raise suspicion of pulmonary embolism
- Close Monitoring of Intermediate High risk patients
- All PTE patients don’t require admission-Hestia Criteria
- Algorithmic approach helpful in guiding management
- NOACs fast becoming the drug of choice
- *Clinical Judgement still of paramount importance*