What Can We Do For "Intermediate Risk" Pulmonary Embolism

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Guy's and St Thomas' Hospital
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Declarations - none

Definitions of PE – “size”

Formally know as…

- massive
- sub-massive
- non-massive

Definitions of PE – “size”

Now know as…

- High Risk
- Intermediate Risk
- Low Risk

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NHS Foundation Trust

Page1: Investigation for Suspected and Confirmed Acute Pulmonary Embolism (PE) for non-pregnant patients

NB: If patient hypotensive and PE suspected, See page 3 for management and contact Clinical Response team (CRT)

Assess clinical probability of PE using Wells Score (**see table A**). Order:
- D-Dimer
- Coagulation screen
- Full Blood Count
- Renal profile and electrolytes
- Oxygen saturations
- Troponin
- ECG
- Chest X-ray.

Key:
DVT – Deep vein thrombosis
PE – Pulmonary Embolism
CTPA – CT pulmonary angiogram
VQ SPECT – Nuclear ventilation perfusion scan

PE unlikely according to WELLS score (PE score ≤4)

PE likely according to WELLS score (PE score >4)

D-dimer **NEGATIVE**

D-dimer **POSITIVE**

Perform VQ SPECT/CTPA (see table B)

VQ SPECT /CTPA negative

VQ SPECT /CTPA positive
OR scan delayed = **TREAT AS PE**

Requires no further imaging or anticoagulation. Seek alternative diagnosis

PE EXCLUDED

PE DIAGNOSED

Assess PESI score (see table C)
PESI ≤ 85 = LOW RISK
PESI ≥ 86 = INTERMEDIATE/HIGH RISK

PESI ≤85
- See page 4 for management

PESI ≥ 86
- See page 2 for classification and management of intermediate/high risk PE
- Assess right ventricular dysfunction by ordering BNP (phone Blood Sciences lab) & view CTPA. If CTPA is not informative then order ECHO.

See page 3 for management of high risk PE

For management of pregnant patients with PE, refer to Management of thrombosis and thromboprophylaxis in pregnancy and the puerperium guideline

Investigation and management of suspected and confirmed acute PE vs 11 DTC submission 5 September 2018.

A: PE Wells Score (Pre-test probability (PTP)

Clinical Feature	Points
Clinical signs of a DVT	3
Alternative diagnosis less likely than a PE	3
Previous DVT or PE	1.5
Recent surgery or immobilisation	1.5
Pulse rate >100bpm	1.5
Cancer	1
Haemoptysis	1
Clinical probability simplified score	
Low- PE unlikely	**≤ 4**
PE likely	**>4**

B: VQ SPECT is the imaging of choice in fertile women
- Also consider if patient has contrast allergy
- Has similar sensitivity for diagnosing PE as CTPA
- Lower radiation dose to breasts compared with CTPA
- Not suitable if patient is unable to lie still for 30 minutes or unable intolerant of a mask.

Available Monday to Friday 9:00am to 5:00pm at STH only.
(CTPA scans available 24 hours a day)

If abnormal Chest X-ray, discuss with Radiology first

C: Pulmonary embolism severity index (PESI) score

is clinical prediction tool to risk stratify patients with PE

Parameter	Point
Age	+ 1 per year
Male sex	+10 points
Cancer	+30 points
Chronic heart failure	+10 points
Pulse rate ≥ 110 bpm	+20 points
Systolic blood pressure <100mmHg	+30 points
Respiration rate >30 breaths/minute	+20 points
Temperature <36^{0}C	+20 points
Altered mental state	+60 points
Arterial oxyhaemoglobin saturation <90%	+20 points

PESI score (ESC guidelines)		
PESI score	30 day Mortality risk	
PESI I ≤ 65	Very low mortality risk	0-1.6 %
PESI II 66-85	Low mortality risk	1.7-3.5 %
PESI III 86-105	Moderate mortality risk	3.2-7.1 %
PESI IV 106-125	High mortality risk	4.0-11.4%
PESI V > 125	Very high mortality risk	10.0-24.5%

“Risk”….. Mortality

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PESI V > 125	Very high mortality risk	10.0-24.5%

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Page 4: Management of Low risk Pulmonary Embolism in Non-Pregnant Patients

-for cancer-associated thrombosis (CAT), please refer to 'management of cancer-associated thrombosis (CAT) guideline

What is the patient's renal function? Use the Cockcroft-Gault equation to calculate creatinine clearance

Creatinine clearance ≤15ml/minute

Admit and prescribe unfractionated heparin infusion

Refer to 'Adult unfractionated heparin infusion' guideline relevant to your clinical area

Bleep Thrombosis team for in-patient review and discharge planning with appropriate anticoagulation therapy

Creatinine clearance >15ml/minute

If no contra-indication to rivaroxaban-(see box A)

prescribe rivaroxaban, depending on renal function

Creatinine clearance 15-29ml/minute:

If no contraindications **(see A)**

prescribe:

Initial dose:

Rivaroxaban 15mg BD orally for 3 weeks

Followed by maintenance dose:

Rivaroxaban 15mg OD* orally thereafter

Creatinine clearance >30ml/minute:

If no contraindications **(see A)**

prescribe:

Initial dose:

Rivaroxaban 15mg BD orally for 3 weeks

Followed by maintenance dose:

Rivaroxaban 20mg OD orally thereafter

If contraindications to rivaroxaban (see box A) AND creatinine clearance >15ml/minute:

Prescribe dalteparin 200units/kg OD according to patient weight for FOUR weeks

Weight	Treatment dose Dalteparin 200 units/kg
<46 kg	7 500 units OD
46-56 kg	10 000 units OD
57-68 kg	12 500 units OD
69-82 kg	15 000 units OD
83 -100kg	18 000 units OD
> 100kg	Seek Haematology advice -contact details below

Consider if the patient is suitable for ambulatory care –see table B

Yes

Consider admitting to Emergency medical unit for review & monitoring for 4-6 hours (if ambulatory patient)

No

- Admit-duration at discretion of admitting consultant
- Request Thrombosis team in-patient review

On discharge:

- Provide anticoagulation for at least FOUR WEEKS (provide sharps bin for patients on low molecular weight heparin).
- Arrange for outpatient GSTT Thrombosis clinic referral via EPR (type in 'OP:VTE' into orders) who will take over ongoing investigation and management within 4 weeks and decide on the duration of anticoagulation
- Provide patient information leaflet on pulmonary embolism
- DO NOT DO A THROMBOPHILIA SCREEN AT THIS TIME (NO VALUE).

*There is limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min). Pharmacokinetic data indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, use rivaroxaban with caution in these patients.
Seek Thrombosis team advice if you need to consider this option.

A: Contra-indications to rivaroxaban
Significant liver disease (Child Pugh score B or C)
Pregnancy/breastfeeding
Creatinine clearance <15ml/minute
Concomitant use of cytochrome P-450 3A4 inhibitors: e.g. fluconazole, protease inhibitors
Concomitant use of cytochrome P-450 3A4 inducers e.g. rifampicin, carbamazepine or phenytoin
Currently not recommended in active cancer – patients should receive dalteparin or UFH
Anticipated compliance problems

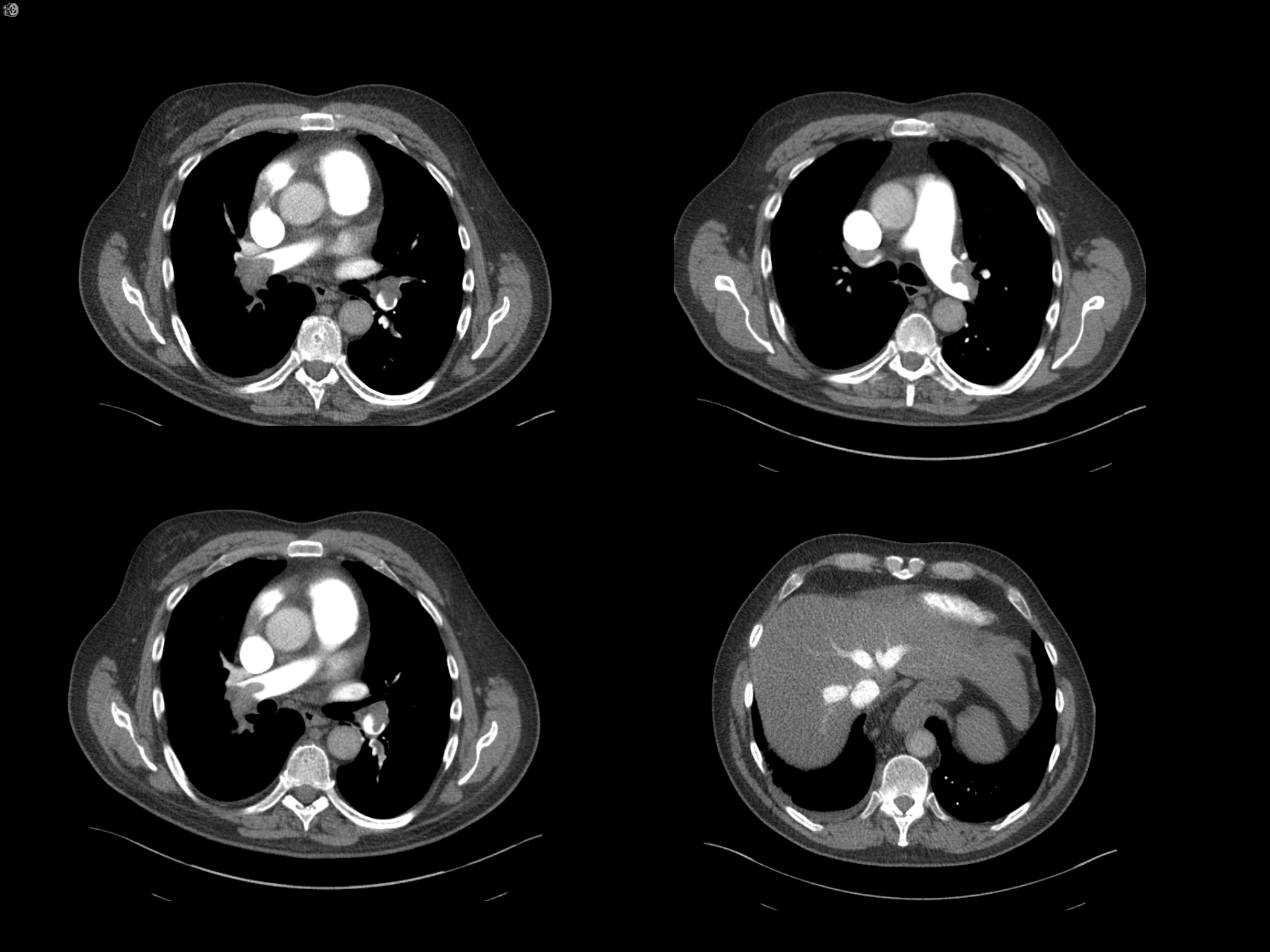
B: Exclusion criteria for ambulatory management
Pregnant
Age < 16 years
GI/GU/intracranial bleed< 4/52 ago
Heparin sensitivity/history of HIT
Systolic BP >180 or diastolic >115
Angina or SOB on minimal exertion
CrCl ≤15ml/minute-give unfractionated infusion- refer to 'Adult unfractionated heparin infusion' guideline relevant to your clinical area.
Platelets <50 x 10^9/L

How to contact the Thrombosis $tR:

During routine hours - bleep 0122;
Out of hours and at weekends - bleep 0294

Massive PE
“High Risk PE”

- SBP < 90 mmHg or drop of >40 mmHg
- >15 mins
- with no other cause
- Up to 5-10% of patients
- Mortality – high (15-58%)



High Risk PE - Treatment

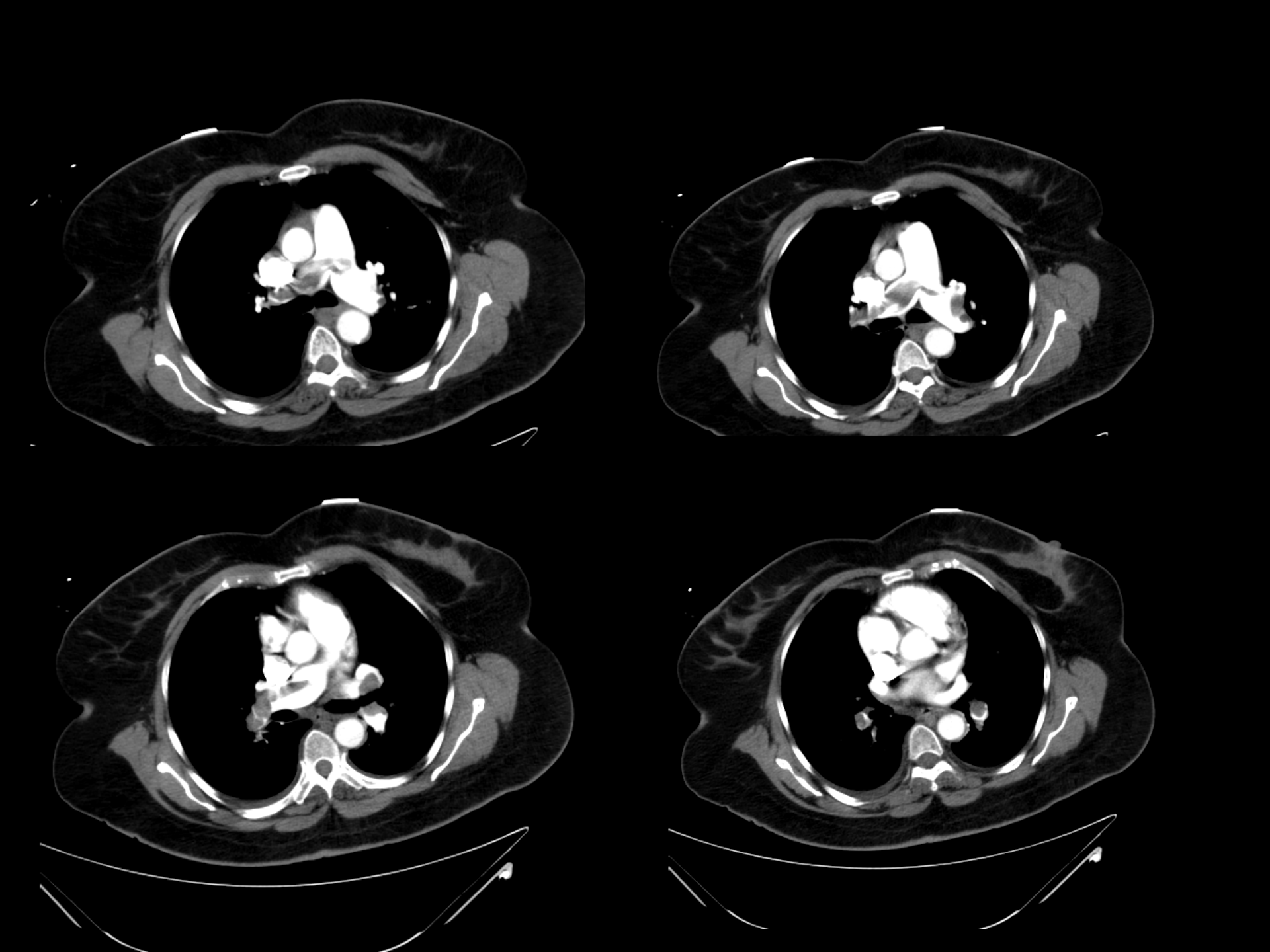
- Resuscitation
- “Full Dose” systemic thrombolysis
- tPA – 10mg bolus, 90mg / 2 hours

- Risk of major bleeding (6-20%)
- Intracranial Haemorrhage (2-6%)
- ….But outweighs risk of death from PE

Sub-massive PE
"Intermediate Risk PE"

- Not hypotensive but…
- Evidence of right heart dysfunction (CT or ECHO)
- Evidence of myocardial injury/strain
  - elevated biomarkers - Troponin & BNP
- Confirmed large clot burden – CTPA (V:Q)

- Mortality or "*Adverse Events*" 3-25%?



So why not thrombolyse "intermediate risk PE" too?

Much "pro/con" debate on going….

Thrombolysis for acute submassive pulmonary embolism: CON viewpoint

A John Simpson

Thrombolytic therapy for submassive pulmonary embolus? PRO viewpoint

Luke S Howard

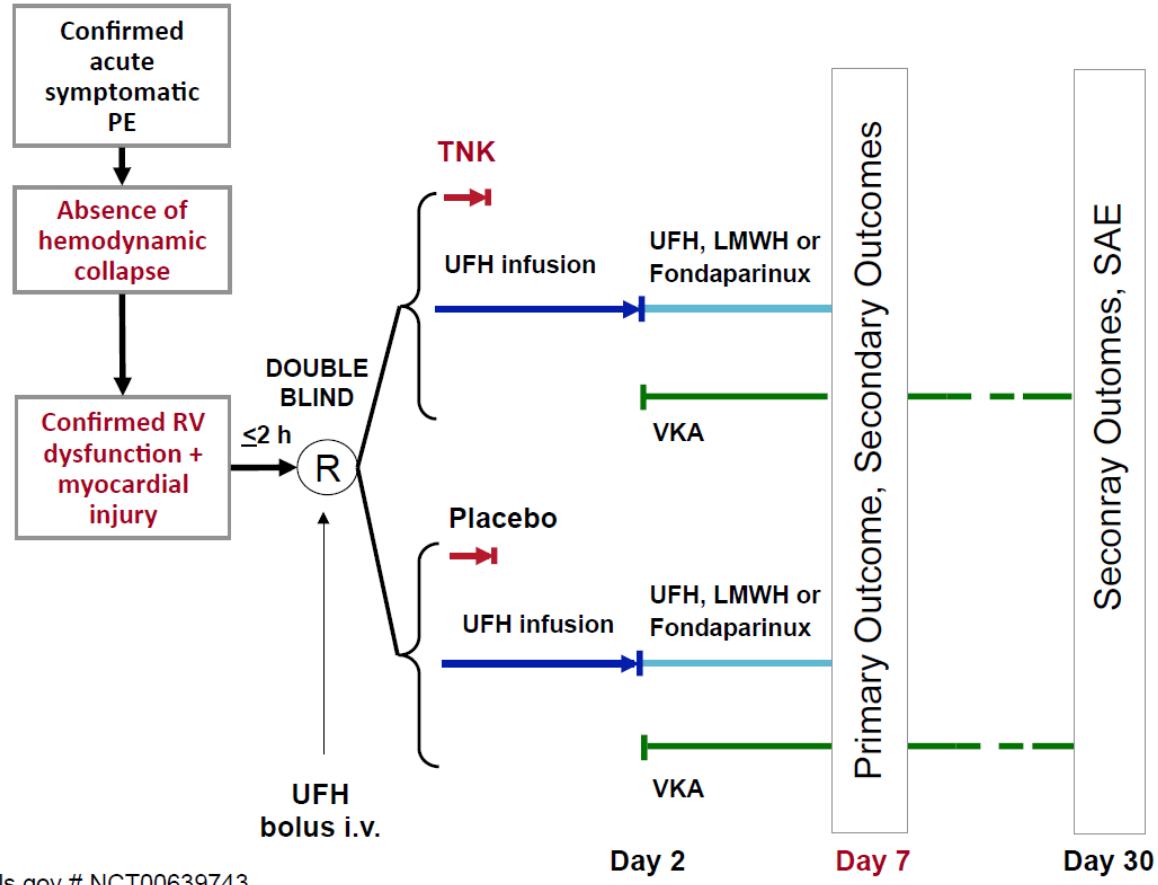
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

PEITHO: Overview of study design



ClinicalTrials.gov # NCT00639743
EudraCT # 2006-005328-18

S Konstantinides for the PEITHO Steering Committee. Am Heart J 2012;163:33-38.e1

PEITHO: Causes of death (within 30 days of randomization)

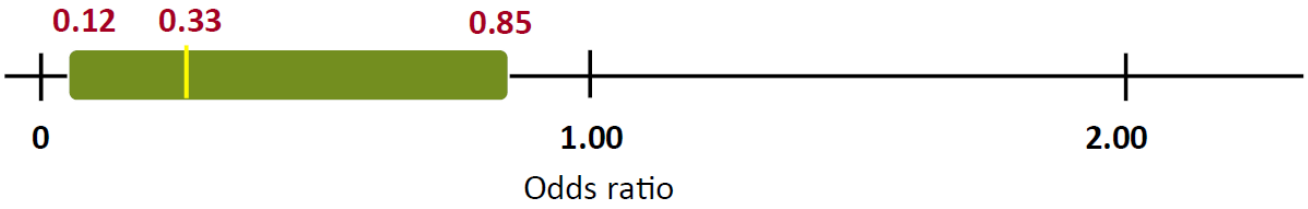
	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality	**12**	**(2.4)**	**16**	**(3.2)**	**0.42**
From hemodynamic collapse	1		3		
From recurrent PE	1		3		
From respiratory failure	0		3		
From stroke	5		1		
From bleeding	2		0		
Other cause	3		6		

ITT population

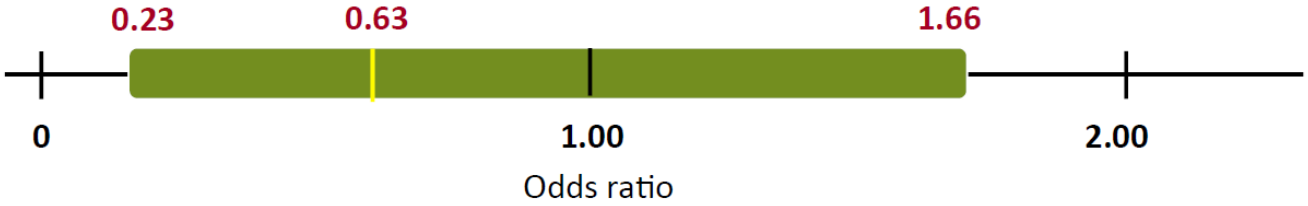
The PEITHO Investigators

PEITHO: Primary end point according to age

Age ≤ 75 years



Age >75 years



ITT population

The PEITHO Investigators

“*Adverse Events*” from Intermediate Risk PE

(This group can be very well!)

PEITHO: Analysis of primary efficacy outcome

	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

The PEITHO Investigators

PEITHO: Other clinical outcomes (within 7 days)

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
PE recurrence	1	(0.2)	5	(1.0)	0.12
Intubation / mechanical ventilation	8	(1.6)	15	(3.0)	0.13
Open-label thrombolysis	4	(0.8)	23	(4.6)	<0.001

ITT population

The PEITHO Investigators

American Guidelines – Chest 2016

- Intermediate risk PE

American Guidelines – Chest 2016

*23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

American Guidelines – Chest 2016

*23. In *selected patients* with acute PE who deteriorate after starting anticoagulant therapy but have *yet to develop hypotension* and who have a *low bleeding risk*, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

….Dose not suggested

Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial)

Mohsen Sharifi, MD[a,b,*], Curt Bay, PhD[b], Laura Skrocki, DO[a], Farnoosh Rahimi, MD[a], and Mahshid Mehdipour, DMD[a,b], "MOPETT" Investigators

The role of low-dose thrombolysis in the reduction of pulmonary artery pressure in moderate pulmonary embolism (PE) has not been investigated. Because the lungs are very sensitive to thrombolysis, we postulated that effective and safe thrombolysis might be achieved by a lower dose of tissue plasminogen activator. The purpose of the present study was to evaluate the role of this "safe dose" thrombolysis in the reduction of pulmonary artery pressure in moderate PE. During a 22-month period, 121 patients with moderate PE were randomized to receive a "safe dose" of tissue plasminogen activator plus anticoagulation (thrombolysis group [TG], n = 61 patients) or anticoagulation alone (control group [CG], n = 60). The primary end points consisted of pulmonary hypertension and the composite end point of pulmonary hypertension and recurrent PE at 28 months. Pulmonary hypertension and the composite end point developed in 9 of 58 patients (16%) in the TG and 32 of 56 patients (57%) in the CG ($p < 0.001$) and 9 of 58 patients (16%) in the TG and 35 of 56 patients (63%) in the CG ($p < 0.001$), respectively. The secondary end points were total mortality, the duration of hospital stay, bleeding at the index hospitalization, recurrent PE, and the combination of mortality and recurrent PE. The duration of hospitalization was 2.2 ± 0.5 days in the TG and 4.9 ± 0.8 days in the CG ($p < 0.001$). The combination of death plus recurrent PE was 1 (1.6%) in TG and 6 (10%) in the CG ($p = 0.0489$). No bleeding occurred in any group, and despite a positive trend in favor of a "safe dose" thrombolysis, no significant difference was noted in the rate of individual outcomes of death and recurrent PE when assessed independently. In conclusion, the results from the present prospective randomized trial suggests that "safe dose" thrombolysis is safe and effective in the treatment of moderate PE, with a significant immediate reduction in the pulmonary artery pressure that was maintained at 28 months. (Am J Cardiol 2012;■:■−■)

MOPETT Trial

- Concept of “Safe Dose Thrombolysis”?
- Cardiac output – Brain 15%, Heart 5%, Pulmonary 100%

- tPA - 10mg bolus
- tPA - 40mg/2 hours (0.5mg/kg if <50kg)

MOPETT Trail

Table 2
Primary end points at 28 ± 5 mo of follow-up

Variable	TG (n = 58; 100%)	CG (n = 56; 100%)	p Value
Pulmonary hypertension*	9 (16%)	32 (57%)	<0.001
Pulmonary hypertension plus recurrent pulmonary embolism	9 (16%)	35 (63%)	<0.001

* Pulmonary artery systolic pressure ≥40 mm Hg.

MOPETT Trail

Table 3
Secondary end points

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Recurrent pulmonary embolism	0	3 (5%)	0.08
Total mortality	1 (1.6%)	3 (5%)	0.30
Total mortality plus recurrent pulmonary embolism	1 (1.6%)	6 (10%)	0.049
Hospital stay (days)	2.2 ± 0.5	4.9 ± 0.8	<0.001
Bleeding	0	0	—

Data are presented as mean ± SD or n (%).

“PERT”

Acute Pulmonary Embolism Network and Multidisciplinary Response Team Approach to Treatment

Tyler L. Bloomer, MD, Eric J. Thomassee, MD, and Pete P. Fong, MD

A Pragmatic British Alternative…

And applicable to DGH as teaching hospitals alike…

PE Lysis Team- “PELT”

- Chest Physicians
- Critical Care
- Haematologists
- Interventional Radiology
- (Obstetric Physician)

PE Lysis Team- “PELT”

- Chest Physicians
- Critical Care
- Haematologists
- Interventional Radiology (pt bleeding risk)
- (Obstetric Physician)

Intermediate Risk PE

- Not shocked but…
- Evidence of right heart dysfunction
- Evidence of myocardial injury
  - elevated Troponin , BNP
- Confirmed large clot burden – CTPA (V:Q)

- Mortality or “Adverse Events” 3-15%?

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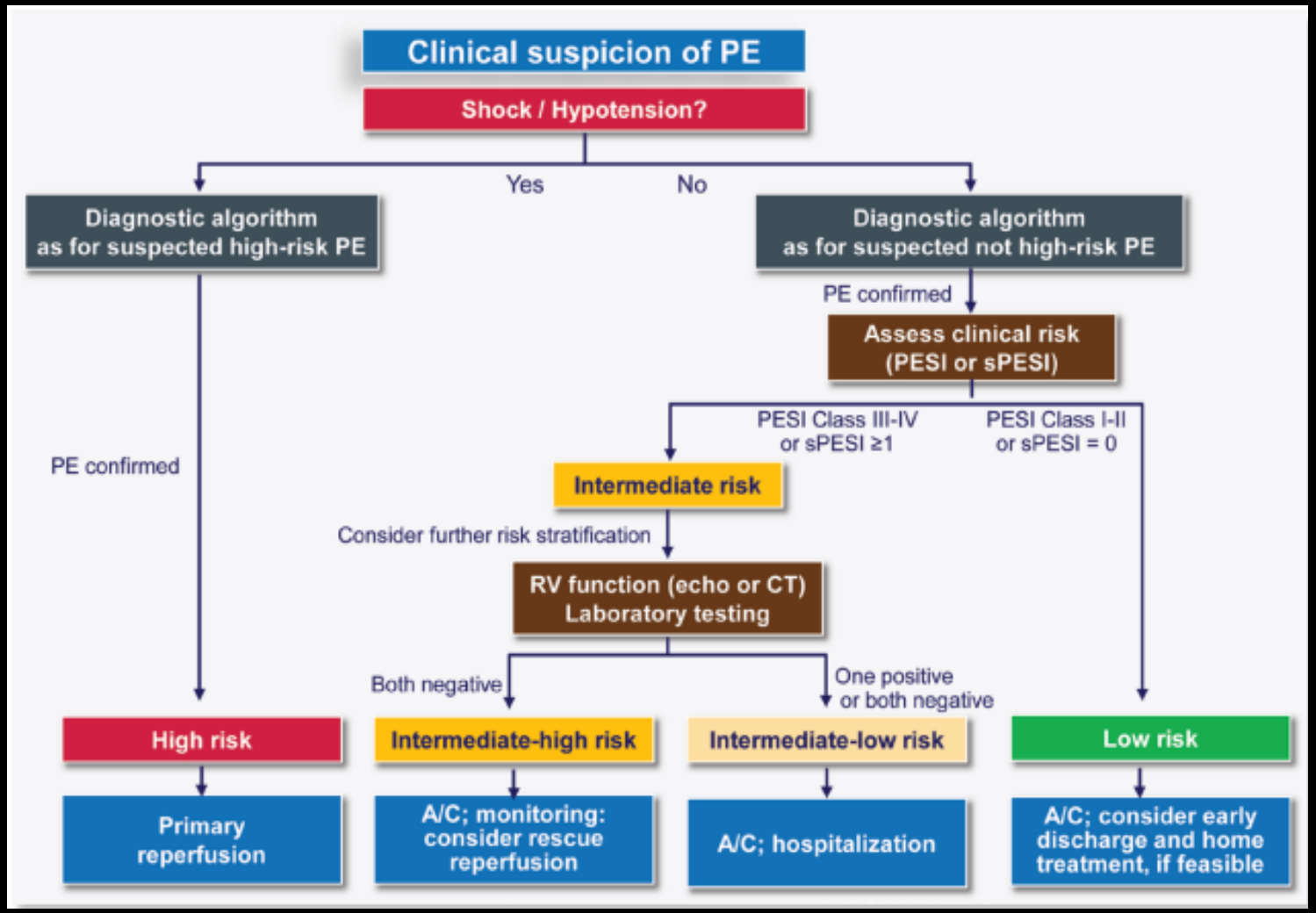
- Not shocked but…
- Evidence of right heart dysfunction*
- Evidence of myocardial injury
  - elevated Troponin*, BNP*
- Confirmed large clot burden* - CTPA (V:Q)

- Mortality or “Adverse Events” 3-15%….
- Predictors* – both +ve and -ve

European Guidelines - 2014



PE Lysis Team- “PELT”

- Initial Clinical Assessment
- ECHO
- Bilateral leg Dopplers
- Bleeding risk (NB age, Pulmonary infarction)

PE Lysis Team- “PELT”

- Initial Clinical Assessment
- ECHO
- Bilateral leg Dopplers
- Bleeding risk (NB age, Pulmonary infarction)
- *Serial Assessment* – review progress
- Patient involvement in decisions/consent
- *…..then you make a TEAM judgement*

Key “Take Home” Message

Is your patient…

Intermediate-High Risk (?Lysis)

Or

Intermediate-Low Risk (Lysis unlikely)

(but can change groups with time and treatment)

Page 2: Classification of confirmed acute PE including management of intermediate risk PE

Classification based on early mortality risk (from European Cardiology Society guidelines 2014): Assess using following table

The management of intermediate risk PE with initial low-dose thrombolysis is not recommended in any international guidance because current evidence shows no improvement in mortality at 6 months.

Risk parameters and scores	Low	Intermediate	High
Shock or hypotension	-	-	+
PESI SCORE ≥ 86	-	+	+
RV dysfunction on imaging	Assessment optional; if assessed, both negative	Intermediate high: Both positive	+
		Intermediate low: Either one (or none) positive	+

Low risk PE

High risk PE, i.e. with SHOCK
Refer to page 3

Management of Intermediate risk PE

Anticoagulation:
Give 5000 units IV BOLUS unfractionated heparin, followed by unfractionated heparin IV infusion – (Refer to the adult unfractionated heparin infusion guideline relevant to your clinical area).
Avoid DOACs or LMWH as it will increase the bleeding risk with potential thrombolysis. If patient already on an anticoagulant - discuss with Haem StR bleep 0122/ 0294 out of hours

Patient stable/improving: continue IV heparin for up to 48 hours

If patient clinically deteriorates – consider thrombolysis

If patient significantly deteriorates, then go to page 3-management of high risk PF

If there is an increased bleeding risk, consider catheter-directed thrombolysis under direction of IR consultant (contact via switchboard)

If there is low bleeding risk, consider systemic thrombolysis
Prescribe alteplase infusion, according to weight
Patient's informed consent is required as alteplase is unlicensed for low dose thrombolysis

Weight < 50kg	Weight ≥ 50kg
Total dose = 0.5mg/kg. Give as a 10mg **IV BOLUS** over 1 minute followed by the remainder of the dose as an **IV INFUSION** over 2 hours	10mg **IV BOLUS** over 1 minute followed by 40mg **IV INFUSION** over 2 hours

Management of intravenous heparin infusion when on thrombolysis: Maintain heparin infusion rate at 5 units/kg/hour whilst alteplase is infused.
At the end of thrombolysis: Monitor fibrinogen levels with Clauss fibrinogen -order as 'coagulation special'.
If BLEEDING, only give cryoprecipitate if fibrinogen <1.5g/L. If NOT BLEEDING, only give cryoprecipitate if fibrinogen <1g/L. Note that 2 pools of cryoprecipitate increases fibrinogen by 1gram

1 hour after alteplase infusion stopped: INCREASE heparin infusion rate, titrating to a target APTT ratio 2.0-2.5.
(Refer to the adult unfractionated heparin infusion guideline relevant to your clinical area). Continue for 24-48 hours.

24-48 hours post thrombolysis: If no major bleeding, consider switch to DOAC/dalteparin or continue unfractionated heparin. Follow advice on page 4 and discuss with the Thrombosis team if necessary (bleep 0122/0294 out of hours/weekends)

Local Protocol for Intermediate Risk PE

- Team decision
- Done in level 2 or 3
- Systemic “half dose” first line
- Catheter direct Thrombolysis for

  - bleeding risk (eg post surgery)
  - Second line (post systemic, including massive PE)
  - “Older Clot”?

- (Local outcome very good… thus far)

Catheter Directed Thrombolysis

- Interventional Radiology
- Time is situ 12-24 hours
- Infuse tPA 0.5-1mg per hour
- Lower total dose
- Mostly bilateral (and each side “adjusted”)

- Still risk of bleeding and arrhythmia

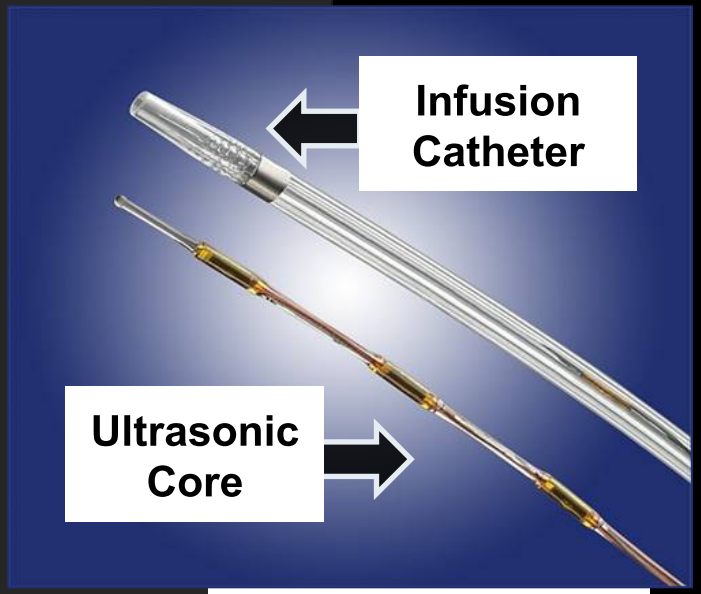
Catheter-Based Thrombus Removal for the Initial Treatment of PE

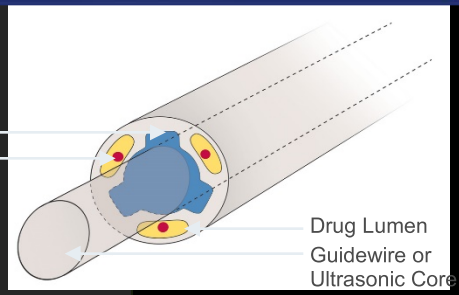
***24. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT (Grade 2C).**

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy.

EKOS™ Endovascular System **Features**

- 5.4 F catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones

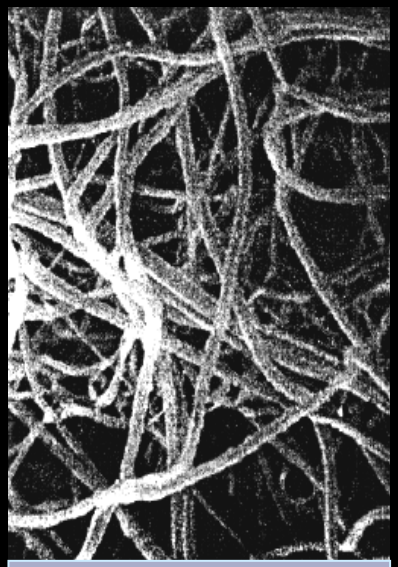




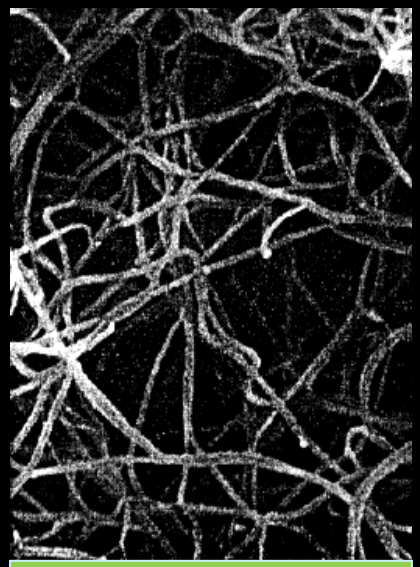
Acoustic Pulse Thrombolysis™ treatment
Mechanism of action

Fibrin Separation

Ultrasound separates fibrin without fragmentation of emboli



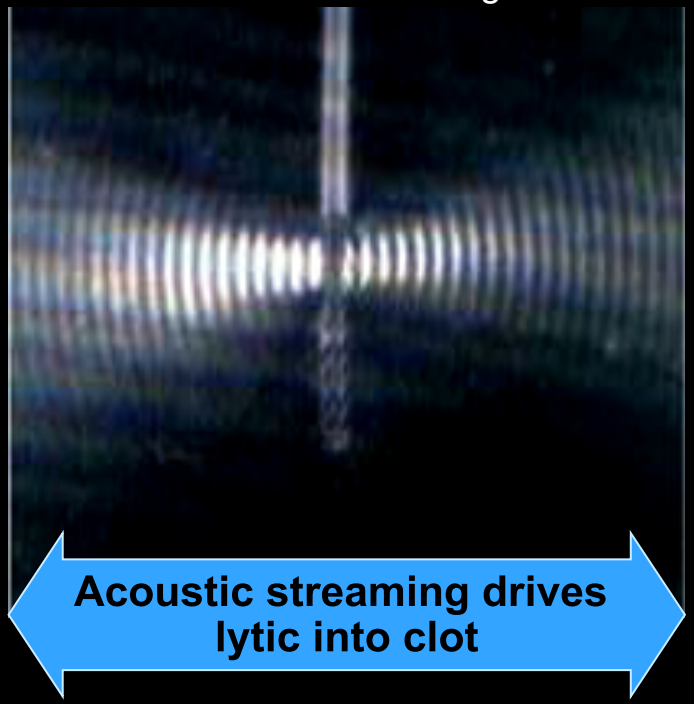
Fibrin without Ultrasound



Fibrin With Ultrasound

Active Drug Delivery

Drug is actively driven into clot by "Acoustic Streaming"



1 Braalen J / el a U trasound revers b y d saggregales f br n f bers Thromb Haemosl 1997 78 1063-8.
2 Franc s C N el a U trasound acce erales transport of recomb nanl l ssue p asm nogen acl valor nlo c ols U trasound n Medicine and Biology,1995;21(5):419-24.
3 S dd q F el a U trasound ncreases f ow through f br n ge s Thromb Haemosl 1995 73(3) 495-8.

Summary

- Ongoing clinical assessment in “place of safety”
- Intermediate-high or intermediate-low risk
- Advances in TEAM decisions for the more severe PEs to enable improved morbidity and mortality