Acute Pulmonary Embolism

Whats in the new ESC Guidelines 2019

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2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC).

Developed in collaboration with the European Respiratory Society (ERS)

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[1] Representing the European Respiratory Society (ERS)

Table 6 Prevalence of symptoms and signs in patients with suspected PE according to final diagnosis

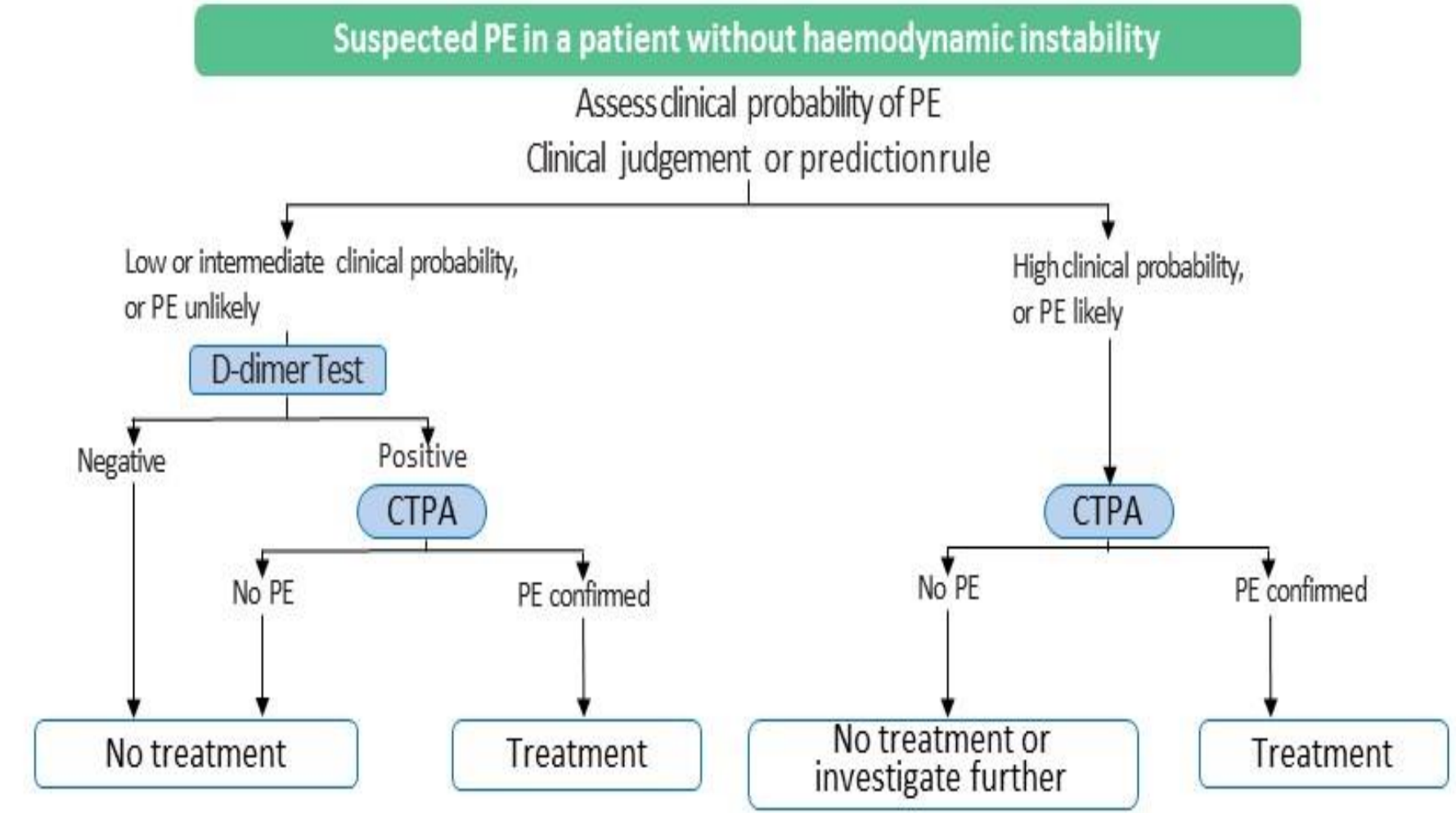
	PE confirmed ($n = 219$)	PE excluded ($n = 546$)
Symptoms		
Dyspnoea	80%	59%
Chest pain (pleuritic)	52%	43%
Chest pain (substernal)	12%	8%
Cough	20%	25%
Haemoptysis	11%	7%
Syncope	19%	11%
Signs		
Tachypnoea (≥20/min)	70%	68%
Tachycardia (>100/min)	26%	23%
Signs of DVT	15%	10%
Fever (>38.5°C)	7%	17%
Cyanosis	11%	9%

Non-Specific!!

90% will have 1 or more of dyspnoea/ tachypnoea/ pleuritic CP

ESC Guidelines. Eur Heart Journal

Figure 4 Diagnostic algorithm for suspected PE without haemodynamic instability



CTPA = computed tomography pulmonary angiography

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(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Table 2 Main new recommendations 2019 (1)

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Diagnosis	
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

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Age adjusted D Dimer

- **Age < 50 years – cut off 500 ug/l**
- **Age > 50 years – (Age in years) x 10 ug/l**

- ADJUST Study – age adjusted d dimer ↑the number of patients in whom PE could be excluded without CTPA from 6.4% to 30% of over 75 year olds

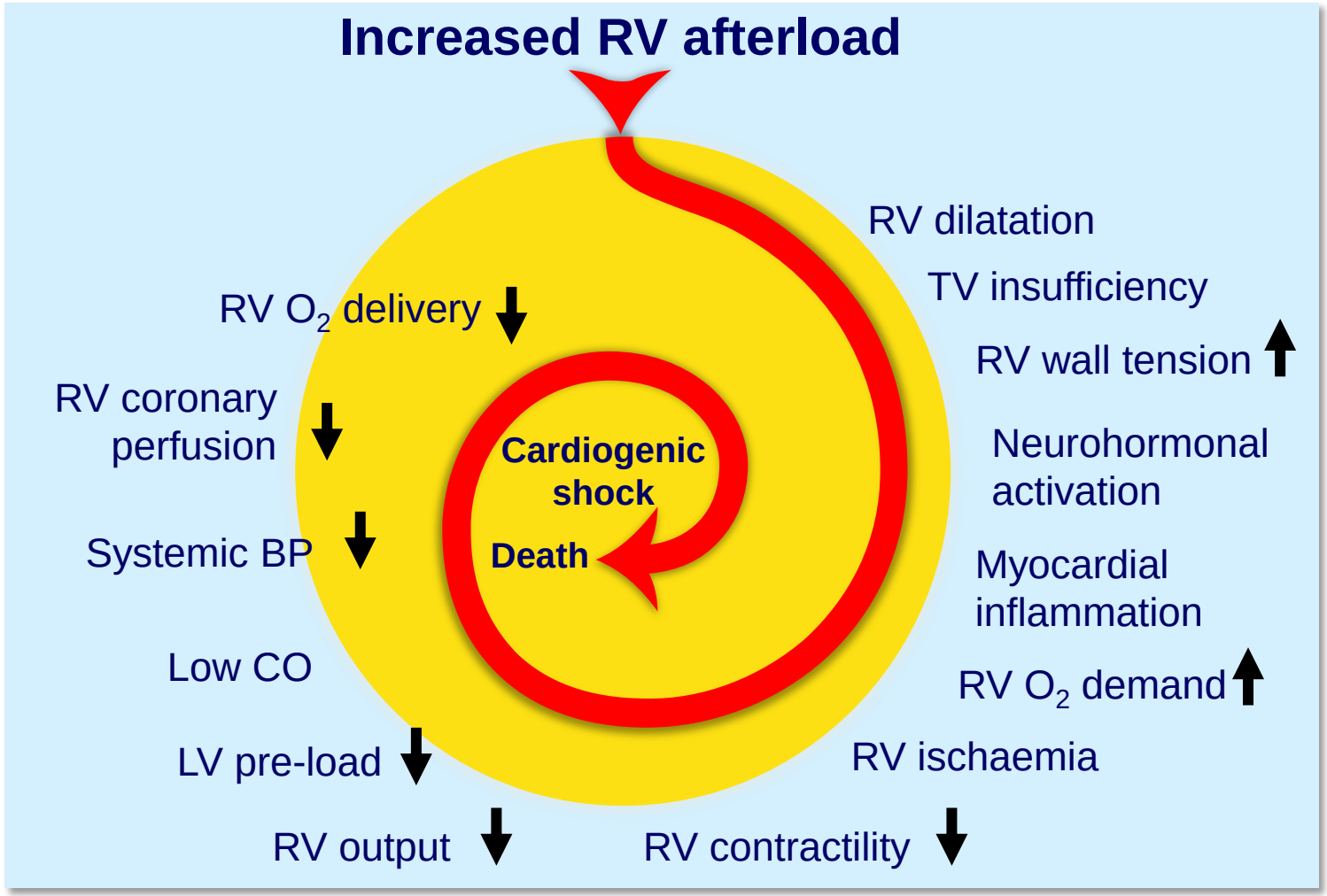
Nomenclature of Risk Stratification

MASSIVE	**HIGH RISK**	3-5% of all PEs	>25% 30 day mortality
SUBMASSIVE	**INTERMEDIATE RISK**	25% of all PEs	3-8% 30 day mortality
LOW RISK	**LOW RISK**	70-75% of all PEs	<1% 30 day mortality

Why need for clinical risk stratification

- PE severity based on risk of early death and complications
- Wide spectrum of severity - <1% mortality if clinically stable low risk to >30% if in cardiogenic shock
- Need tailored management strategies
  - Who can be managed as outpatient ?
  - If admitted, Who to closely monitor and where ?
  - For Anticoagulation or Reperfusion (Thrombolysis) strategies ?
  - Who needs follow up ?

Spiral of Acute RV Failure and hemodynamic collapse in PE



Konstantinides S, et al. *European Heart Journal* (2014):doi:10.1093/eurheartj/ehu283

Figure 5 Risk-adjusted management strategy for acute PE (1)

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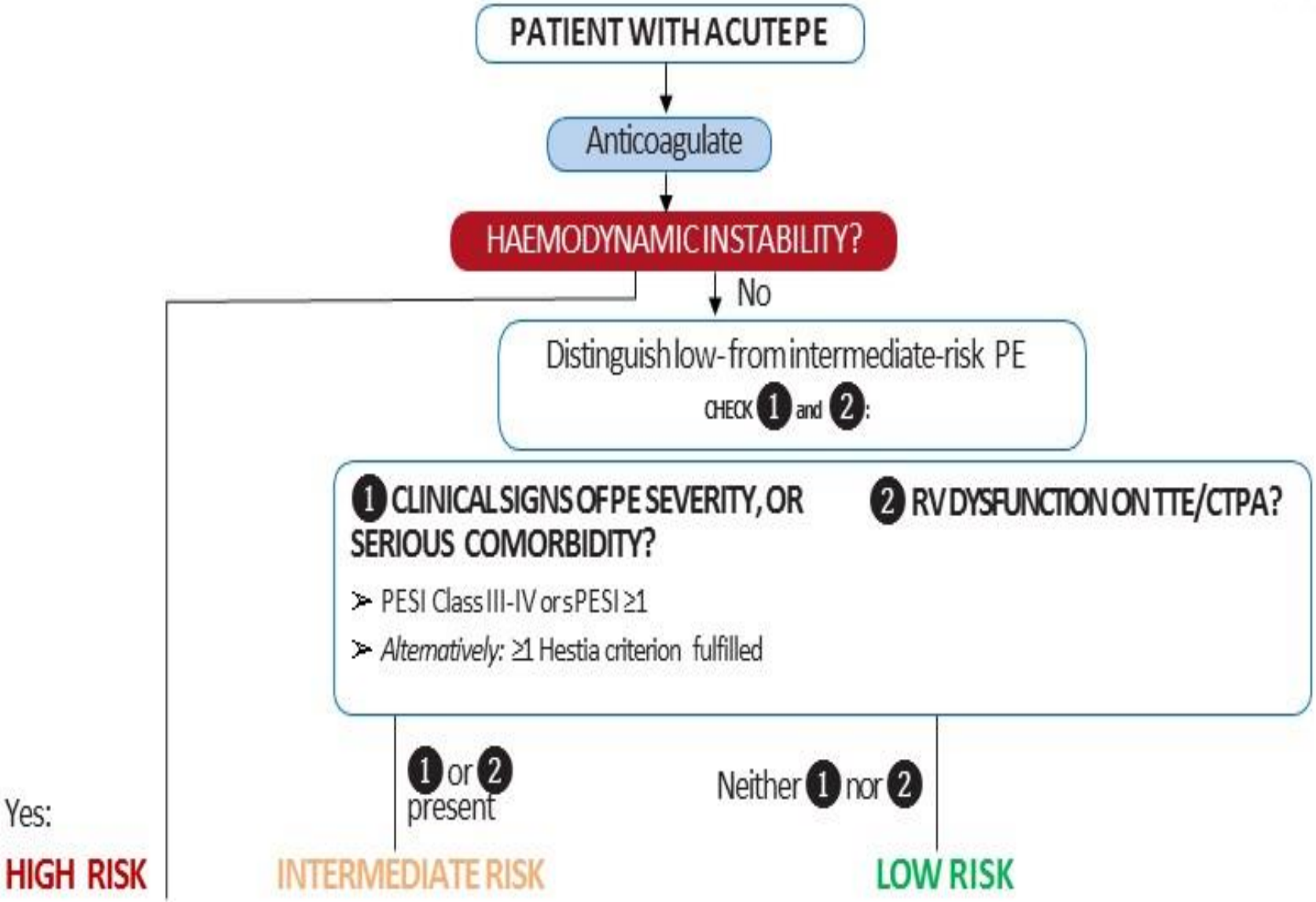

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Table 4 Definition of haemodynamic instability

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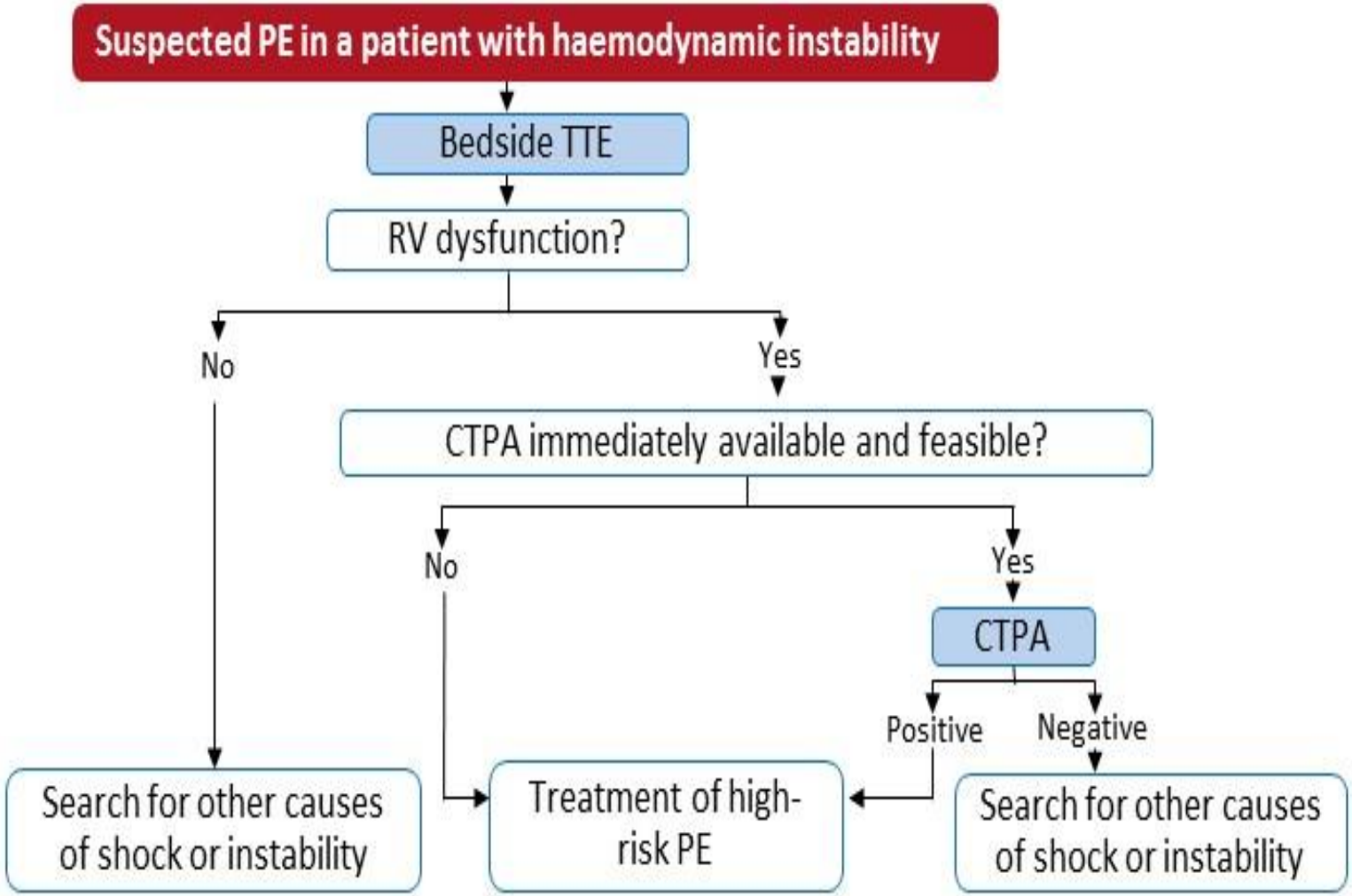
(1) Cardiac arrest	(2) Obstructive shock	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP <90 mmHg, or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP <90 mmHg, or systolic BP drop ≥40 mmHg, either lasting longer than 15 minutes 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)	

Figure 3 Diagnostic algorithm for suspected high-risk PE



CTPA = computed tomography pulmonary angiography; RV = right ventricular; TTE = transthoracic echocardiography

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High Risk (Massive) PE

- Is PE driving the patients haemodynamic instability ?
- Other associated process – ?hypovolaemia ?sepsis
- Does clinical state correlate with clot burden
- Echo assessment impt
  - RV must be dilated if massive PE
  - collapsed IVC suggests hypovolaemia
- Cautious with IV Fluid. Do not give any if IVC is dilated. No more than 500 ml is collapsed IVC
- Prompt reperfusion – full dose thrombolysis
- Avoid concurrent Heparin. Start IV Heparin Only after thrombolysis infusion complete and APTT <2
- Avoid Intubation if possible
- Inotropic support - Adrenaline infusion
- Inhaled Pulmonary Vasodilators
- ECMO as bridge to surgery in high risk PE and refractory circulatory collapse

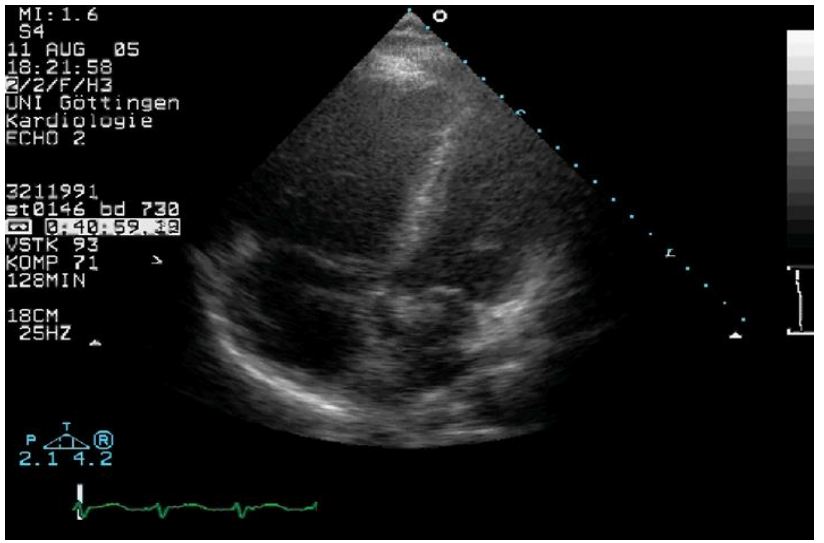
Intermediate Risk (Submassive) PE Definition

- SBP > 90 mmHg

  AND
- Presence of RV Dysfunction. Any of :
  - Dilated RV on CT
  - RVD on Echo
  - Positive BNP
  - Myocardial necrosis - Troponin +ve

- ~25% of all PEs
- ~ 10% of these will progress to haemodynamic collapse/shock
- ~ 3-8% mortality

Tools to identify intermediate risk in PE: Echo



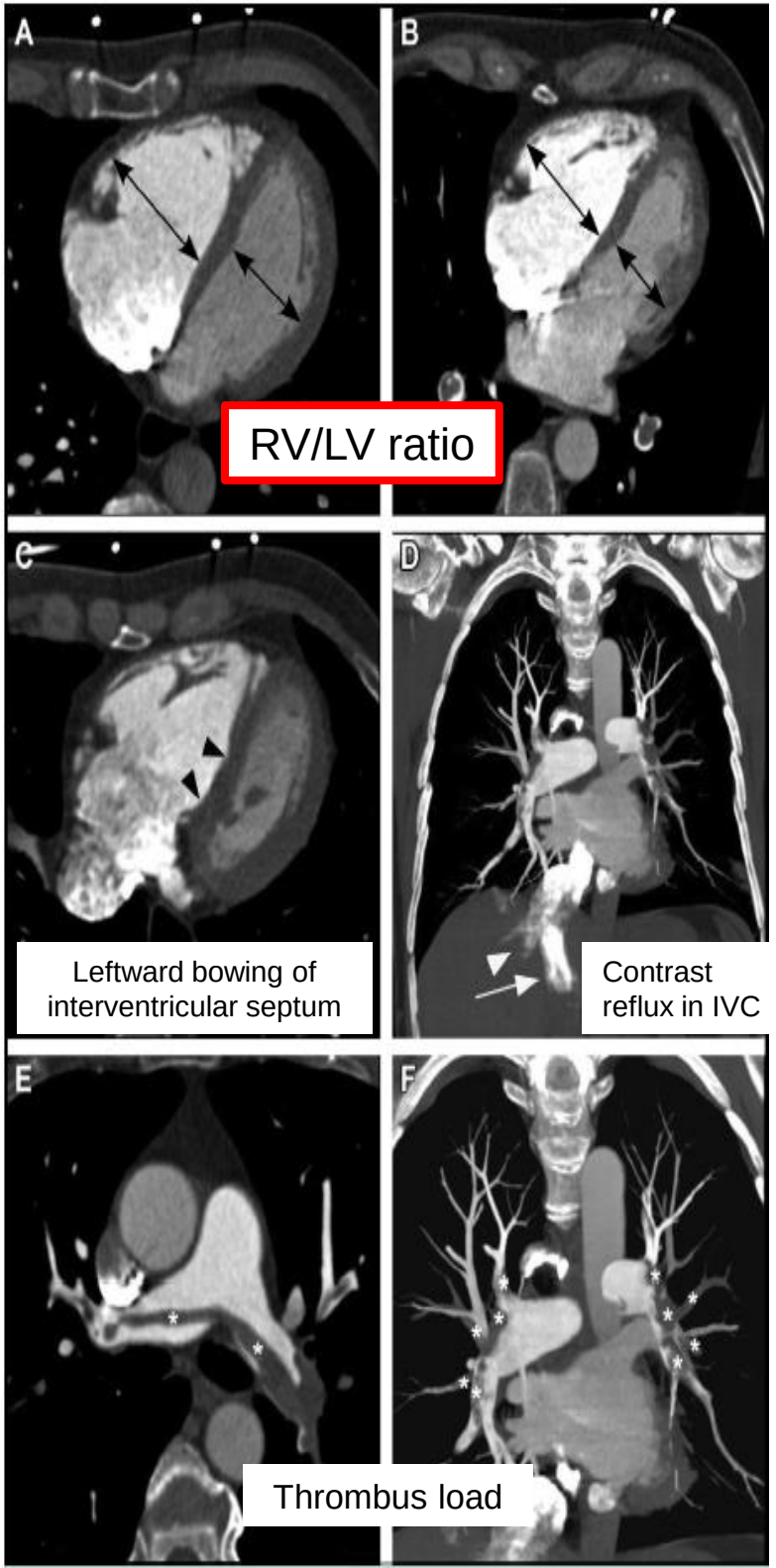
- Meta-analysis 8 studies (1249 patients with PE)
- RV dysfunction on TTE:
  - In ~40% of patients with normotensive PE
  - OR 2.36 (95%CI,1.3-4.3) all-cause mortality

Coutance et coll Crit Care 2011; 15:R103

Echo criteria of RVD

- RV dilatation (RV/LV >1 or RVEDD >30 mm)
- Impaired systolic function
- Hypokinesia of RV free wall
- Paradoxical septal wall motion
- ↑Pulm Art Pressure
- Distended IVC
- May see free thrombus in RA,RV,PA

S Konstantinides. Curr Opin Cardiol 2005; N Engl J Med 2008



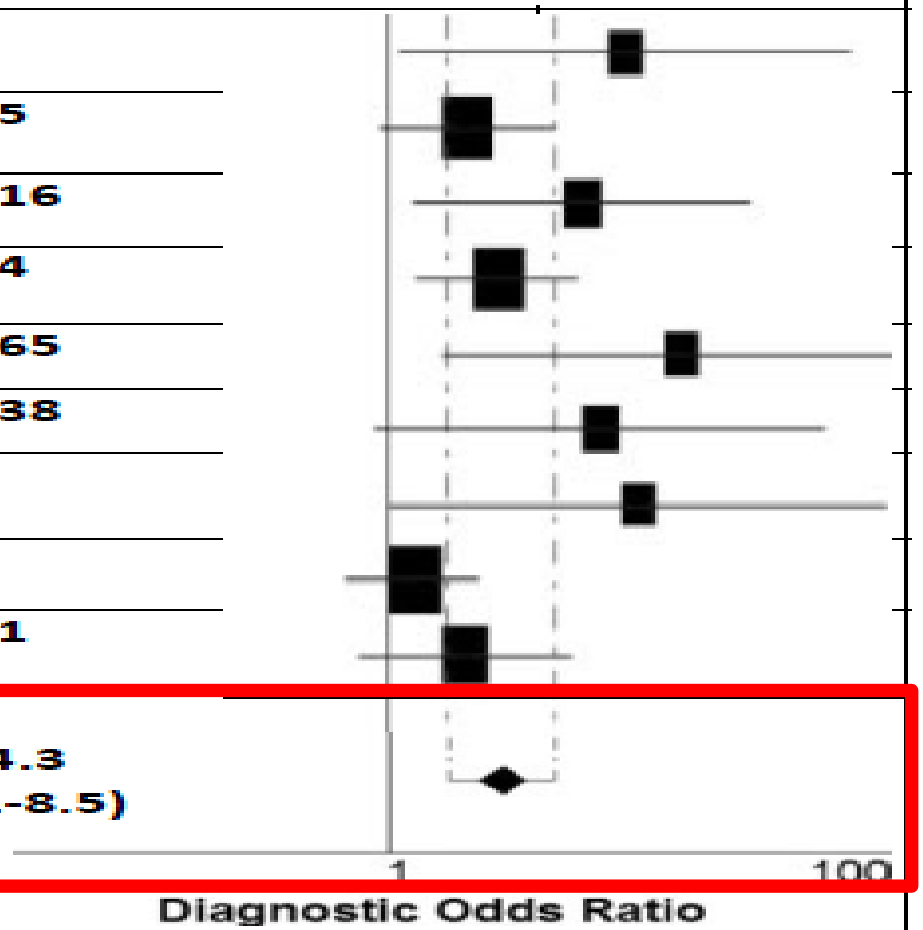
Imaging of RV dysfunction on CTPA

- Meta-analysis 49 studies (13162 patients with PE)
- **RV/LV ≥ 1.0**
  - OR 2.5 (95%CI, 1.8-3.5) all-cause mortality
  - OR 5.0 (95%CI, 2.7-9.2) PE-related mortality
  - **Independant predictor of adverse outcome**

Meinel et coll Am J Med 2015;128:747-59

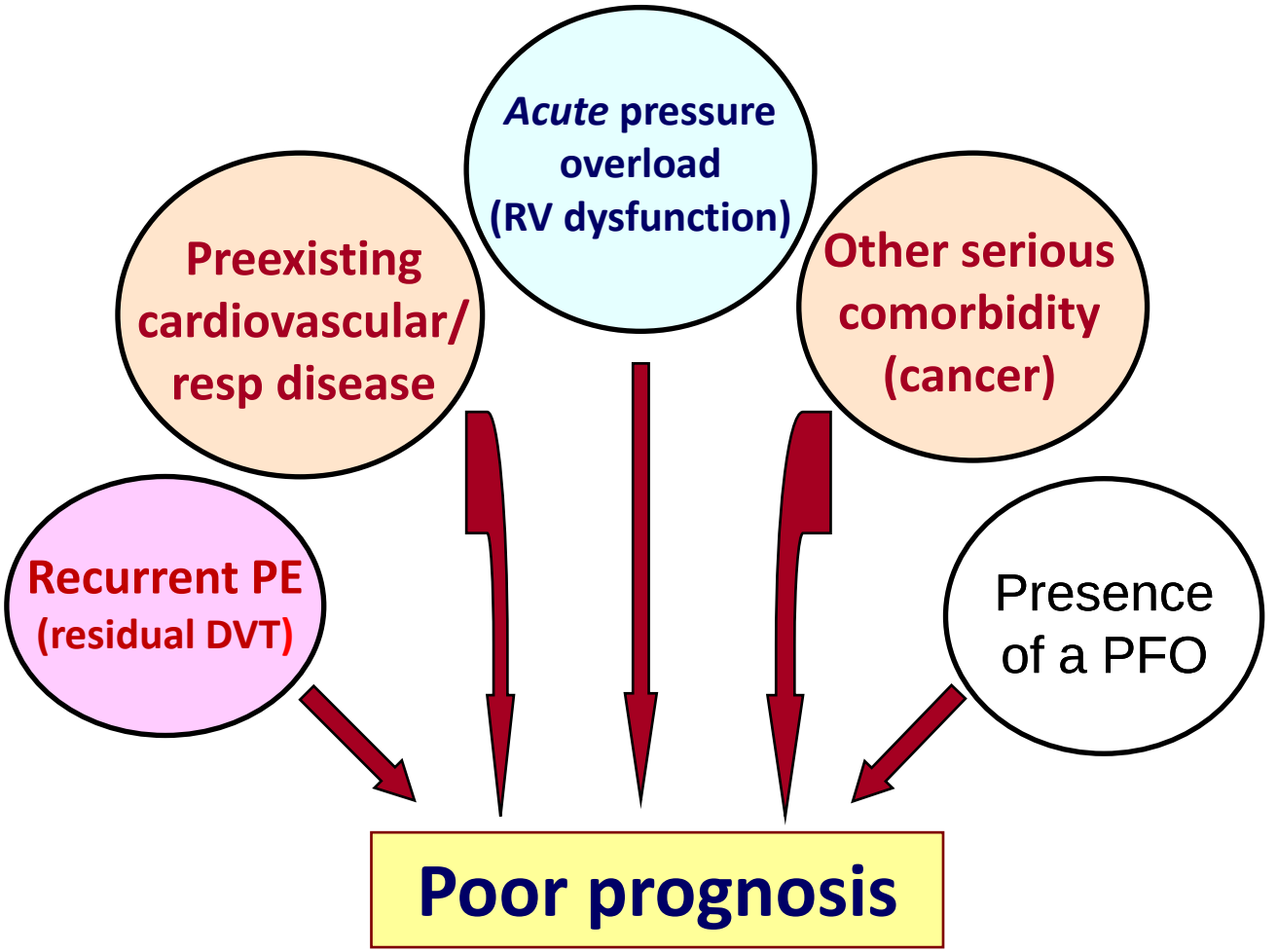
Troponin for risk stratification

Studies	Troponin Cut-off	OR, random 95% CI
Pruszczyk '03	TnT >0.01	21
Kostrubiec '05	TnT >0.07	2.75
Bova '05	TnT >0.01	12.16
Douketis '05	TnI >0.5	4.14
Kline '06	TnT >0.1	43.65
Logeart '06	TnI >0.06	15.38
Tulevski '07	TnT >0.01	25
Jimenz '07	TnI >0.1	1.4
Gallota '07	TnI >0.03	2.71
All cause short-term mortality (IH-90d)	N=1366	4.3 (2.1-8.5)



Jimenez D, Chest 2009

What about *clinical* prognostic indicators in PE?



Clinical parameters: PESI and sPESI

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%)

Aujesky et al. AJRCCM 2005; 172: 1041-6; Jimenez et al. Arch Intern Med 2010;170:1383-9

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Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
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	Risk strata[a]	
LOW RISK	**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%)
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Figure 5 Risk-adjusted management strategy for acute PE (1)

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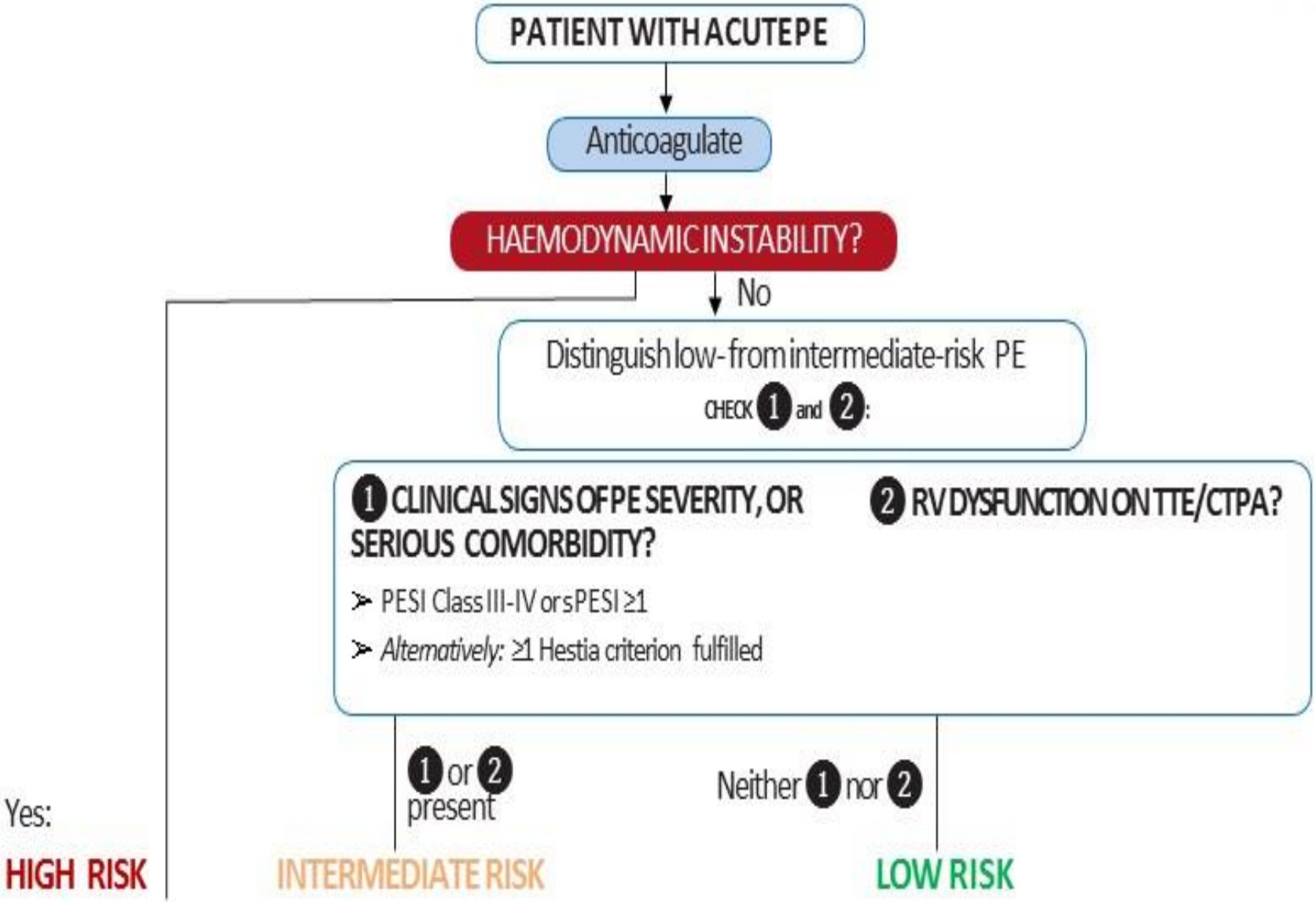

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Figure 5 Risk-adjusted management strategy for acute PE (2)

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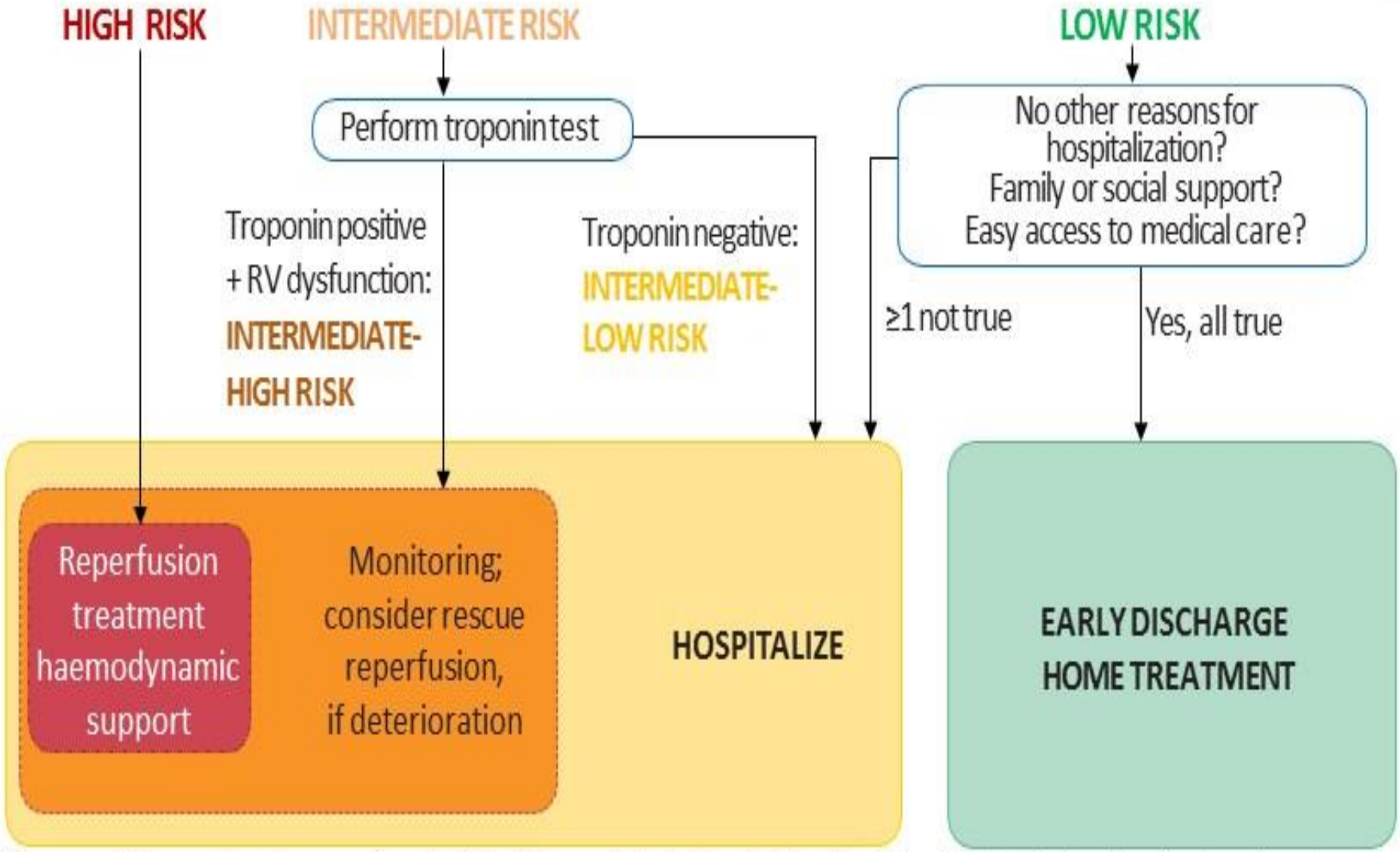

CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

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Table 9 Classification of PE based on early mortality risk

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Early mortality risk		Indicators of risk			
		Haemo-dynamic instability	Clinical parameters of PE severity/ comorbidity: PESI III–V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels
High		+	(+)	+	(+)
Interme-diate	Intermediate–high	-	+	+	+
	Intermediate–low	-	+	One (or none) positive	
Low		-	-	-	Assessment optional; if assessed, negative

CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; TTE = transthoracic echocardiography.

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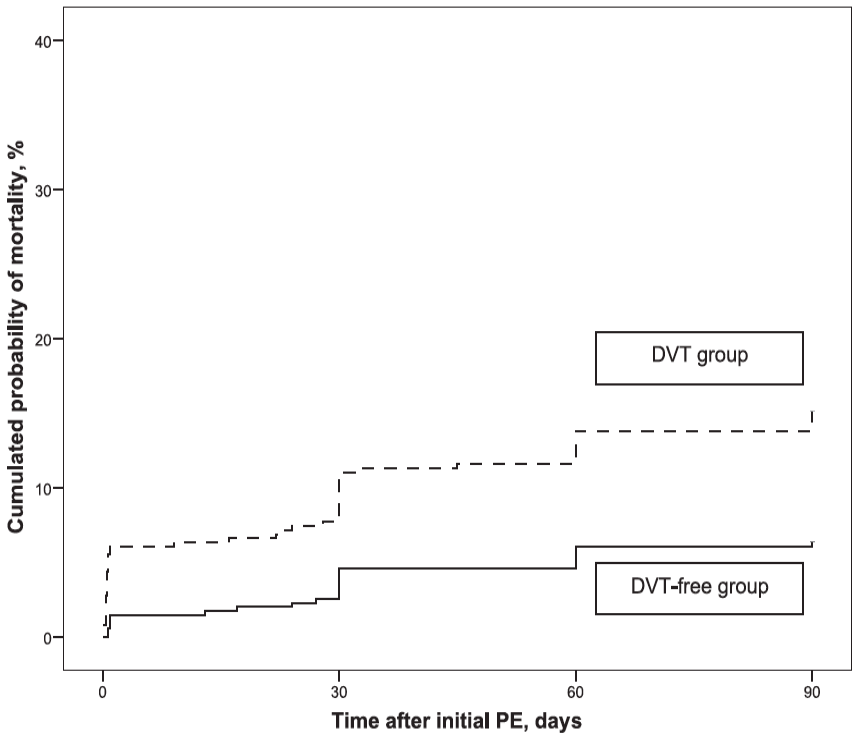
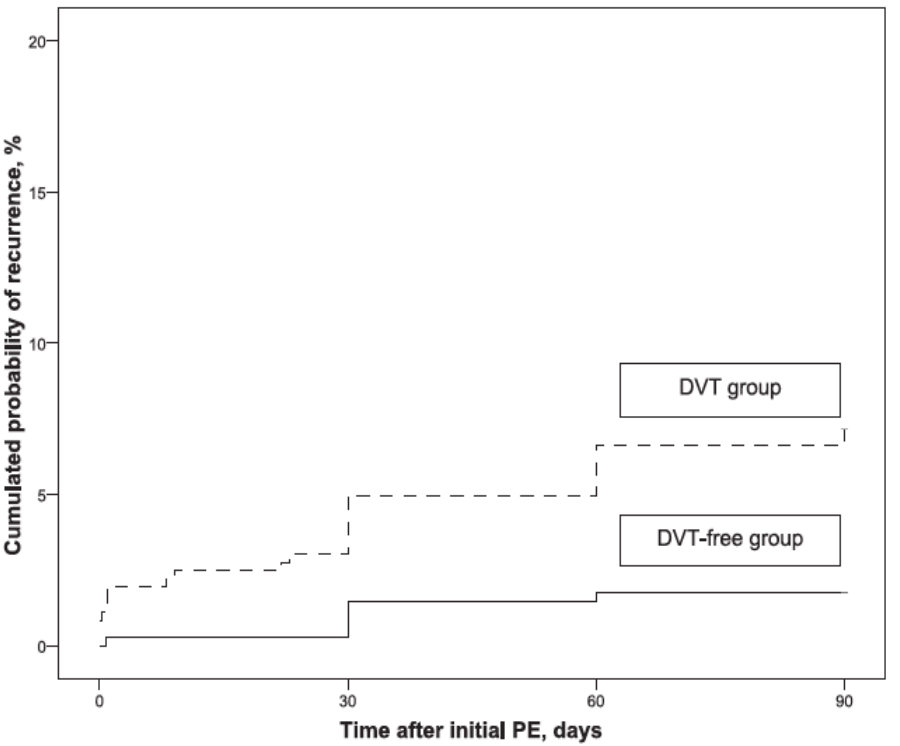
Residual DVT and prognosis in patients with acute PE

Derivation cohort: 707 patients, 51% with DVT at CCUS
Validation cohort (RIETE): 4,476 patients, 63% with DVT

MORTALITY



SYMPTOMATIC PE



Jiménez D, Am J Respir Crit Care Med 2010

Combination of prognostic tools improves prediction of PE mortality

Table 2 Clinical, laboratory and echo parameters predicting 30-day PE-related mortality in normotensive patients (adapted from Jimenez *et al*[11])

	PPV (%)
Trop	10.5
RVD	11.7
DVT	9.6
Trop and RVD	15.2
Trop and DVT	17.1
RVD and DVT	19.6
Trop, RVD and DVT	20.8
High-risk PESI, Trop and RVD	20.7
High-risk PESI, Trop and DVT	24.4
High-risk PESI, RVD and DVT	25.0

DVT, deep venous thrombosis on compression ultrasound; PESI, PE severity index; PPV, positive predictive value; RVD, right ventricular dysfunction on echocardiography; Trop, elevated troponin I.

Jimenez et al. Thorax 2011;66:75-81

Aims of treatment

- Prevent death and morbidity acutely
- Reduce incidence of recurrence
- Prevent long term complications – CTEPH

➢ Mainstay of Rx is Anticoagulation

Role of Thrombolysis in PE ?

- Haemodynamic benefits
  - Much faster clot resolution and improved lung perfusion when compared to heparin alone
  - Reduction in PAP and improved RV function

- BUT no real difference between heparin and thrombolysis at 7 days (60-65% reduction total defect)

- ? Improved clinical outcomes – mortality, PE recurrence
- ? Improved functional outcomes – cardiopulmonary function, less CTEPH, QOL

- **Any Benefit must outweigh Risk of bleeding**

  (major bleeding 6-10%, ICH 1-3%)

When to thrombolyse a PE

- Cardiac arrest due to suspected PE
- High Risk (Massive) PE with Hypotension
- Right heart mobile thrombus
- ??Intermediate Risk (Submassive) PE

ESC Guideline 2019

- Routine use of primary systemic thrombolysis is **not recommended** in patients with intermediate risk PE

- Rescue thrombolytic therapy is recommended in patients with haemodynamic deterioration on anticoagulation treatment

Non-high-risk PE

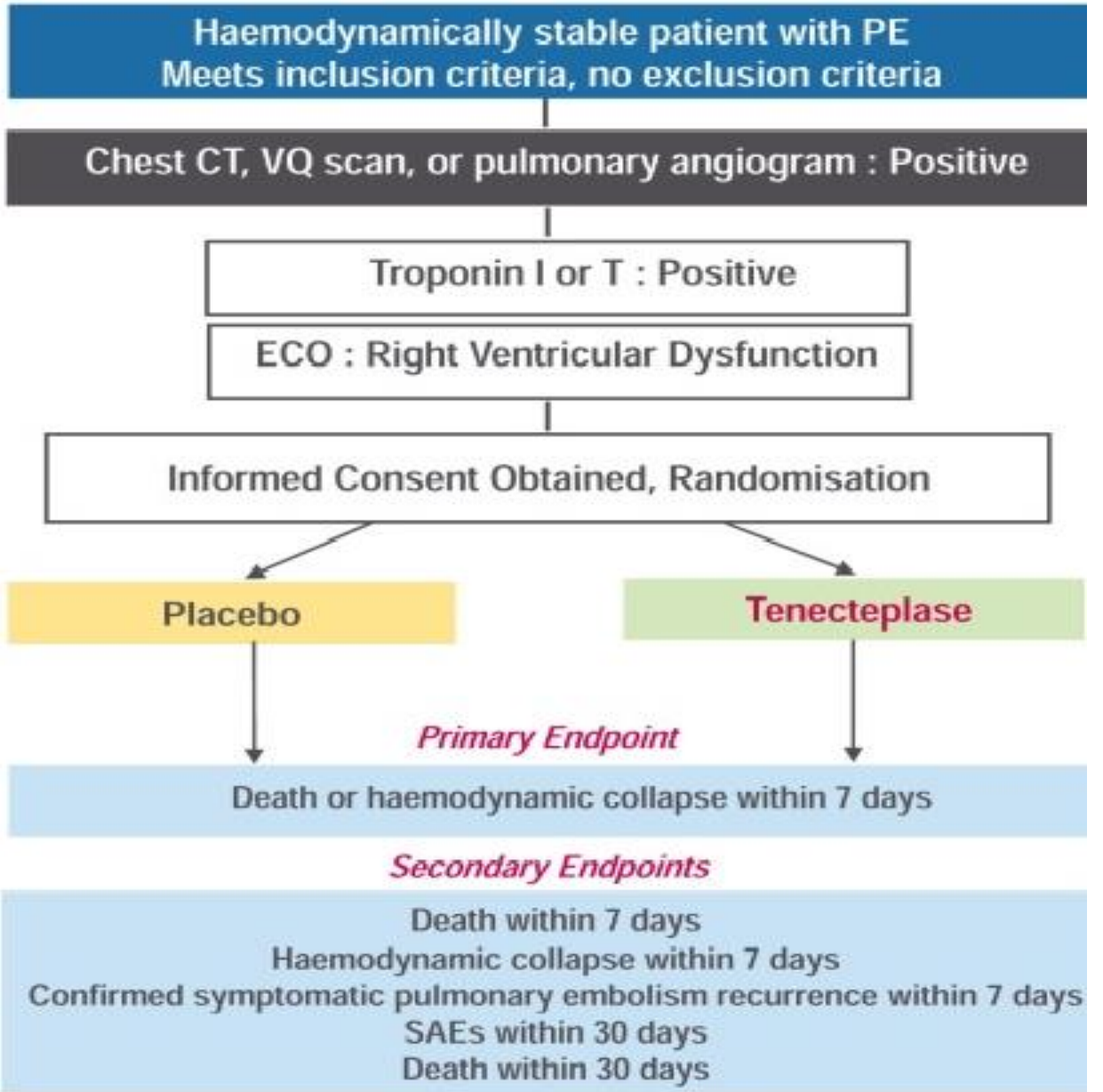
Thrombolysis for Non-High-Risk PE : Metaanalysis

Studies That Excluded Patients With High-Risk-PE

S Wan. Circulation 2004;110:744-749

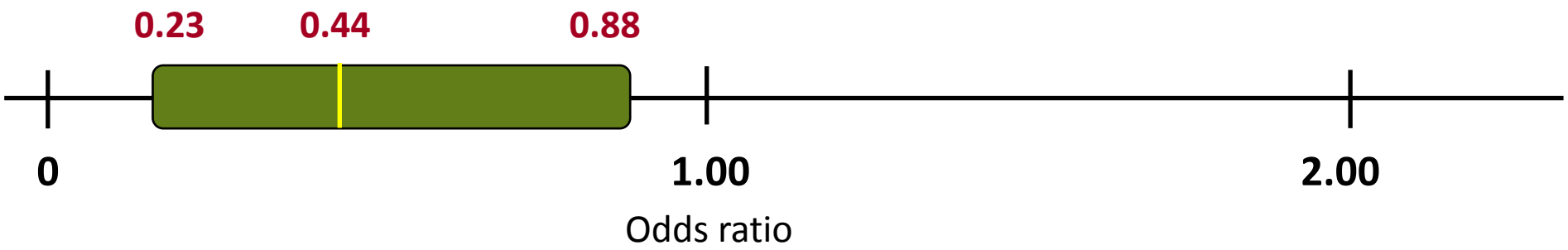
Outcome	Thrombolysis n/N	Heparin n/N	OR (95% CI)
Recurrent PE or Death	**13/246 (5.3%)**	**12/248 (4.8%)**	**1.07 (0.50-2.30)**
Recurrent PE	5/246 (2.0%)	7/248 (2.8%)	0.76 (0.28-2.08)
Death	8/246 (3.3%)	6/248 (2.4%)	1.16 (0.44-3.05)
Major Bleeding	6/246 (2.4%)	8/248 (3.2%)	0.67 (0.24-1.86)

The PEITHO (**P**ulmonary **E**mbol**I**sm **T**Hr**O**mbolysis) Trial 2014



PEITHO: Primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	**13**	**(2.6)**	**28**	**(5.6)**	**0.015**



Thrombolysis superior

ITT population

PEITHO: Secondary efficacy outcomes

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	**6**	**(1.2)**	**9**	**(1.8)**	**0.43**
Hemodynamic collapse within 7 days	**8**	**(1.6)**	**25**	**(5.0)**	**0.002**
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

ITT population

PEITHO: Safety outcomes (within 7 days of randomization)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(32.6)	43	(8.6)	<0.001
Strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischemic	2		0		

PEITHO: Causes of death (within 30 days)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All--cause mortality	**12**	**(2.4)**	**16**	**(3.2)**	**0.42**
From hemodynamic collapse	1		3		
From recurrent PE	1		3		
From respiratory failure	0		3		
From stroke	5		1		
From bleeding	2		0		
Other cause	3		6		

ITT population

Why little evidence for mortality benefit in Intermediate Risk (Submassive) PE

- Low patient numbers, studies underpowered to detect mortality benefit

- **Patients recruited in trials may have less severe disease**
  - wide spectrum of severity submassive PE
  - Trials maybe underrepresentative of true mortality of submassive PE

- In trials mortality for submassive PE <3%, so difficult to detect true mortality benefit even if thrombolysis was effective

- Studies allow for thrombolysis in event of haemodynamic collapse in heparin group

- Any Mortality benefit cancelled out by mortality from haemorrhage complications

- Studies include patients symptomatic for several days (in PEITHO incl upto 15 days).
- Studies overlap thrombolysis and heparin anticoagulation
- Studies involve different thrombolytic drugs and varying dosages

Long term benefits of Thrombolysis?

- PEITHO Long term Outcomes Study :

- Thrombolysis in Intermediate Risk PE **did not** :
  - Reduce mortality at 2 years
  - Reduce functional limitation and chronic dyspnoea (occurred in 1/3 of patients)
  - Reduce frequency of RV dysfunction on ECHO
  - Reduce confirmed cases of CTEPH

Konstantinides et al. J Am Coll Card 2017;69:1536

Improving use of thrombolysis in Intermediate risk (Submassive) PE – increase benefit to risk ratio

- Select patients at higher risk of adverse PE-related outcomes
- Select patients at lower risk of bleeding
- Use safer thrombolytic regimens
  - Lower dose systemic tPA
  - Catheter-directed

Patients at higher risk of adverse outcome ?

- Post hoc analysis PEITHO study

➢ patients with RVD, Elevated Troponin, and at least one of the following :

- SBP < 110
- RR > 20 or SaO2 < 90%
- Hx of heart failure

➢ Risk of adverse outcome 11% in heparin only group compared to 3.7% in thrombolysis group

Barco et al ERJ 2018, 51: 1701

Combination of prognostic tools improves prediction of PE mortality

Table 2 Clinical, laboratory and echo parameters predicting 30-day PE-related mortality in normotensive patients (adapted from Jimenez *et al*[11])

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Trop, RVD and DVT	20.8
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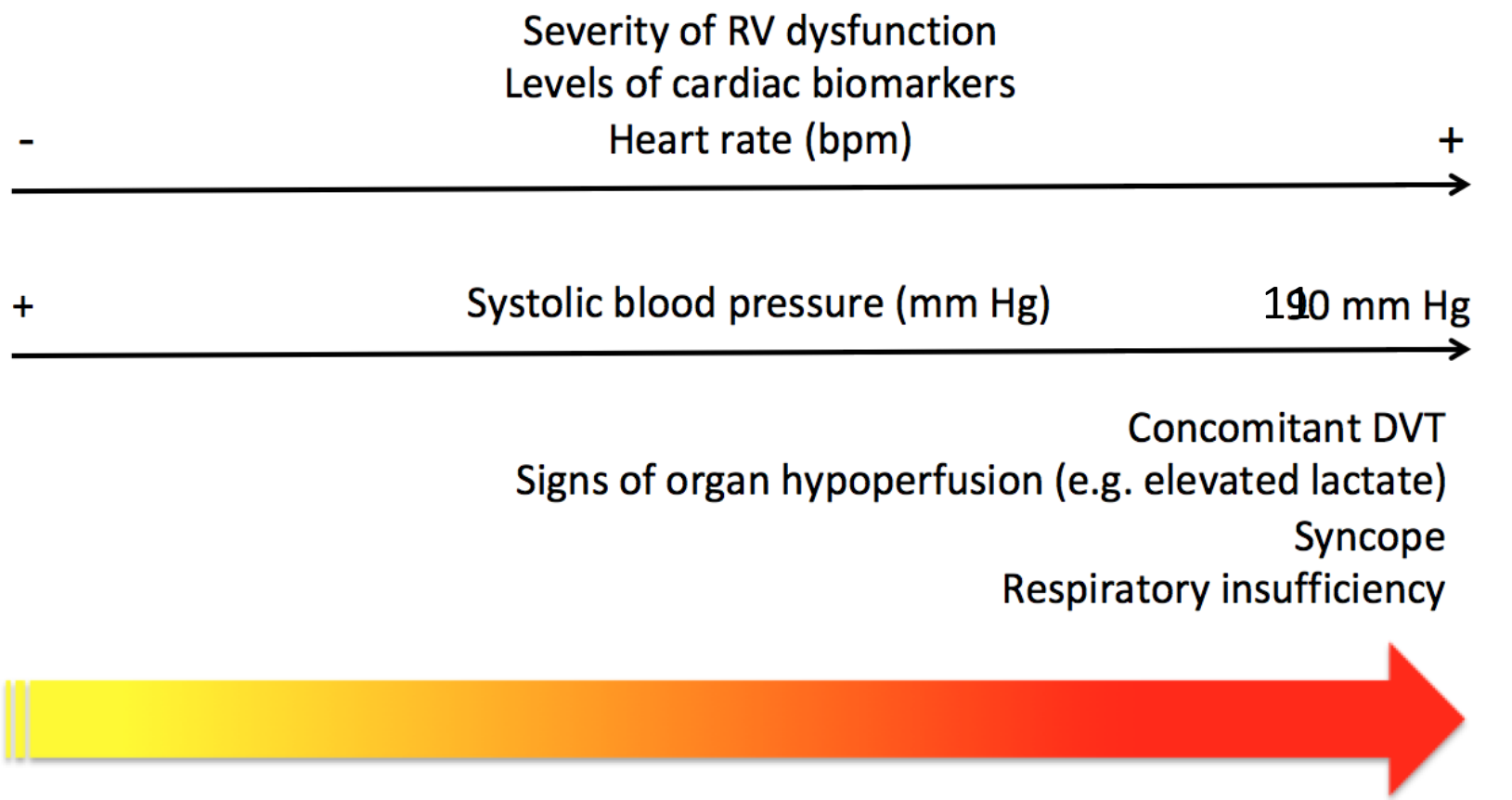
Jimenez et al. Thorax 2011;66:75-81

Identification of intermediate-high risk PE



Risk Stratify Intermediate Risk (Submassive) PE

- History of Syncope ?
- Duration of symptoms
- CTPA – Assess Clot burden and Dilated RV
- Bedside Echo – severity of RV Dysfunction
- Is there a clot in RA/RV ?
- Lactate
- Troponin
- Bedside US to assess for Proximal DVT

- Does the patient look ill ?
  - Diaphoresis, Pallor, Resp distress, Sense of impending doom, signs of hypoperfusion

- Vital Signs and trend
  - Tachycardia
  - BP
  - Shock Index >1 (Pulse/SBP)
  - RR
  - O2 Sats on air and Oxygen requirements

- What is the patients age and overall bleeding risk

Meta-analysis:Thrombolysis for Pulmonary Embolism and Risk of All-cause Mortality, Major bleeding, and Intracranial Haemorrhage - 16 trials, 2115 patients

Chatterjee et al JAMA 2014; 311:2414

Table 2. Absolute Risk Metrics of Outcomes of Major Interest

Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (0.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age >65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Major bleeding (5)[a]	87/673 (12.93)	27/658 (4.10)	NNH = 11	<.001
Age ≤65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT = 51	.09
Major bleeding (11)[a]	11/388 (2.84)	9/396 (2.27)	NNH = 176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Patients ≤ 65 years who are thrombolysed have similar major bleeding rates to those treated with anticoagulants

Chaterjee S*et al*, *JAMA* 2014;311:2414–2421

Reduced dose thrombolysis ?

Rationale for efficacy :

- Pulmonary blood flow = entire CO
- Almost all tPA molecules converge in lungs
- Thromboembolus in pulmonary arterial circulation exquisitely sensitive to lysis
- Different than in thromboembolic CVA and acute MI
- Brain receives 15% of CO; Heart 5%.
- Hence same dose needed for clinical effect should not necessarily apply
- In IHR PE only need to reduce Pulm Pressure & RV Afterload enough to prevent haemodynamic collapse

Reduced dose thrombolysis trials

Sharifi et al. Moderate pulmonary embolism treated with thrombolysis (MOPETT trial)

Am J Cardiol 2013;111(2):273-7

- 112 patients with 'moderate' PE : >70% obstruction on CT
- ½ dose tPA 50 mg, 0.5 mg/kg if < 50 kg

➢ **Reduction in pulmonary hypertension at 48 hours and up to 2 years (16% vs 57%)**

➢ No survival benefit, but underpowered to detect mortality difference

➢ <u>No bleeding events</u>

Wang et al. Efficacy and Safety of Low Dose Tissue Type Plasminogen Activator for the Treatment of Acute Pulmonary Embolism : A Randomised Multicenter Controlled Trial.

Chest 2010;137:254-62

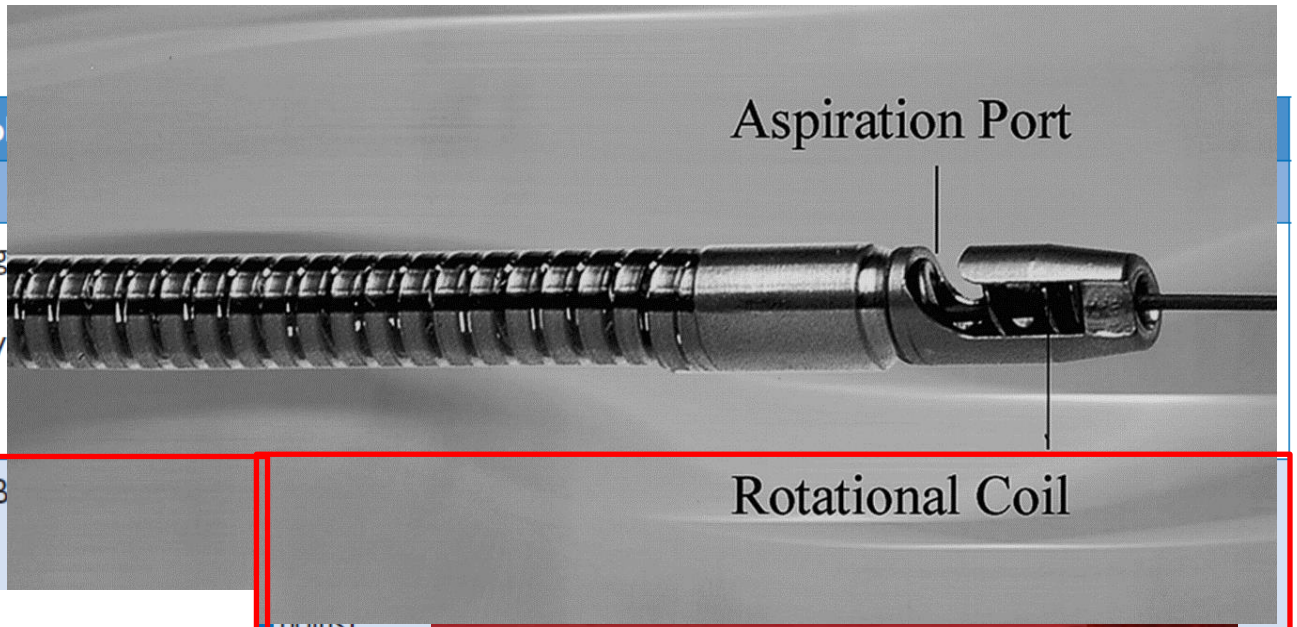
- 118 patients with acute PE
  - Cardiogenic shock (31%) or massive PA obstruction with RVD on CT (69%)
- rtPA 100mg / 2h vs rtPA 50 mg / 2h

- Similar Efficacy
  - Improvement at day 1 and day 14 in :
  - RV:LV Ratio
  - Pulmonary vascular obstruction on V/Q lung scan or CT

- less bleeding complications with low dose regime (major bleeding 3% Vs 10%)

Mechanical Disruption by Catheter / Local Thrombolysis

Catheter interventions without local thrombo	
Technique	**Device examples**
Thrombus fragmentation	Pigtail catheter frag Balloon angioplasty balloon catheters
Rheolytic thrombectomy	AngioJet 6 F PE® (B
	Pharmacom
Combined techniques	Pigtail fragmentation (5F) plus AngioJet 6 F PE® Power Pulse™ thrombolysis and thrombectomy (Bayer, Germany)



ESC Guidelines 2014

Ultrasound-assisted catheter-directed thrombolysis - EKOS

- Ultrasound aids thrombolysis by increasing thrombus permeability & penetration of thrombolytic agent
- One catheter in each lower lobe PA (through 6F femoral sheaths)
- rtPA infused bilaterally at 1mg/hr for 5hrs then 0.5mg/hr for 15 hours; maximal dose 20mg

e

EKOS
EkoSonic®

Kucher Circulation 2014

Ultrasound-assisted catheter-directed thrombolysis

Study	**ULTIMA** Kucher N et al., Circulation 2014; 129:479-486	**SEATTLE II** Piazza G et al., JACC Cardiovasc Interv 2015; 8:1382-1392	**OPTALYSE PE** Tapson VF et al., JACC Cardiovasc Interv 2018; 11:1401-10
Study design	prospective, multicentre, randomized	prospective, multicentre, single-arm	prospective, multicentre, randomized
Intervention	10-20 mg rtPA over 15h (n=30) vs. UFH (n=29)	24 mg rtPA over 12h	Arm 1: 8 mg rtPA over 2h (n=22 Arm 2: 8 mg rtPA over 4 h (n=21) Arm 3: 12 mg rtPA over 6h (n=24) Arm 4: 24 mg rtPA over 6h (n=16, terminated early)
Patients	59 normotensive patients with RV/LV ≥1.0	31 „massive“ 119 „submassive“	101 normotensive patients with RV/LV ratio ≥0.9 (no biomarkers)
Efficacy endpoint	Reduction of RV/LV ratio after 24h (1.28 vs. 0.99; p<0.001)	Reduction of RV/LV ratio after 24h (1.55 vs. 1.13; p<0.001)	Reduction of RV/LV ratio after 48h (mPPP*: reduction by ~25% in all arms)
Safety endpoint	Major bleeding: 0%	Major bleeding: 0.7% moderate bleeding: 10%	Major bleeding: 4.0% ICH: 2.0%

Future Studies

- PEITHO 3 TRIAL
- Comparing reduced dose thrombolysis to Heparin in Intermediate High Risk PE (RVD and Trop +ve)

  with
- ≥ 1 criterion of severity (SBP <110, RR >20, SaO2 <90%, CCF)

- Catheter directed thrombolysis RCT

Who to consider for pre-emptive thrombolysis in Intermediate Risk PE ?

- NOT FOR ALL
- ONLY VERY HIGHLY SELECTED CASES AT HIGH RISK OF ADVERSE OUTCOME + LOW BLEEDING RISK

- RV Strain on CT and/or ECHO
- Troponin +ve

  AND

- Look ill/distressed :
  - Tachycardic ≥ 110/min
  - Shock Index (Pulse/SBP) >1
  - High or rising Lactate
  - ↑RR, ↑O2 requirements
- Concurrent proximal DVT

- **Age < 65 years**
- **No other bleeding RFs**

Mx of Intermediate High Risk (Submassive) PE

- Anticoagulation for most – LMWH Clexane 1 mg/kg BD
- IV Heparin if thrombolysis could be considered – 80 U/kg stat, then infusion
- Admit to HDU for 48-72 hours
- Consider pre-emptive thrombolysis in highly selected cases – Use ½ dose
- For thrombolysis if haemodynamic decompensation (SBP < 90mmHg). Use full dose if low bleeding risk

Thrombolysis and Anticoagulation choice - Balancing Risk Vs Benefit

	No Lytic Contraindication	Relative Lytic Contraindication	Absolute Lytic Contraindication
High Risk PE	100 mg tPA over 2 hours Then IV Heparin	50 mg tPA over 2 hours Then IV Heparin	IR Catheter Mechanical Thrombectomy Or Surgical Embolectomy
Intermediate High-Risk PE	Anticoagulate – IV Heparin -> LMWH 50 mg tPA over 2 hours (in selected patients)	Anticoagulate – IV Heparin -> LMWH ?CDT if available	Anticoagulate – IV Heparin-> LMWH
Intermediate Low-Risk PE	LMWH -> NOAC	LMWH -> NOAC	LMWH -> NOAC
Low Risk PE	NOAC	NOAC	NOAC

Thrombolysis dose - tPA

- 50 mg bolus in cardiac arrest or if arrest imminent

- Infusion :

➢ **10 mg IV bolus** over 1-2 mins, Then **90 mg over 2 hours**

N.B. If <65 kg, then max total dose1.5mg/kg, bolus dose same)

➢ Reduced ½ dose

- 10 mg bolus, then 40 mg over 2 hours
- If weight < 50kg - Total 0.5 mg/kg

- Stop IV Heparin infusion during thrombolysis. Check APTT 2 hours after thrombolysis completed. Restart when APTT ratio <2.
- If LMWH given before thrombolysis, delay Heparin infusion for 18 hours after LMWH dose
- If good response to thrombolysis, switch to LMWH after 24-48 hours

“Contraindications” to thrombolysis

Absolute contraindications[a]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury (within preceding 3 weeks)
- Gastrointestinal bleeding within the last month
- Known bleeding

Relative contraindications

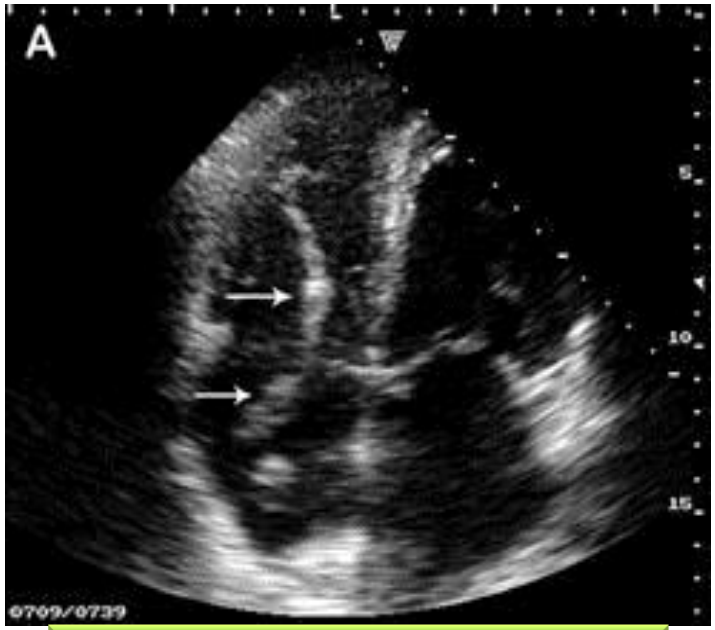
- Transient ischaemic attack in preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1 week post partum
- Non-compressible punctures
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

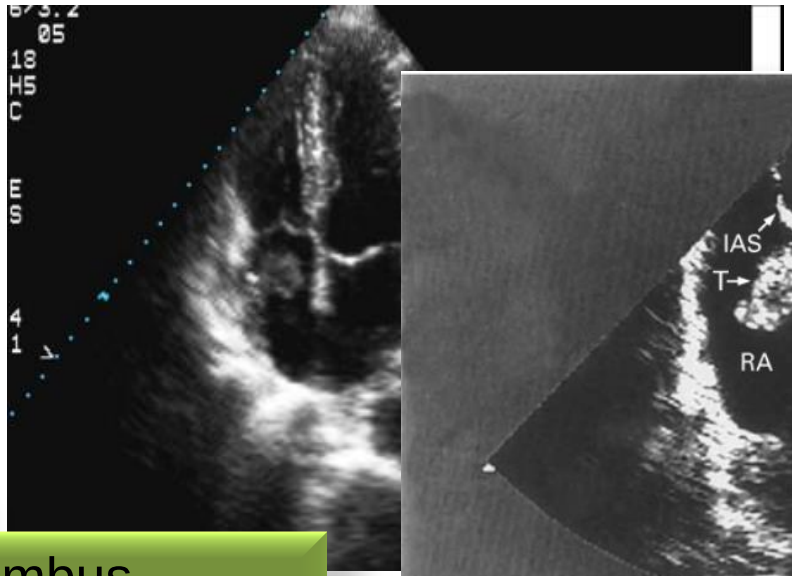
Contraindications to thrombolysis that are considered absolute in MI may become relative in a patient with immediately life threatening PE

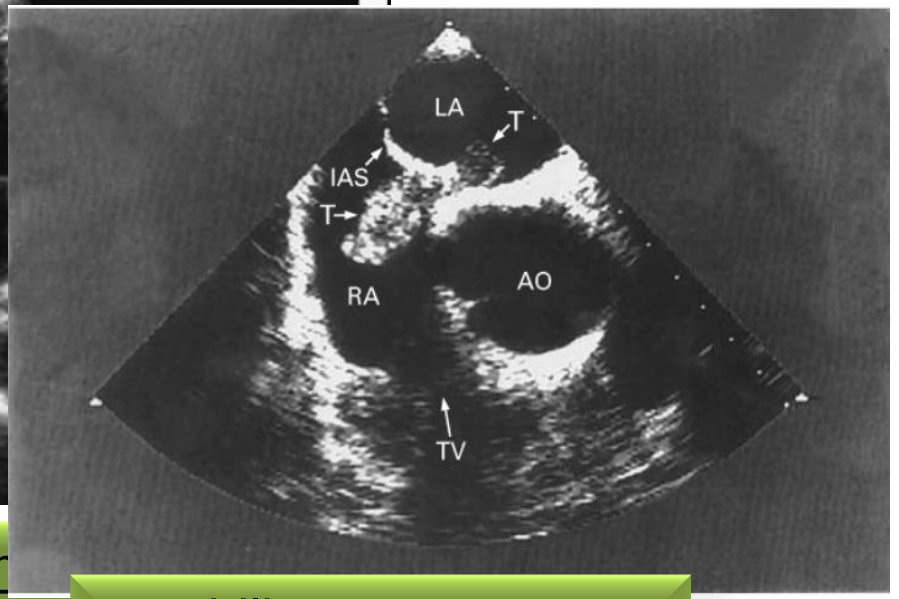
What if thrombolysis contraindicated or fails ?

- Surgical Embolectomy
- Mechanical thrombectomy by catheter
- Catheter directed local low dose thrombolysis
- Supportive on ITU (Inotropes, ECMO)

RA Clot







Type A thrombus

Serpiginous, as
with PE

Thrombolysis
Surgical embol

Type B thrombus

Immobile, no as
PE

Anticoagulate

Type C thron

Mobile, mass-li

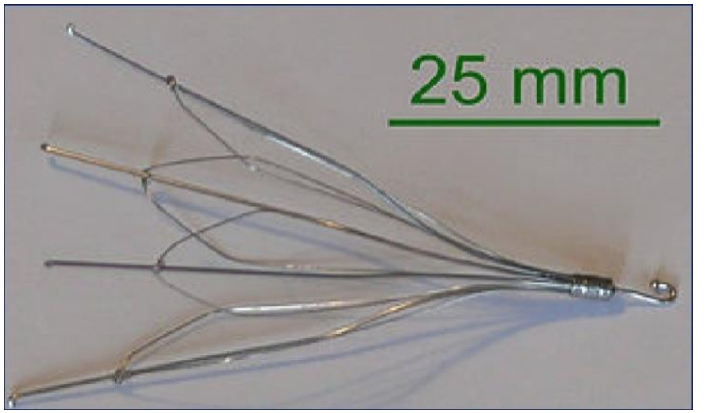
Surgical embol

Straddling PFO

High risk of systemic embolisation

Surgical embolectomy

Acute PE and IVC Filters



- Only indicated if anticoagulation contraindicated. Use retrievable filters
- If temporary cessation (preop) of anticoagulation within 1 month of PE
- Recurrent acute PE despite therapeutic anticoagulation (target INR 3.5 or high dose LMWH)

- Recent RCT of PE and DVT – no effect on recurrent PE, complications, or mortality

Anticoagulation ESC recommendations

- NOACs are recommended as first choice over VKAs for anticoagulation
- Warfarin if Antiphospholipid syndrome or prosthetic valve, or other CIs to NOACs
- NOACs not recommended in severe renal impairment, APS, pregnancy or lactation
- PE in Cancer - Edoxaban or Rivaroxaban should be considered as an alternative to LMWH, with the exception of gastrointestinal cancers (due to increased bleeding risk with NOACs)

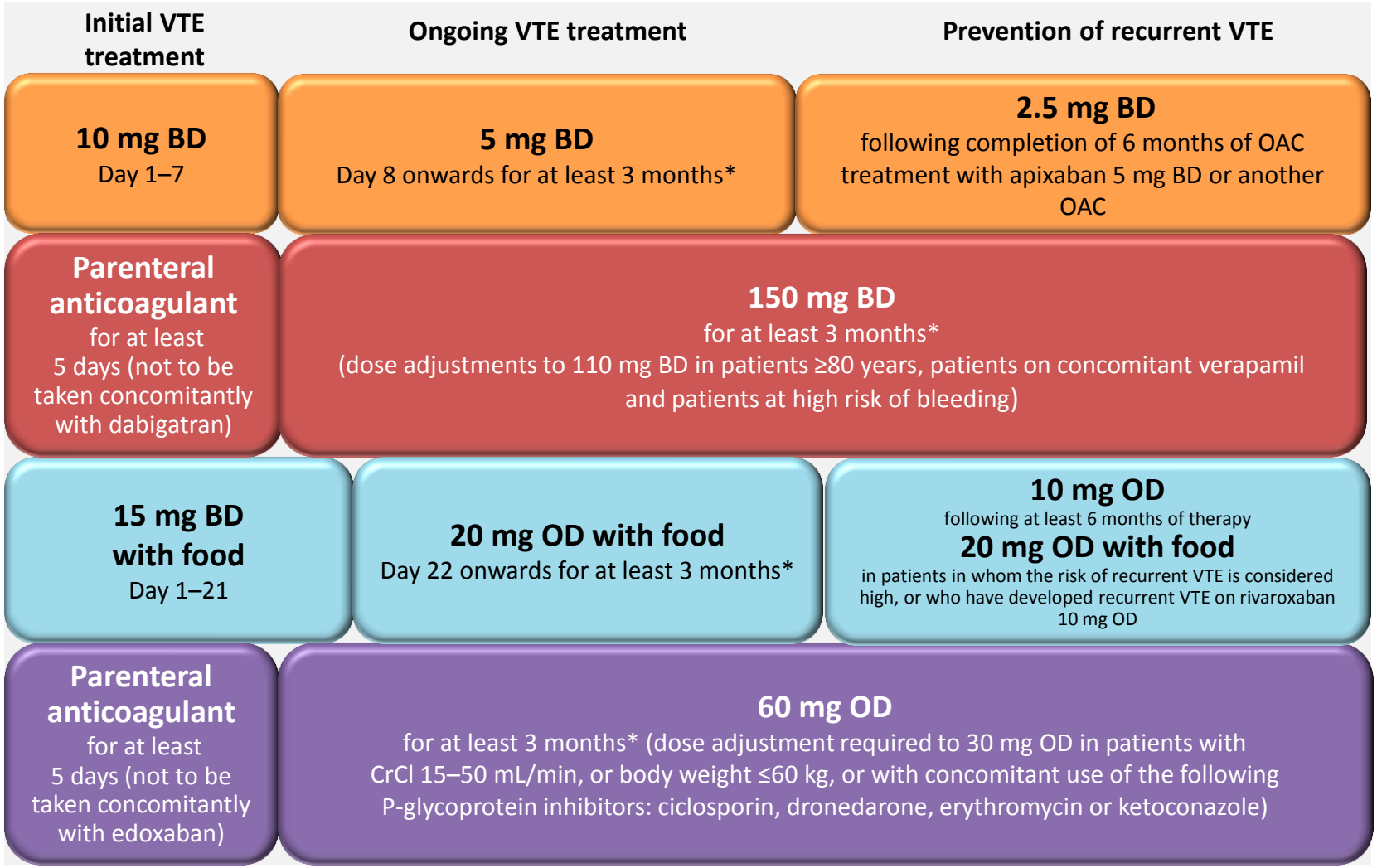
Table 2 Main new recommendations 2019 (4)

ESC
European Society of Cardiology

Chronic treatment and prevention of recurrence in patients without cancer	
Indefinite treatment with a VKA is recommended in patients with the 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 in patients with a persistent risk factor other than the antiphospholipid antibody syndrome.	IIa
Extended anticoagulation should be considered for patients with a minor transient/reversible risk factor for the index PE event.	IIa
Reduced dose of apixaban or rivaroxaban should be considered after the first 6 months.	IIa

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

DOAC dosing regimens across each stage of VTE treatment



Please refer to the individual DOAC SmPCs for full dosing recommendations

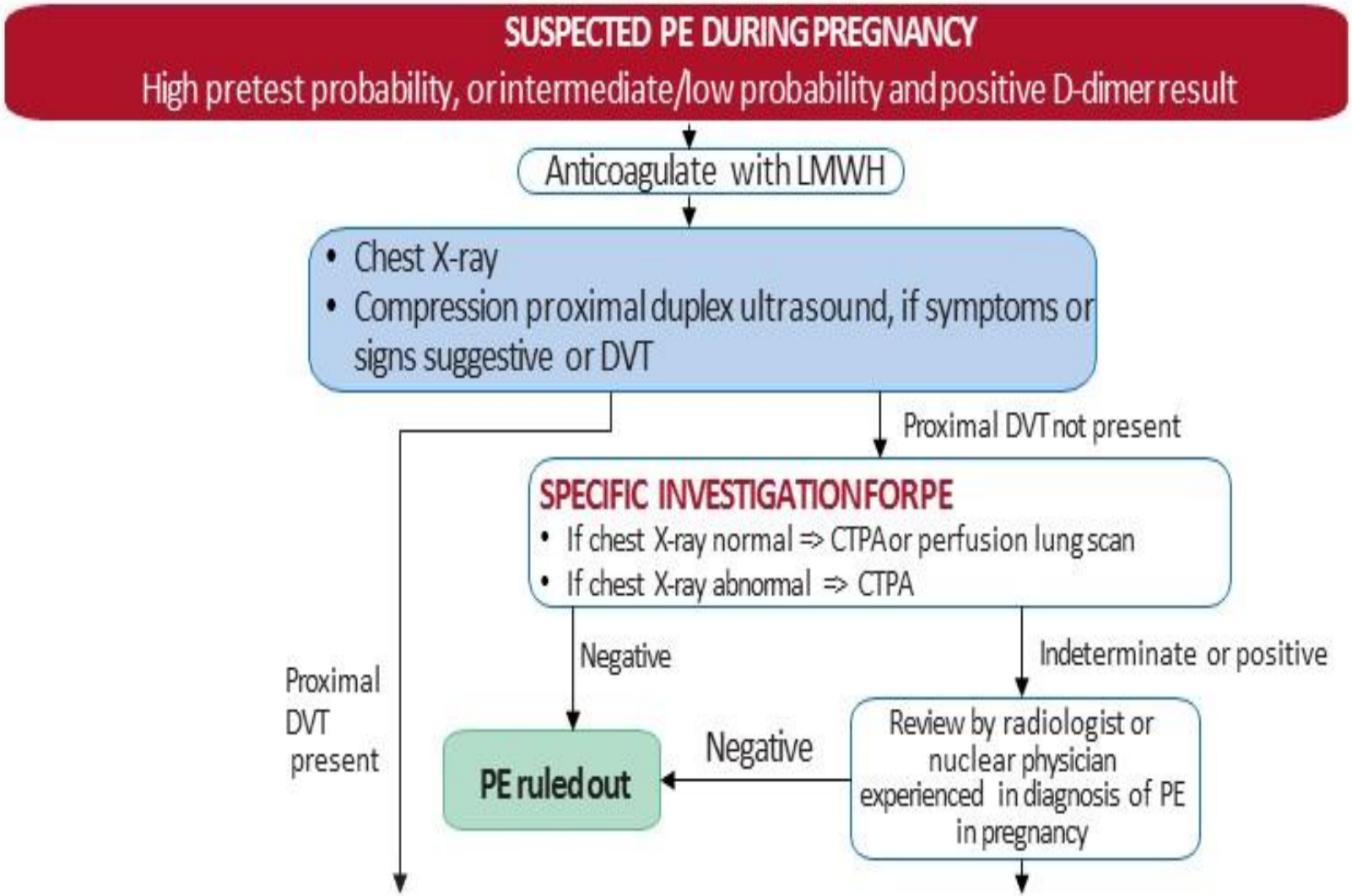
The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.
Short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).* ***Apixaban**: Use with caution in severe renal impairment (CrCl 15–29 mL/min). Not recommended in CrCl <15 mL/min or in patients undergoing dialysis.* ***Dabigatran****: Contraindicated in CrCl <30 mL/min.* ***Rivaroxaban:*** *Consider reduction from 20 mg OD to 15 mg OD (after the initial 15 mg BD for 3 weeks) in patients with moderate (CrCl 30–49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment if patient's assessed bleeding risk outweighs risk for recurrent DVT and PE. When the recommended dose is 10 mg OD, no dose adjustment is necessary. Use with caution in severe renal impairment. Not recommended in CrCl <15 mL/min.* ***Edoxaban:*** *In patients with moderate or severe renal impairment (CrCl 15–50 ml/min), the recommended dose is 30 mg OD. Not recommended in CrCl <15 ml/min or in patients undergoing dialysis.*

PP-ELI-GBR-5232
Date of preparation: August 2019

1. Apixaban SmPC. Available at: www.medicines.org.uk; 2. Dabigatran SmPC. Available at: www.medicines.org.uk;
3. Rivaroxaban SmPC. Available at: www.medicines.org.uk; 4. Edoxaban SmPC. Available at: www.medicines.org.uk.

Figure 6 Diagnostic work-up for suspected PE during pregnancy and up to 6 weeks postpartum (1)

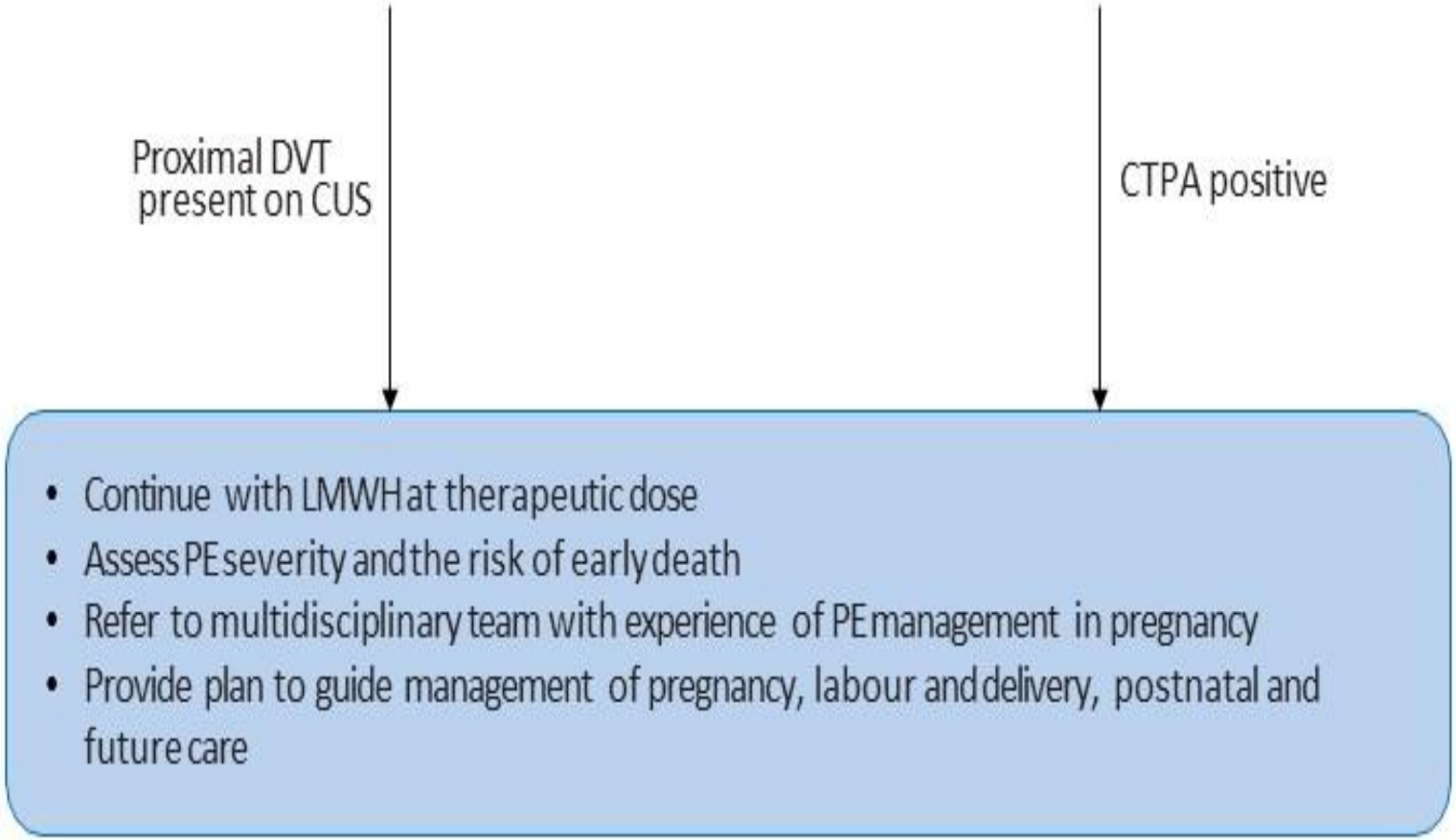
ESC European Society of Cardiology



2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

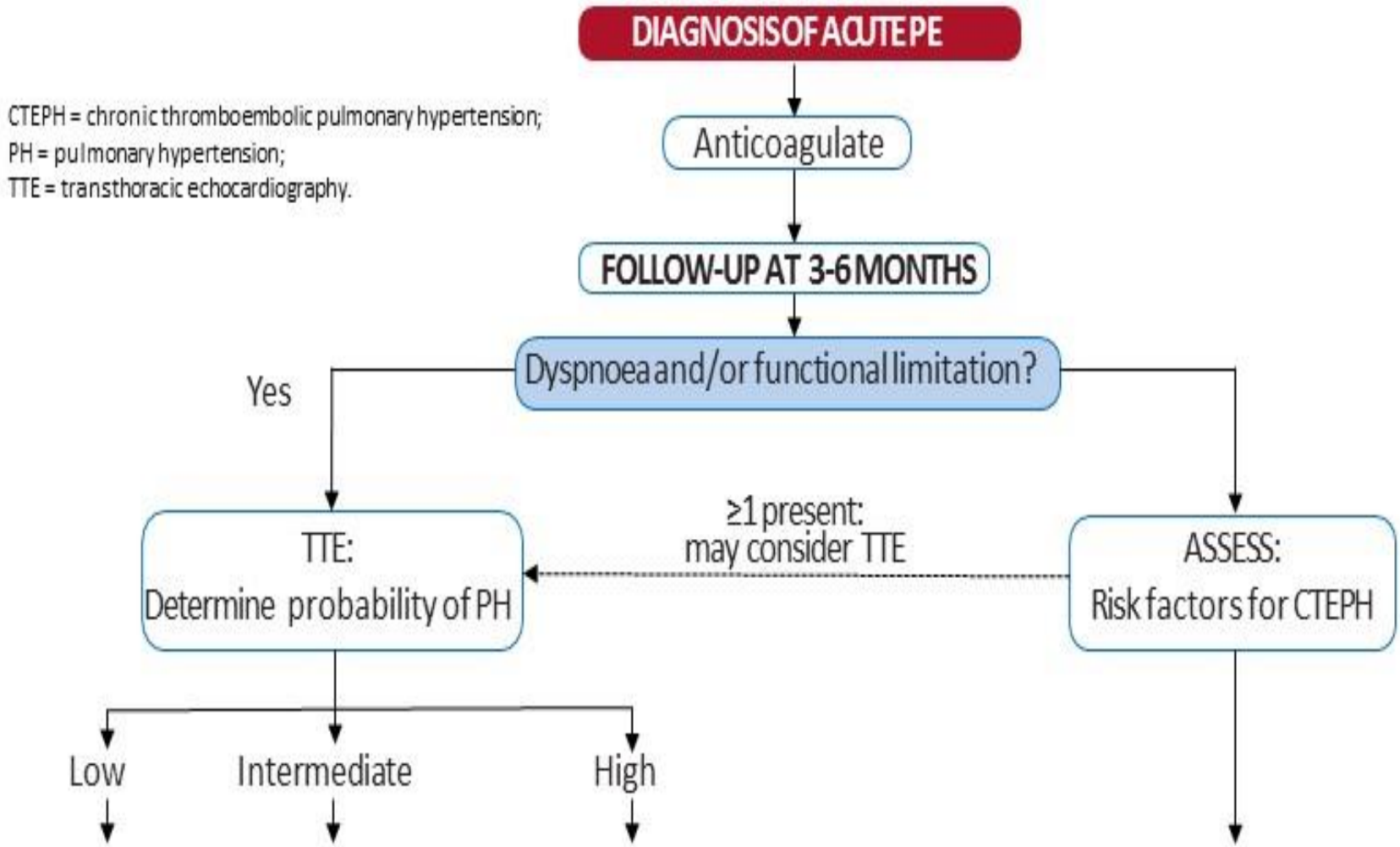
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Figure 6 Diagnostic work-up for suspected PE during pregnancy and up to 6 weeks postpartum (2)



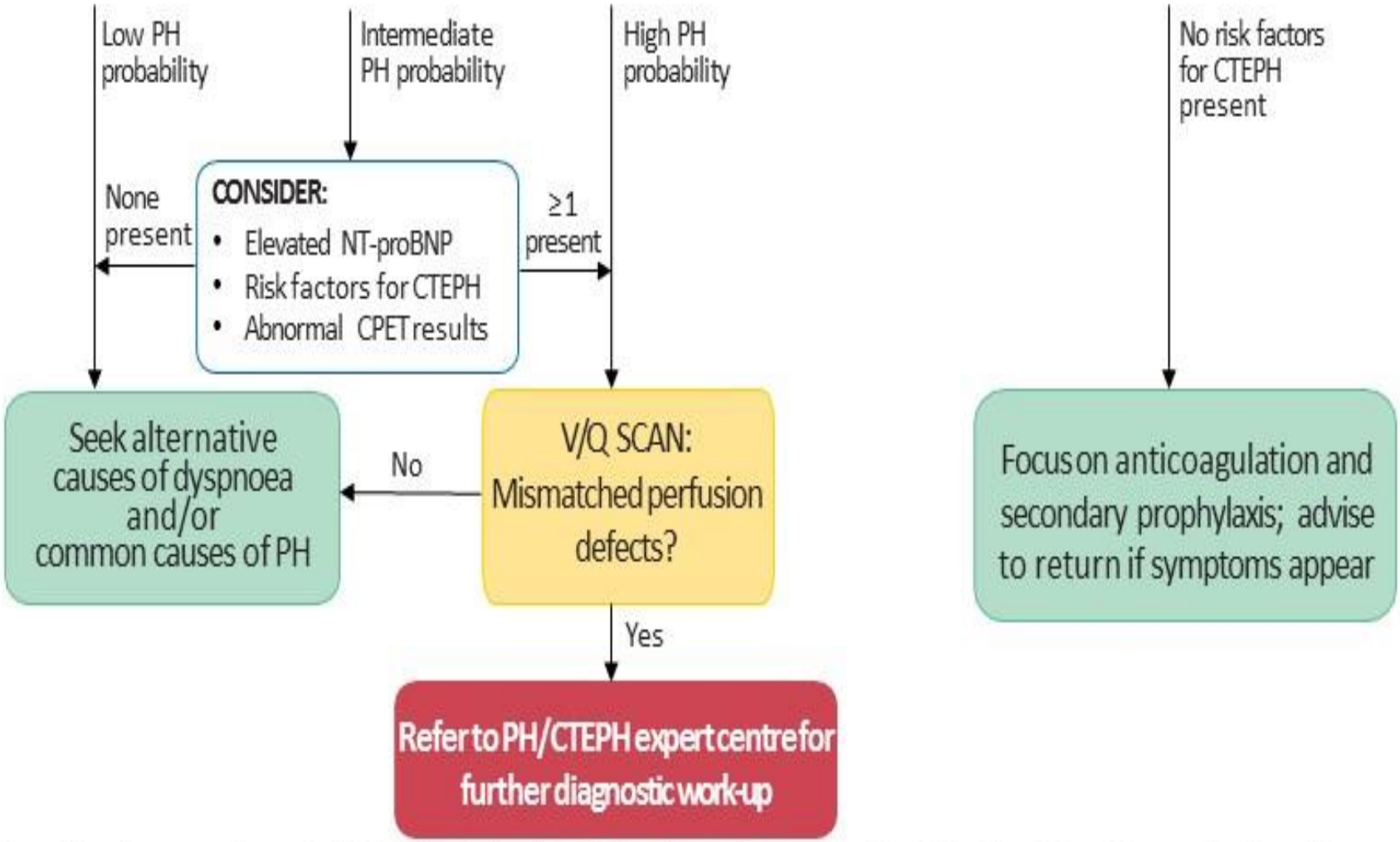
CTPA = computed tomography pulmonary angiography; CUS = compression venous ultrasound; DVT = deep vein thrombosis; LMWH = low molecular weight heparin.

Figure 7 Follow-up strategy and diagnostic work-up for long-term sequelae of PE (1)



2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Figure 7 Follow-up strategy and diagnostic work-up for long-term sequelae of PE (2)



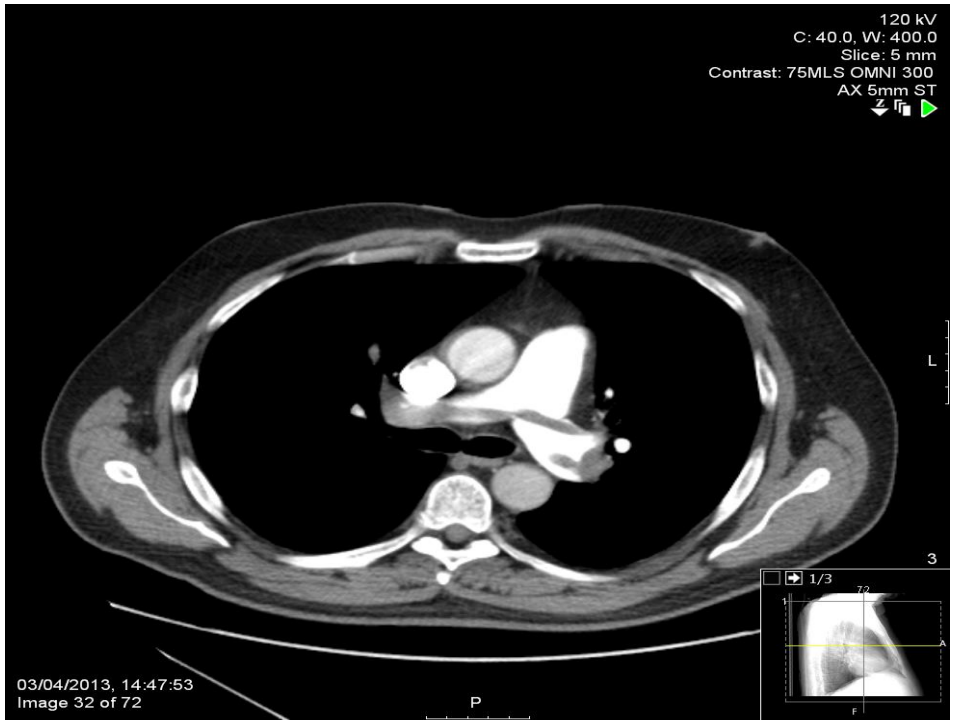
CPET = cardiopulmonary exercise testing; CTEPH = chronic thromboembolic pulmonary hypertension; NT-proBNP = N-terminal pro B-type natriuretic peptide; PH = pulmonary hypertension; V/Q = ventilation/perfusion.

Case 1

- 53 year old man. Previously fit and well.
- SOB for 1 week, acutely worse since am
- Some left leg pain
- No RFs for VTE

- O/E :
  - Unwell, pale
  - RR 30 /min
  - Sats 90-94% (15 L/min)
  - Pulse 120 /min
  - **BP 115/80**

  - ECG – RAD, t inv V1- V4
  - CXR NAD
  - Troponin +ve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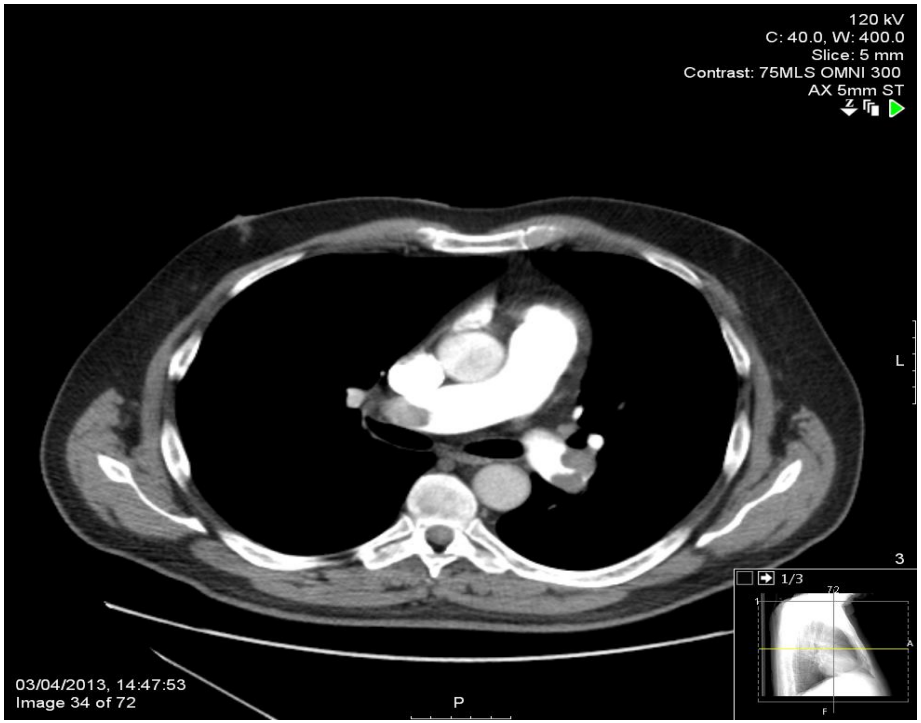
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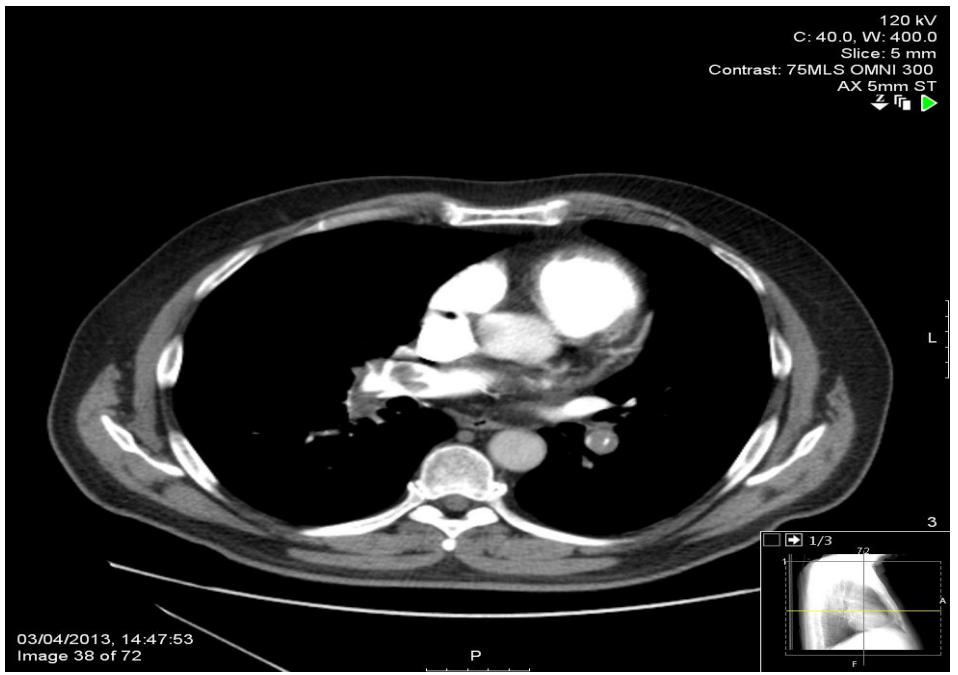
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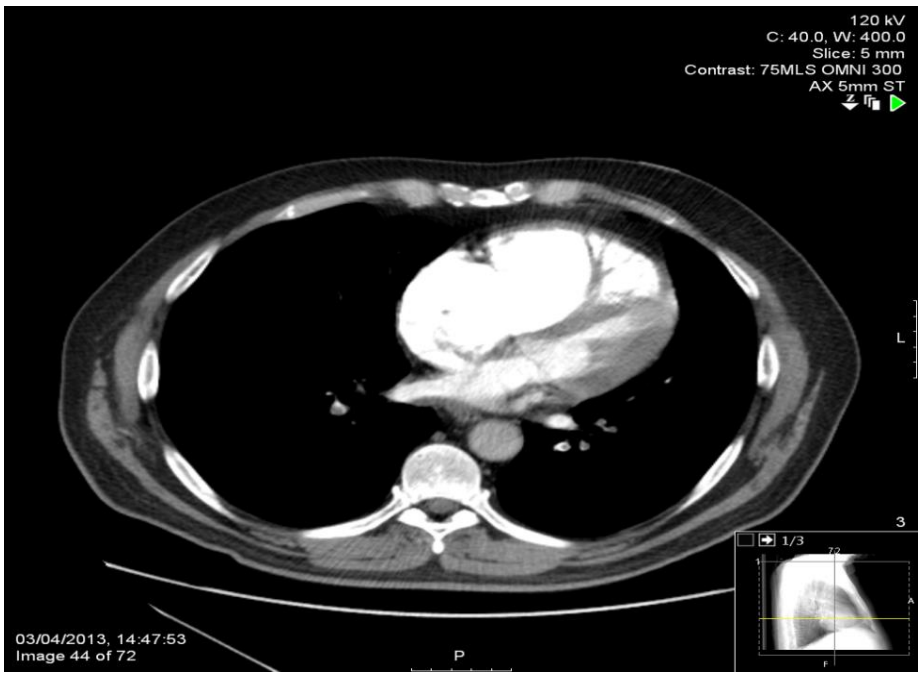
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Case 1 contd…

- ECHO in resus – Dilated RV with reduced systolic function

- Diagnosis – Intermediate High Risk (Submassive) PE
- N.B. BP remains stable around 110-120 systolic

- LMWH only ?
- IV Heparin infusion ?
- Thrombolyse ?
- Insertion of IVC Filter
- Transfer to cardiothoracic centre ?

Case 1 contd...

- IV Heparin bolus given
- Decision to Thrombolyse – tPA 100 mg over 2 hours
- Patient and wife consented re risks
- Followed by IV Heparin infusion

- Within 2 hours of tPA infusion :
  - Better colour
  - RR 16/min
  - Sats 96% (2 L/min)
  - Pulse 90 /min
  - BP 120 /80

- Discharged after 7 days. F/U 6 months – Normal Echo

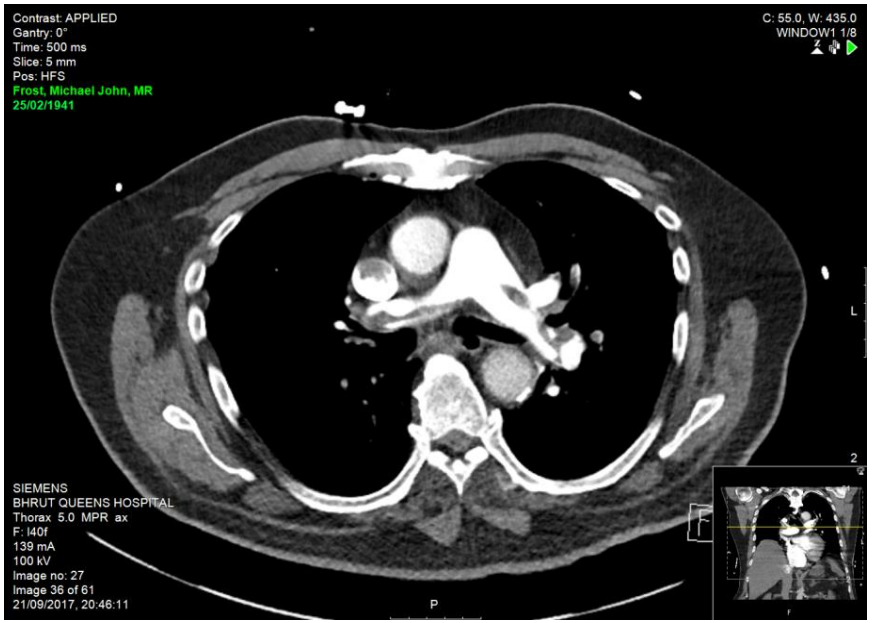
Why thrombolysis ?

- Looked unwell, pale, clammy
- Significant Resp distress and Hypoxia
- Tachycardic
- Trop +ve
- ECHO – significant RVD
- PESI Score Class 4 (Mortality 4-12%)
- Low Bleeding risk

Case 2

- 76 year old male. No PMH. Ex smoker
- SOB for 3 days
- No RFs for VTE
- O/E :
  - RR 22/min
  - Sats 94% 4 L/min
  - Pulse 120
  - BP 101/65 on admission
- ABG – pH 7.39, pCO2 3.8, pO2 9.2, BE-6.7, **Lac 5.45**

- Trop 645
- ECG – Sinus Tachy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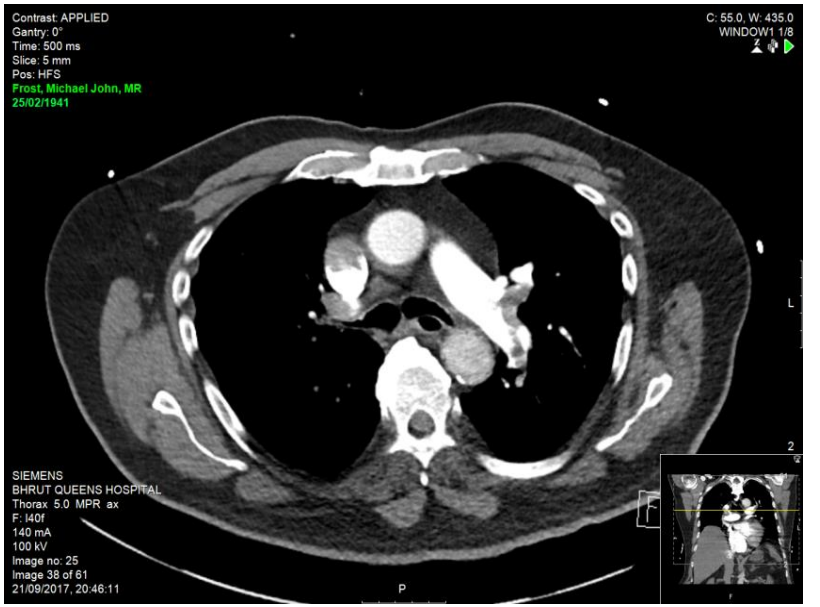
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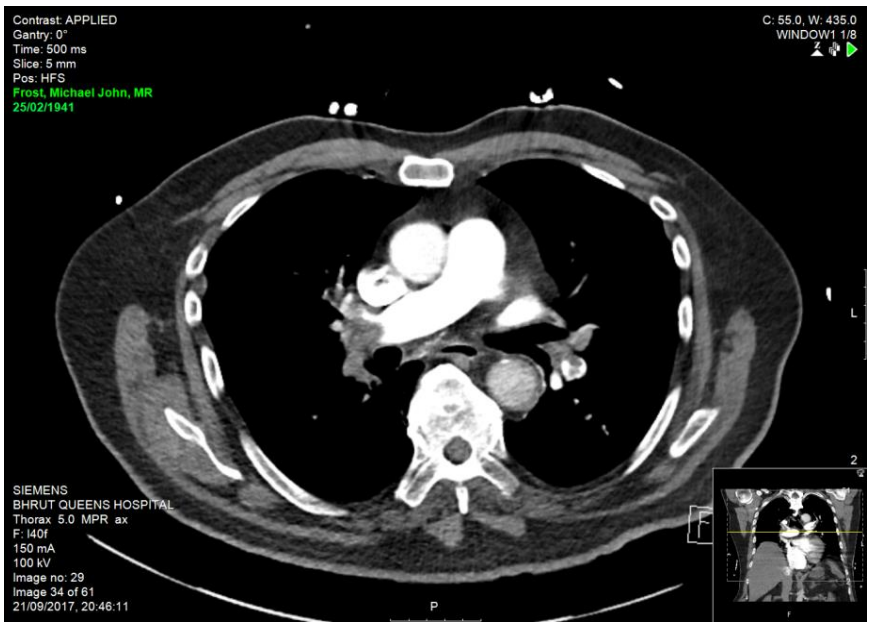
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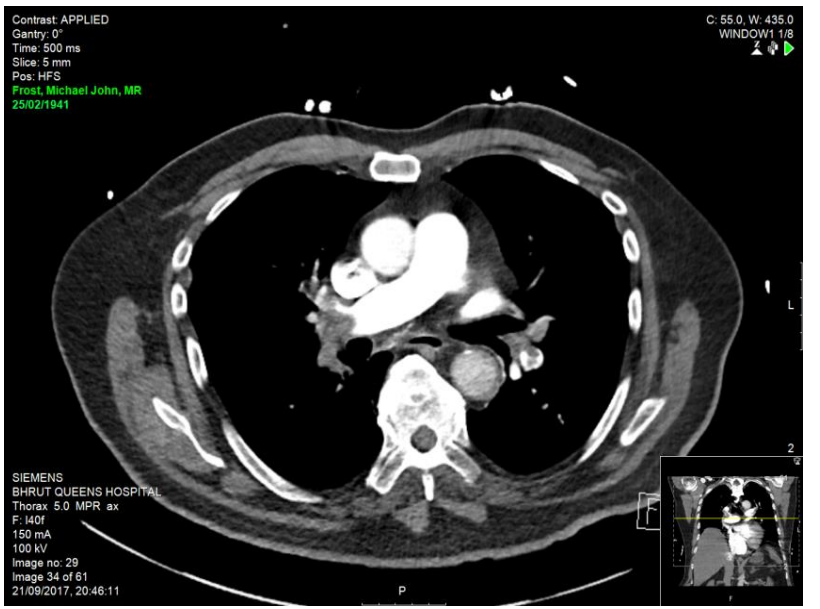
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- T/F HDU for observation. Rx LMWH

- Resp RV next day
- BP Stable 100/70
- Remained tachycardic, hypoxic

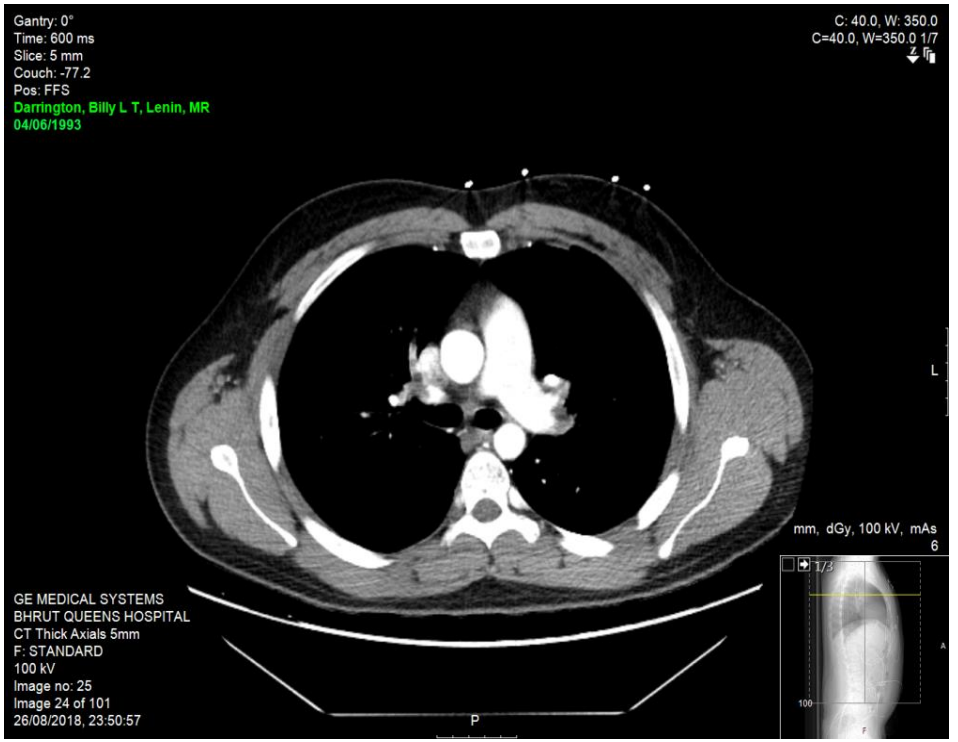
- Decision for Thrombolysis – full dose 100mg tPA

- Post thrombolysis – Sats 98% air. BP 180/100. Started labetalol infusion
- Day 4 – Sats 98% air. BP 130/70 (on 2 antihypertensives)

Case 3

- 25 year old. No PMH or VTE RFs
- Sudden onset central chest pain, sweaty, syncope with LOC for 2 mins

- In ED O/E:
  - Pulse 128/min
  - BP 115/80
  - Sats 90% on air,
  - RR 24/min
  - ↑Troponin 307
  - ECG - T inv V2-V4, RBBB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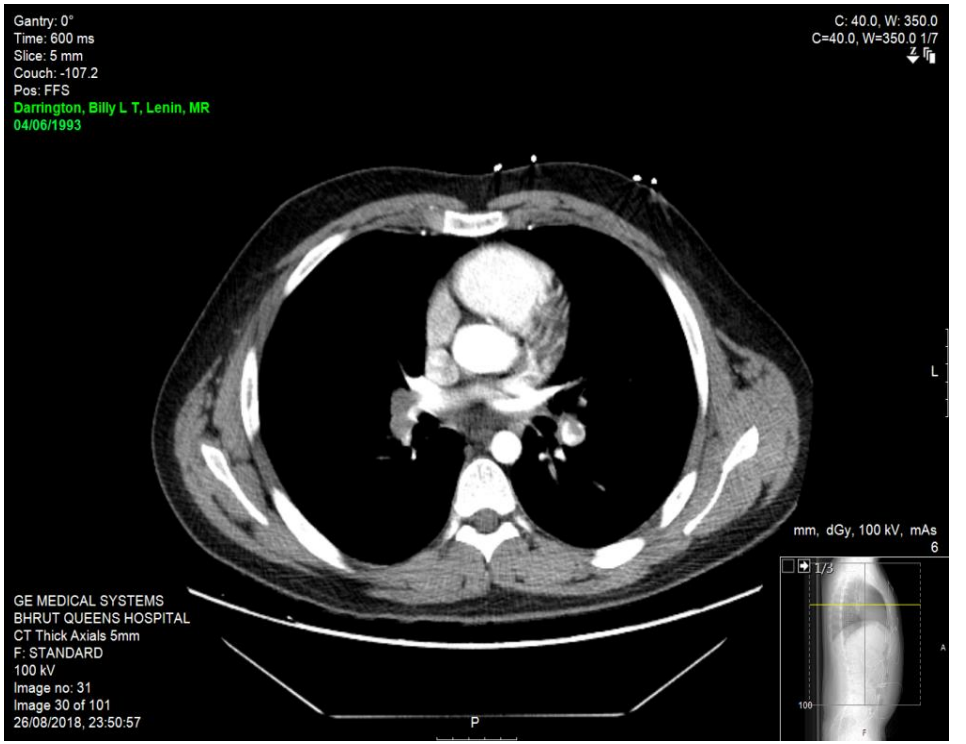
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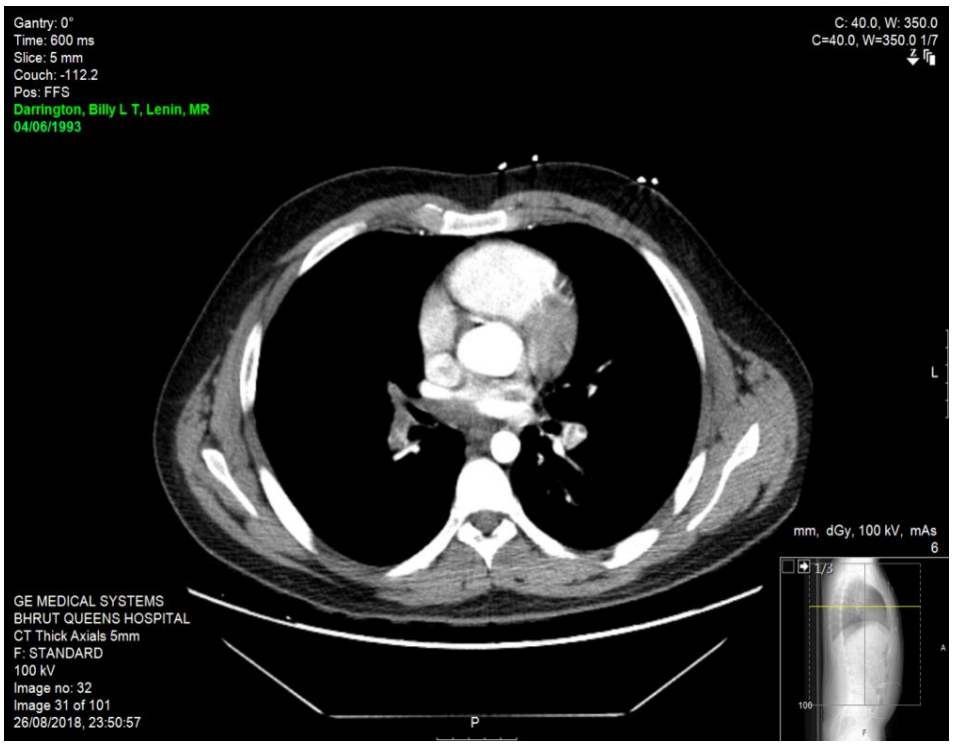
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Pos: FFS
Darrington, Billy L T, Lenin, MR
04/06/1993
C: 40.0, W: 350.0
C=40.0, W=350.0 1/7
L
mm, dGy, 100 kV, mAs
6
GE MEDICAL SYSTEMS
BHRUT QUEENS HOSPITAL
CT Thick Axials 5mm
F: STANDARD
100 kV
Image no: 32
Image 31 of 101
26/08/2018, 23:50:57
P

Case 3 contd

- Rx LMWH od and T/F HDU for monitoring

- Next day RV :
- Still c/o severe pain
- Looked distressed, Clammy, Pale
- RR 32/min, Sats 98% on 4l/min
- Pulse 125/min
- **BP 140/80**
- Bedside Echo by ITU – Dilated RV

Case 3 contd

- Half dose tPA – 10 mg bolus, 40 mg/2 hours
- IV Heparin Infusion post tPA

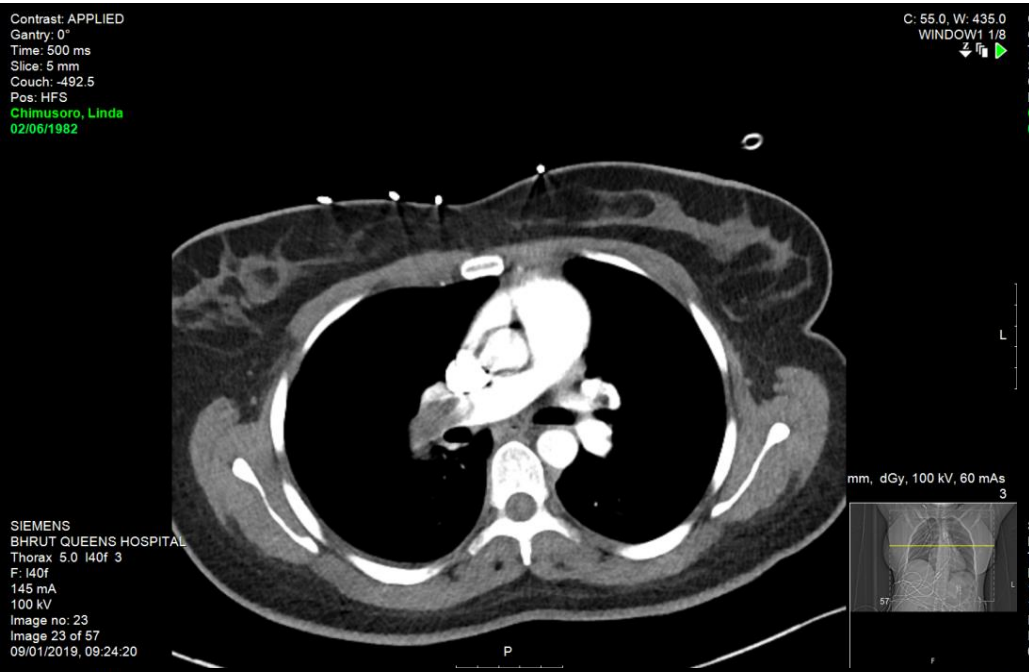
- 4 hours post tPA infusion :
- Looked comfortable
- RR 18/min, Sats 98% air, Pulse 90/min, BP 130/65

- Discharge home **day 4** on Clexane. Noted obs Pulse 60/min, Sats 98% air
- For long term anticoagulation as unprovoked PE

Case 4

- 32 year old lady. Fit and well
- Acute SOB and collapse at home. No LOC

- Sats 80% with LAS
- In A&E :
  - Pulse 110/min
  - BP 105/70
  - RR 24/min
  - SaO_2 98% on 4 l/min
  - ECG – Sinus Tachy, T inv V2-V4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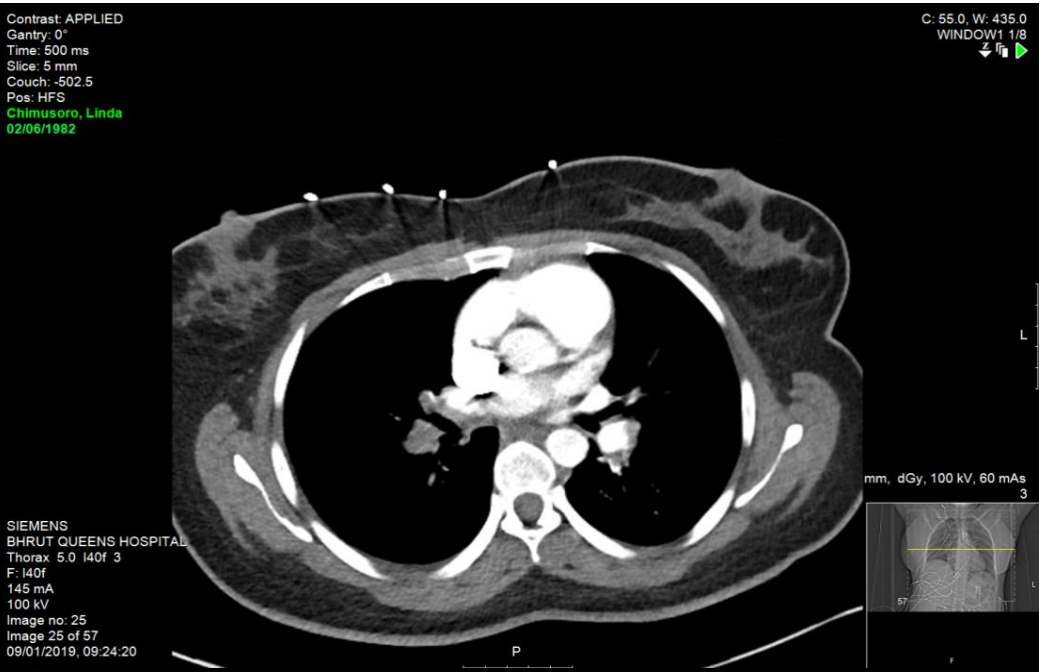
Pos: HFS
Chimusoro, Linda
02/06/1982
C: 55.0, W: 435.0
WINDOW1 1/8
L
mm, dGy, 100 kV, 60 mAs
3
SIEMENS
BHRUT QUEENS HOSPITAL
Thorax 5.0 I40f 3
F: I40f
145 mA
100 kV
Image no: 23
Image 23 of 57
09/01/2019, 09:24:20
P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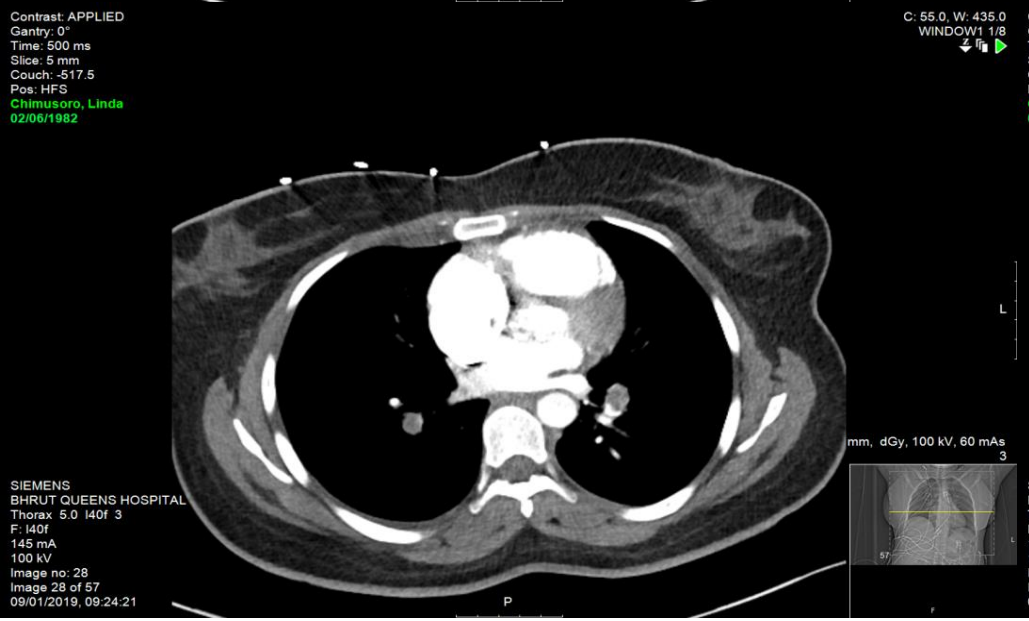
Chimusoro, Linda
02/06/1982
C: 55.0, W: 435.0
WINDOW1 1/8
L
mm, dGy, 100 kV, 60 mAs
3
SIEMENS
BHRUT QUEENS HOSPITAL
Thorax 5.0 I40f 3
F: I40f
145 mA
100 kV
Image no: 25
Image 25 of 57
09/01/2019, 09:24:20
P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Chimusoro, Linda
02/06/1982
C: 55.0, W: 435.0
WINDOW1 1/8
L
mm, dGy, 100 kV, 60 mAs
3
SIEMENS
BHRUT QUEENS HOSPITAL
Thorax 5.0 I40f 3
F: I40f
145 mA
100 kV
Image no: 28
Image 28 of 57
09/01/2019, 09:24:21
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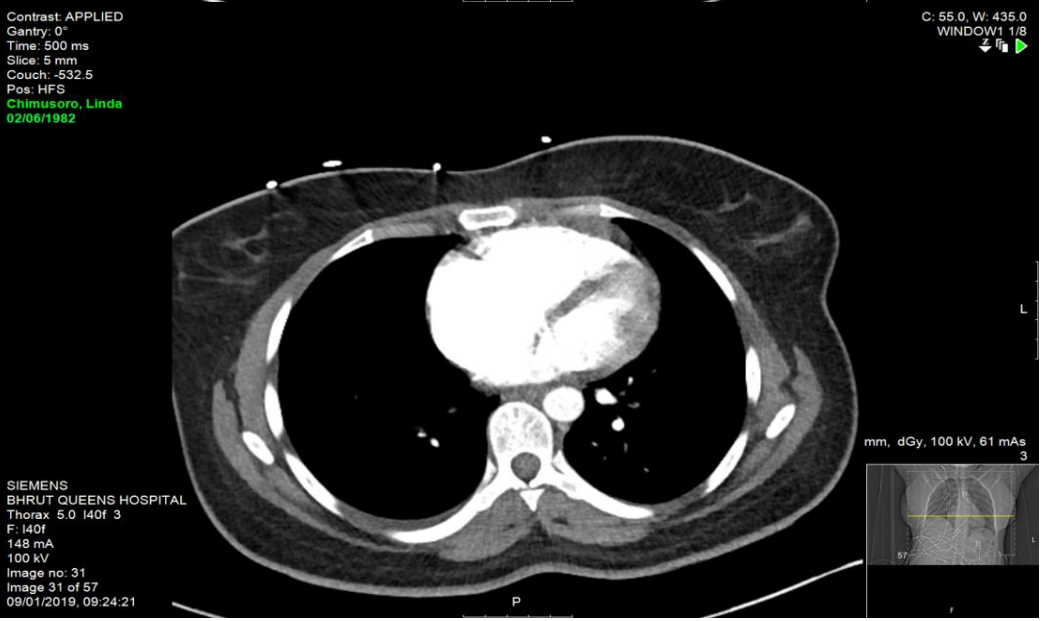
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Couch: -532.5
Pos: HFS
Chimusoro, Linda
02/06/1982
C: 55.0, W: 435.0
WINDOW1 1/8
L
mm, dGy, 100 kV, 61 mAs
3
SIEMENS
BHRUT QUEENS HOSPITAL
Thorax 5.0 I40f 3
F: I40f
148 mA
100 kV
Image no: 31
Image 31 of 57
09/01/2019, 09:24:21
P

Case 4 contd

- Bedside ECHO – dilated RV
- Trop 120
- Bilateral Doppler US
  - DVT in IVC and left iliac vein, large pelvis mass
- Pulse 105/min
- BP 105/70
- SaO2 98% on 4L/min
- RR 24/min

Case 4 contd

- Already had given LMWH
- Decision for thrombolysis - ½ dose tPA

- 4 hours post tPA review :
  - Pulse 75/min
  - BP 120/80
  - SaO2 98% air

- Abdo US next day – large fibroid, and proximal DVT still present

Case 5

- 67 year old
- Recent 10/7 hospital admission for pneumonia
- 3 day history of R leg pain
- Acute SOB over 24 hours

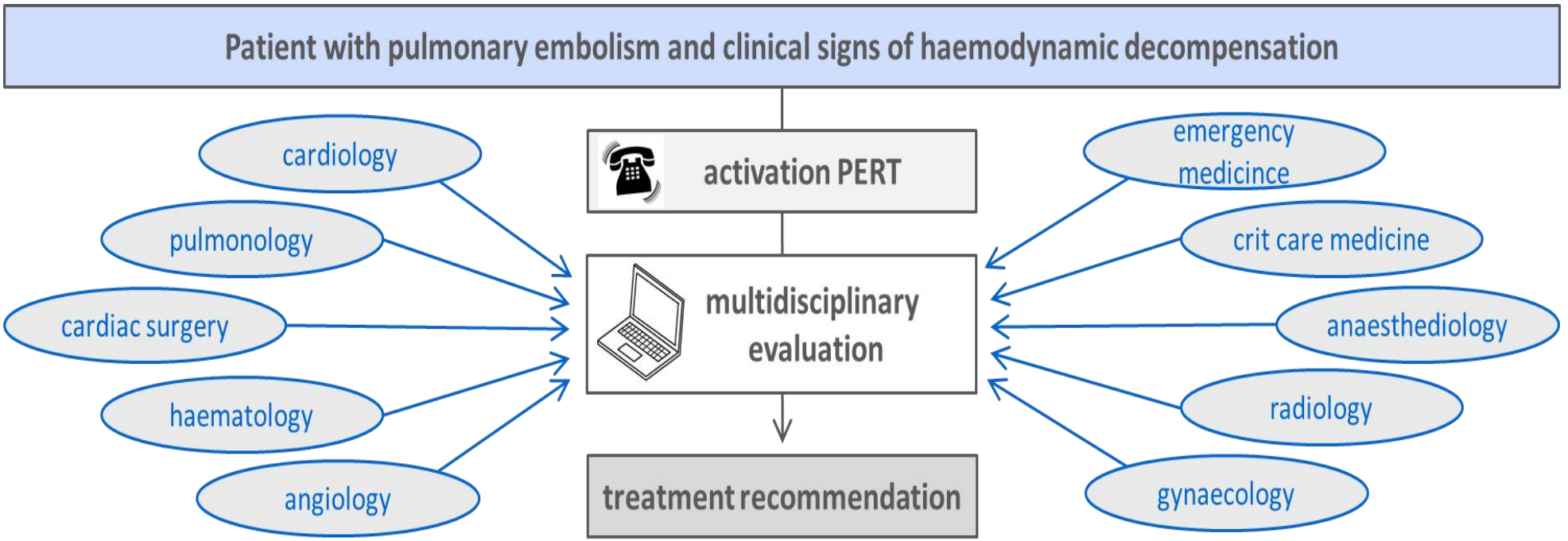
- O/E :
  - Pulse 90/min
  - BP 130/80
  - RR 20/min
  - SaO2 98% on 2 l/min

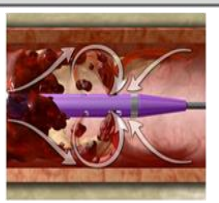
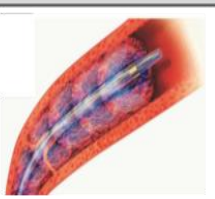
- Troponin 24

- CTPA – saddle embolus and bilateral clot main PA/lobar/segmental
  mild RV strain on CT (RV:LV 1.1)

For Thrombolysis?
Only LMWH

Pulmonary embolism response team (PERT)



systemic thrombolysis	surgical embolectomy	rheolytic thrombectomy	rotational thrombectomy	ultrasound-assisted catheter-directed thrombolysis	v/a ECMO
					

Dudzinski DM, Piazza G, Circulation 2016; 133:98-103; Kabrhel C et al., Chest 2016; 150:384-393; Jaber WA et al. J Am Coll Cardiol 2016; 67:991-1002

Summary Points

- Use age adjusted D Dimer in diagnostic algorithm
- Use of D Dimer and Clinical Prediction in Pregnancy diagnostic work up
- Risk Stratification and risk adjusted management of PE
- Low risk PE patients for home treatment with NOAC
- Risk Stratify Intermediate Risk PE for adverse prognostic factors and risk of bleeding
- Consider reduced dose thrombolysis only in highly selected Intermediate High Risk PE
- NOAC is the anticoagulation of choice
- Extended anticoagulation with low dose NOAC unless major transient risk factor