LOW DOSE THROMBOLYSIS IN PULMONARY THROMBOEMBOLISM

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BACKGROUND

- Mortality of 10 % (approx.) within 3 months in acute pulmonary embolism
- For patients without systemic hypotension or hemodynamic compromise, anticoagulation considered adequate treatment
- Dreaded complication of thrombolysis is intracerebral haemorrhage: 0.7 – 6.4%

Aujesky et al. Circulation 2009;119:962-8
Kearon et al. Chest 2012:141:Suppl:e419S-e494S
Berkowitz et al. Circulation 1997;95:2508-2516

IS RV DYSFUNCTION ASSOCIATED WITH INCREASED MORTALITY??

European Heart Journal (2008) **29**, 1569–1577
doi:10.1093/eurheartj/ehn208

Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review

EURO – 2008

Meta analysis done in 2008 – Increased mortality in non massive PE with increased cardiac markers and RV dysfunction demonstrated echocardiography and CT

CONCLUSION:

To be interpreted with CAUTION – Clinical and methodological diversity

Requirement of well designed prospective studies

American Guidelines for VTE

- In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B)
- 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)

Kearon et al. Chest 2016;149:315–352

- Retrospective study
- Enrolled 64,037 patients
- Participating U.S. hospitals - 363
- Hemodynamically stable acute pulmonary embolism (2008 and 2011)

RESULT :

- Hospitals with high rates of pulmonary embolism–associated trans-thoracic echocardiography use did not achieve different patient mortality outcomes but had higher resource use and costs

RECOMMENDED SELECTIVE, RATHER THAN ROUTINE, USE OF TRANS-THORACIC ECHOCARDIOGRAPHY TO RISK STRATIFY PATIENTS WITH HEMODYNAMICALLY STABLE PULMONARY EMBOLISM

Outcome	Cohort Mean	Adjusted Effect Estimate (95% CI)*	*P* Value
Mortality	2.0%	1.02 (0.89–1.16)	0.83†
ICU admission	19.3%	2.07 (1.93–2.22)	< 0.01†
Thrombolytic use	1.3%	5.58 (4.40–7.09)	< 0.01†
Major bleeding	2.9%	1.37 (1.24–1.51)	< 0.01‡
Hospital LOS, d	5.4	1.15 (1.14–1.16)	< 0.01§
Hospitalization cost, USD	$ 9,587	1.31 (1.30–1.32)	< 0.01‖

Cohen et al.: Echocardiogram in the Evaluation of Acute PE. Ann Am Thorac Soc May 2018

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 902–910
doi:10.1093/eurheartj/ehy873

Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis

- Normotensive patients
- Objectively confirmed diagnosis of acute PE
- Categorized - low risk - Either the (s)PESI (PESI Classes I or II, PESI < 86 points, or sPESI = 0) or Hestia (all criteria absent)
- Total studies – 21 (PESI/sPESI – 19 and HESTIA – 2)

PULMONARY EMBOLISM SEVERITY INDEX

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%)	**0 points** = 30 day mortality risk 1.0% (95% CI 0.0–2.1%)
Class II: 66–85 points low mortality risk (1.7–3.5%)	
Class III: 86–105 points moderate mortality risk (3.2–7.1%)	**≥1 point(s)** = 30 day mortality risk 10.9% (95% CI 8.5–13.2%)
Class IV: 106–125 points high mortality risk (4.0–11.4%)	
Class V: >125 points very high mortality risk (10.0–24.5%)	

HESTIA CRITERIA

Hestia Criteria
1. Hemodynamically unstable? 2. Thrombolysis or embolectomy necessary? 3. Active bleeding or high risk of bleeding? 4. Oxygen supply to maintain oxygen > 90% > 24 hr? 5. Pulmonary embolism diagnosed during anticoagulant treatment? 6. Intravenous pain medication > 24 hr? 7. Medical or social reason for treatment in hospital > 24 hr? 8. Creatinine clearance less than 30 mL/min? 9. Severe liver impairment? 10. Pregnant? 11. Documented history of heparin-induced thrombocytopenia?
-If any of the above are answered “yes,” the patient should NOT be treated as outpatient -An answer of “no” to all of the above meets criteria for outpatient therapy

CRITERIA FOR RV DYSFUNCTION

- Dilation of RV (i.e. diastolic diameter ≥ 30 mm in parasternal short axis view
- Elevated RV/LVEDD (cut off of 0.9 or 1) on echo/CTPA
- Hypokinesia of RV free wall or abnormal movement of interventricular septum
- Tricuspid valve regurgitation velocity (cut off 2.7 or 2.8m/s)

Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910

STUDIES	POPULATION LOW RISK	INTERVENTION	COMPARISON	OUTCOME
PREP (1,2)	529 Normotensive 329 – LOW RISK	Echocardiography Assays of cardiac trop I and BNP along with PESI	Only PESI	30 days events – death, shock and recurrent PE In PESI class I-II rate of outcome higher in abnormal biomarkers and ECHO
PROTECT (3)	848 313 – LOW RISK	RV Dysfunction (echo and CTPA) Trop I and Pro BNP	sPESI	Incorporation of echo to MDCT along with sPESI improve detection of short term complications
Cote *et al (4)*	779 779 – LOW RISK	MDCT assessed RVD	sPESI	Increasing RV/LV diameter > 0.9 and > 1 in sPESI 0 associated with worse prognosis
Lankeit *et al(5)*	688 Normotensive 258 – LOW RISK	NT-proBNP and ECHO Cut off of 600	sPESI	PE related death or complications NT-proBNP has additive value with sPESI and ECHO

1. Sanchez et al. Eur Respir J 2013; 42: 681–688
2. Barrios et al. Assessment of right ventricular function in acute pulmonary embolism, American Heart Journal (2016)
3. Jim´enez et al.: A Risk Model for PE Prognosis. Am J Respir Crit Care Med 2014
4. Cote et al. Eur Respir J 2017; 50: 1701611
5. Lankeit et al. Eur Respir J 2014; 43: 1669–1677

STUDIES	POPULATION LOW RISK	INTERVENTION	COMPARISON	OUTCOME
SWIVTER	369 106 – LOW RISK	hs TROP T and I	sPESI	cTrop doesn't add up to prognosis of low risk
CHOI et al	657 363 – LOW RISK	RVD-CT	PESI	Independent prognostic marker
FEW OF THE STUDIES HAVE BEEN DISCUSSED AS REST OF THEM HAD LOW NUMBER OF PATIENT COHORT				rding NT-proBNP
HESTIA	530 297 – LOW RISK	ESC	HESTIA criteria	Useful even in low risk patients
Moores *et al*	567	cTROP – I	PESI	Mortality at day 30 PESI better than cTrop I
Vanni *et al*	540 145 – LOW RISK	ESC guidelines (European society of Cardiology) – troponin I and echo	PESI	ESC – Higher accuracy

1. Spirk et al. Thrombosis and Haemostasis 106.5/2011
2. Choi et al. j.thromres.2013.11.020
3. Den Exter et al. Am J Respir Crit Care Med Oct 15, 2016
4. Zondag et al. Pulmonary embolism outpatient treatment selection J Thromb Haemost 2013; 11: 686–92
5. Moores et al. Risk-stratification of PE patients. Journal of Thrombosis and Haemostasis 2009
6. Vanni et al. Comparison of two prognostic models for acute pulmonary embolism. Journal of Thrombosis and Haemostasis 2011

ADVERSE EVENTS IN LOW RISK PATIENTS

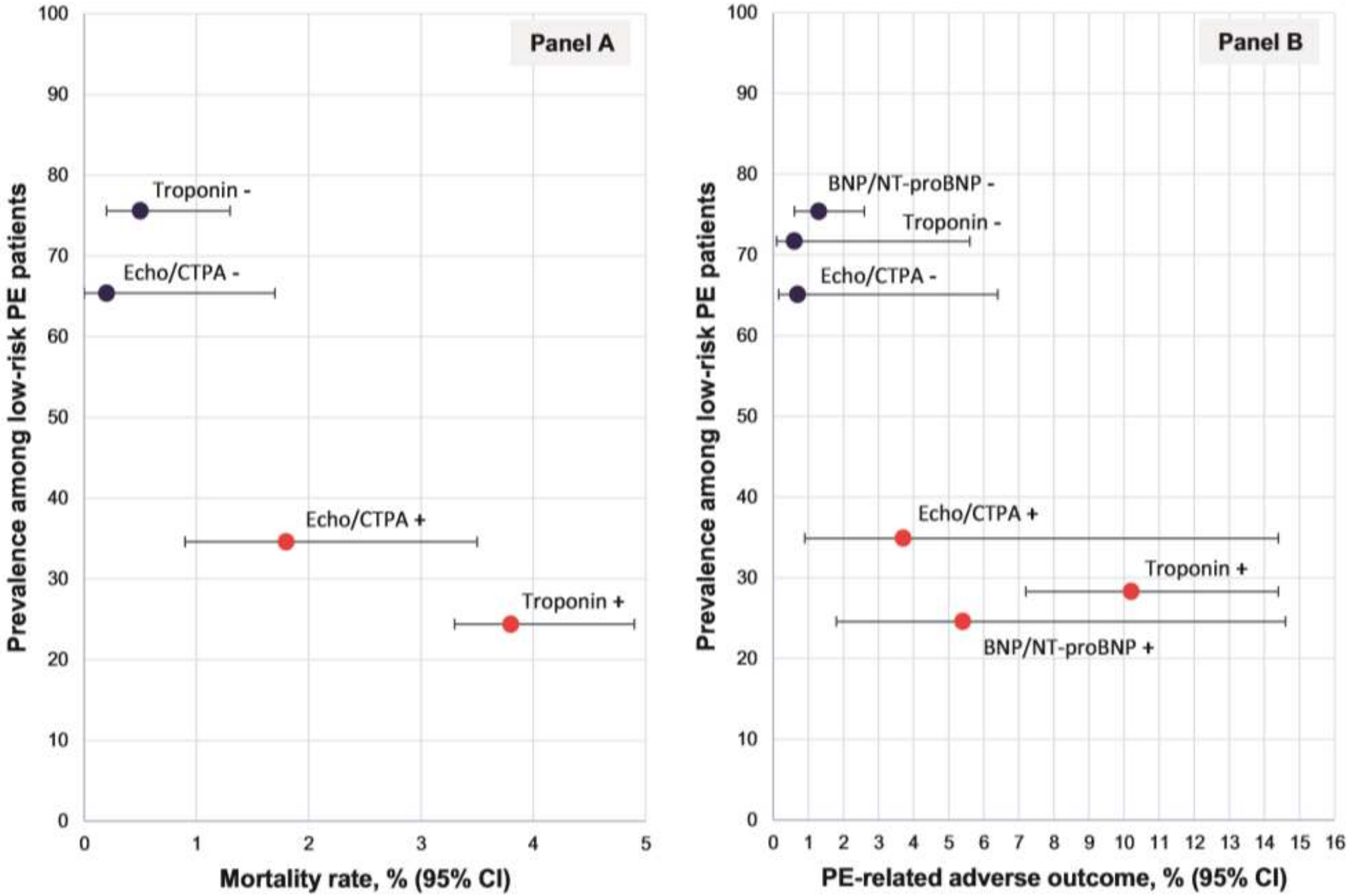
	RV dysfunction (exposure)	Study population (*n* studies)	With RV dysfunction, % (95% CI)	Without RV dysfunction, % (95% CI)
Early all-cause mortality	RV pressure overload (echo/CTPA)	1597 (7)	1.8 (0.9–3.5)	0.2 (0.03–1.7)
	Troponin	1176 (11)	3.8 (2.1–6.8)	0.5 (0.2–1.3)
	BNP/NT-proBNP	—	—	—
Early PE-related adverse outcome	RV pressure overload (echo/CTPA)	1488 (6)	3.7 (0.9–14.4)	0.7 (0.06–6.4)
	Troponin	1137 (8)	10.2 (7.2–14.3)	0.6 (0.1–5.6)
	BNP/NT-proBNP	1405 (6)	5.4 (1.8–14.6)	1.3 (0.6–2.6)

Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910

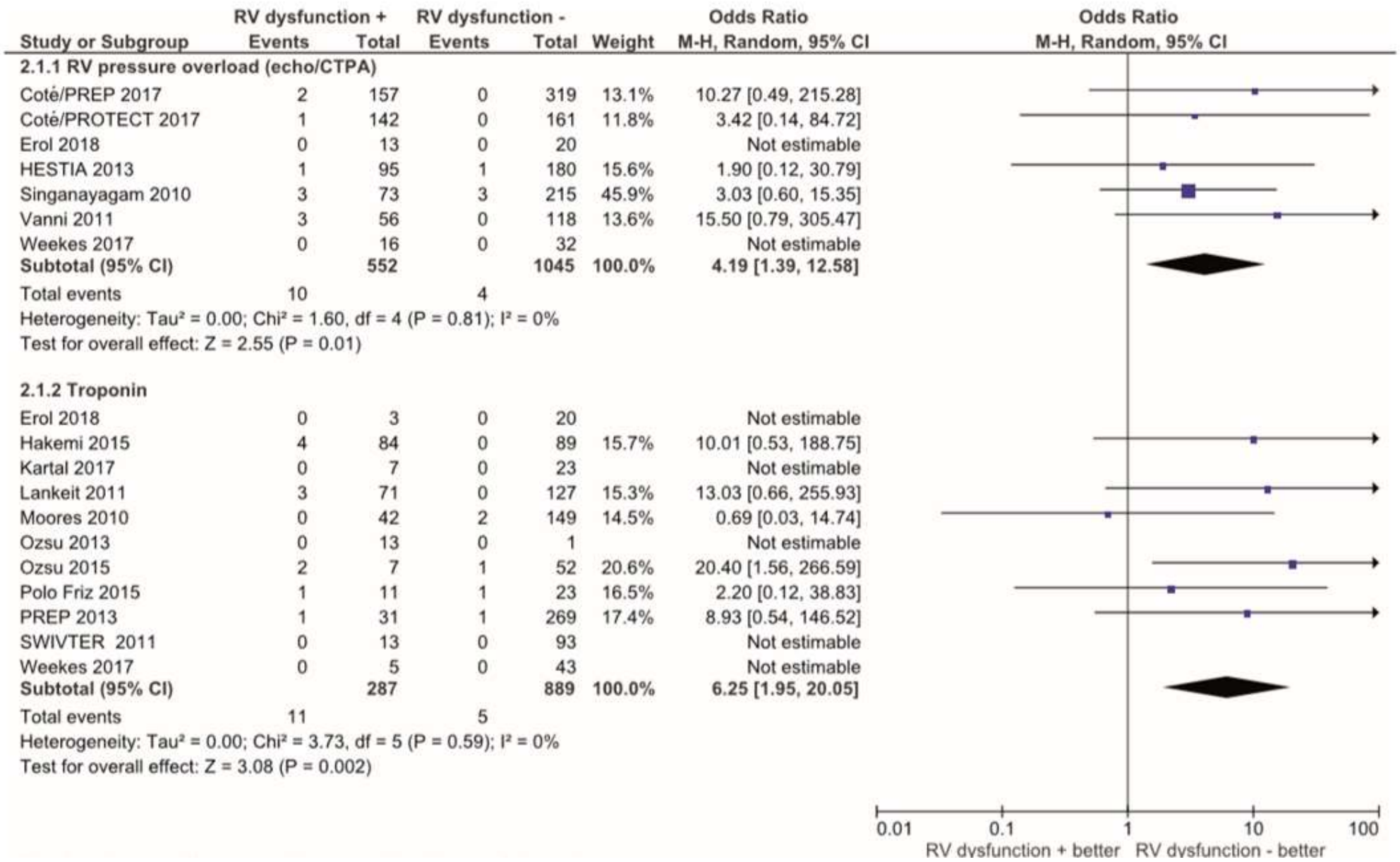
EARLY PE RELATED MORTALITY

PARAMETERS	POSITIVE (95% CI)	NEGATIVE
RV DYSFUNCTION	1.3% (CI- 0.5-3.1%)	0.02% (CI- 0.01-21.4%)
TROPONIN LEVELS	1.3% (CI- 0.3-5.4%)	0.4% (CI- 0.1-2%)
ProBNP/NT-ProBNP	1.7% (CI- 0.4-6.9%)	0.4% (CI- 0.1-1.1%)

Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910

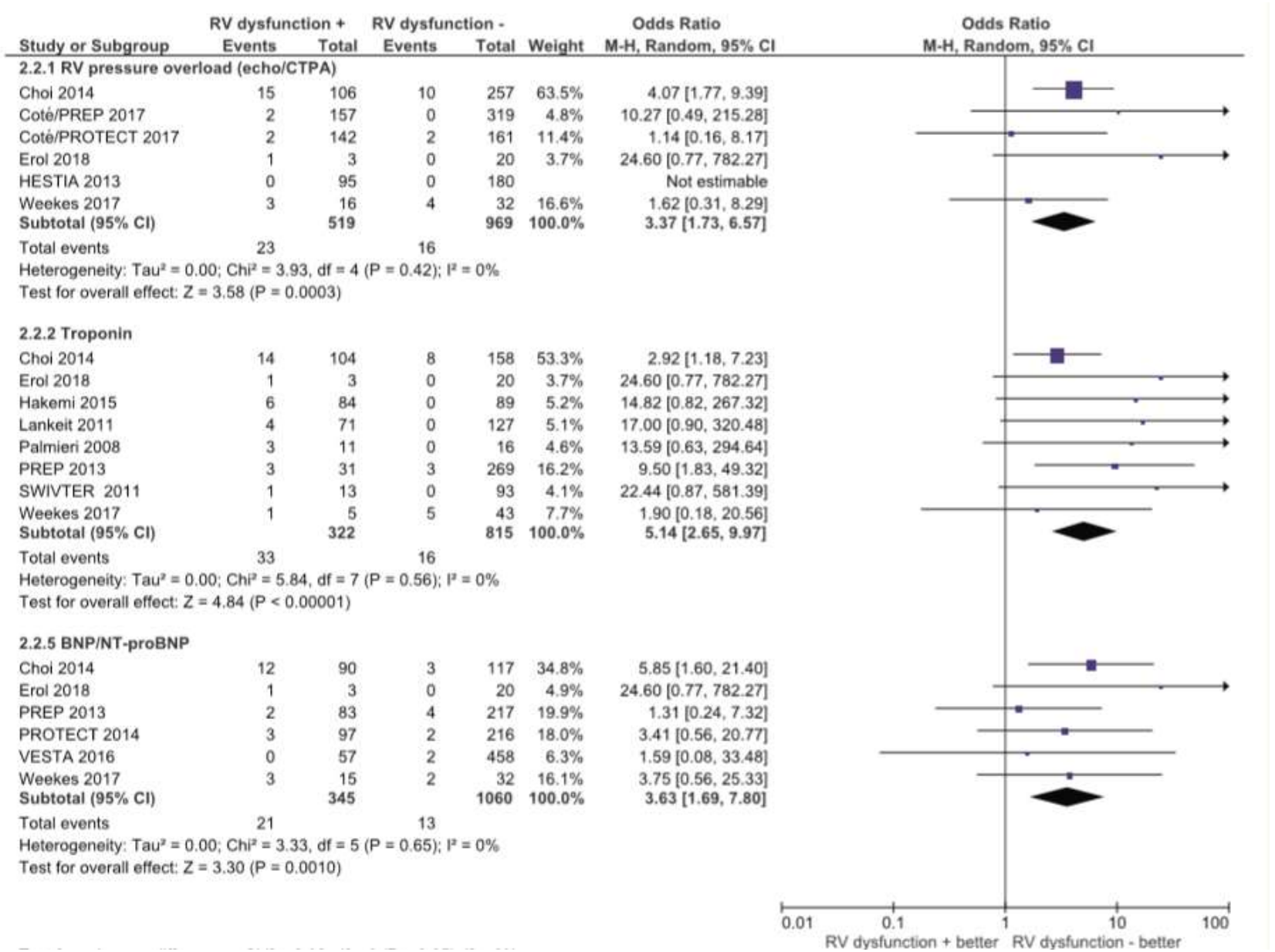


Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910



Prognostic value of imaging and laboratory indicators of right ventricular dysfunction or myocardial injury for early all-cause mortality in low-risk patients

Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910



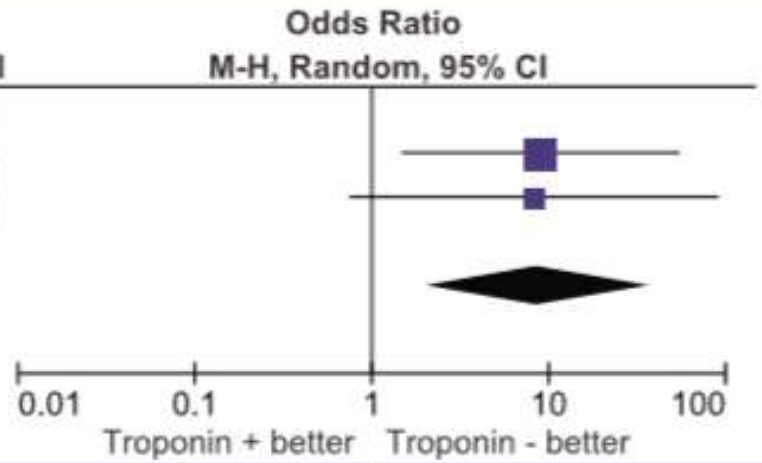
Prognostic value of imaging and laboratory indicators of right ventricular dysfunction or myocardial injury for early pulmonary embolism related adverse outcome in low-risk patients

Barco et al. RV dysfunction in low risk PE European Heart Journal (2019) 40, 902–910

PROGNOSIS RELATED TO 3 MTHS MORTALITY

Study or Subgroup	Troponin + Events	Total	Troponin - Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Erol 2018	0	3	0	20		Not estimable
Ozsu 2015	3	7	4	52	63.8%	9.00 [1.47, 55.07]
Polo Friz 2015	3	11	1	23	36.2%	8.25 [0.75, 91.26]
Total (95% CI)		**21**		**95**	**100.0%**	**8.72 [2.05, 37.05]**
Total events	6		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)



STUDIES	POPULATION	INTERVENTION	COMPARISON	OUTCOME
Polo Friz et al Retrospective	470	hscTnT	PESI	Adding troponin testing does improve sPESI ability to predict mortality in elderly patients
Ozsu et al Retrospective	489	Cardiac troponin Echo	Shock index	Shock index and cardiac troponin Can used in combination for determination of intermediate risk in PE

1. Polo Friz *et al.* Mortality at 30 and 90 days in elderly patients with pulmonary embolism. *Intern Emerg Med* **10,** 431–436 (2015)
2. S. Ozsu et al. Classification of high-risk with cardiac troponin and shock index in normotensive patients. J Thromb Thrombolysis 2016

EURO GUIDELINES 2019

Recommendations	Class[a]	Level[b]
Initial risk stratification of suspected or confirmed PE, based on the presence of haemodynamic instability, is recommended to identify patients at high risk of early mortality.[218,219,235]	I	B
In patients without haemodynamic instability, further stratification of patients with acute PE into intermediate- and low-risk categories is recommended.[179,218,219,235]	I	B
In patients without haemodynamic instability, use of clinical prediction rules integrating PE severity and comorbidity, preferably the PESI or sPESI, should be considered for risk assessment in the acute phase of PE.[178,226,229]	IIa	B
Assessment of the RV by imaging methods[c] or laboratory biomarkers[d] should be considered, even in the presence of a low PESI or a negative sPESI.[234]	IIa	B
In patients without haemodynamic instability, use of validated scores combining clinical, imaging, and laboratory PE-related prognostic factors may be considered to further stratify the severity of the acute PE episode.[218–223]	IIb	C

ESC Guidelines, European Heart Journal (2019)

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

- Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I-II or an sPESI of 0.
- Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

ESC Guidelines, European Heart Journal (2019)

QUESTIONS TO BE ANSWERED??

1. Role of fibrinolytics therapy in patients with intermediate risk pulmonary embolism??

2. Role of fibrinolytic therapy in reduction of pulmonary artery pressure in sub massive pulmonary embolism??

3. Consideration for potential complications associated with thrombolysis?

The Pulmonary Embolism Thrombolysis (PEITHO) trial

- Multicenter, double-blind, placebo controlled randomized trial
- COHORT - 1006 patients
- DESIGN - Comparison of tenecteplase plus heparin with placebo plus heparin in normotensive patients with intermediate-risk pulmonary embolism

PEITHO – INCLUSION CRITERIA

- Age ≥ 18 years
- Acute PE (first symptoms occurring 15 days or less before randomisation) confirmed by echo or CT chest and myocardial injury confirmed by positive test for troponin I and troponin T

THE PEITHO trial. N Engl J Med 2014;370:1402-11

EXCLUSION CRITERIA

- Uncontrolled BP (systolic BP > 180 mm of Hg and/or diastolic BP >110 mm of Hg)
- Known hypersensitivity to tenecteplase, alteplase, UFH
- Pregnancy, lactation or parturition within previous 30 days
- Known coagulation disorders
- Hemodynamic collapse at presentation
- Known significant bleeding risk
- Administration of thrombolytic agent within previous 4 days
- Vena cava filter insertion or pulmonary thrombectomy within previous 4 days

THE PEITHO trial. N Engl J Med 2014;370:1402-11

CRITERIA FOR RV DYSFUNCTION

Atleast one of the following echocardiographic criteria:

- Right ventricular end diastolic diameter (RVEDD) >30mm (parasternal long or short axis)
- RVEDD/LVEDD > 0.9 (apical or subcoastal view)
- Hypokinesia of RV free wall (any view)
- Tricuspid systolic velocity >2.6 m/s from apical or subcoastal 4 chamber view

OR

CT – Minor axis of right and left ventricle in transverse plane and calculating RVd/LVd ratio (ratio > 0.9 denotes RVD)

THE PEITHO trial. N Engl J Med 2014;370:1402-11

TROPONIN I OR T TESTING

- Criteria for positive cardiac troponin test:

  Troponin I (ng/ml)

  Centaur, Bayer > 0.06

  Axsym, Abbott > 0.06

  Troponin T (ng/ml)

  Elecsys, Roche > 0.04

THE PEITHO trial. N Engl J Med 2014;370:1402-11

Randomization within 2 hours of RV dysfunction detection

Single weight based iv bolus of tenecteplase

Weight (kg)	Dose (mg)	Dose (units)	Volume (mL)
<60	30	6000	6
≥60 to <70	35	7000	7
≥70 to <80	40	8000	8
≥80 to <90	45	9000	9
≥90	50	10,000	10

Heparin infusion rate was adjusted to achieve and maintain aPTT – 2-2.5 upper limit of normal

Initial heparin bolus immediately after randomization in both groups

- Not given to patients who already received a bolus or infusion of UFH
- Use of anticoagulant agent other than UFH was not allowed until 48hrs after randomization

THE PEITHO trial. N Engl J Med 2014;370:1402-11

Characteristic	Tenecteplase (N=506)	Placebo (N=499)
Demographic data		
Age — yr		
Mean	66.5±14.7	65.8±15.9
Median (interquartile range)	70.0 (59.0–77.0)	70.0 (57.0–78.0)
Male sex — no. (%)	242 (47.8)	231 (46.3)
Mean weight — kg	82.5±17.9	82.6±18.2
Clinical status		
Systolic blood pressure — mm Hg	130.8±18.3	131.3±18.5
Missing data — no. (%)	3 (0.6)	4 (0.8)
Heart rate — beats per min	94.5±17.1	92.3±16.7
Missing data — no. (%)	6 (1.2)	7 (1.4)
Respiratory rate — breaths per min	21.8±5.8	21.6±5.7
Missing data — no. (%)	95 (18.8)	107 (21.4)
Oxygen treatment — no. (%)	436 (86.2)	421 (84.4)
Medical history		
Chronic pulmonary disease — no. (%)	26 (5.1)	34 (6.8)
Missing data	6 (1.2)	6 (1.2)
Chronic heart failure — no. (%)	21 (4.2)	26 (5.2)
Missing data	5 (1.0)	7 (1.4)
Previous venous thromboembolism — no. (%)	126 (24.9)	147 (29.5)
Missing data	2 (0.4)	9 (1.8)
Active cancer — no. (%)	41 (8.1)	32 (6.4)
Missing data	20 (4.0)	20 (4.0)
Surgery or major trauma in previous month — no. (%)	31 (6.1)	27 (5.4)
Missing data	1 (0.2)	4 (0.8)
Immobilization — no. (%)	55 (10.9)	56 (11.2)
Missing data	5 (1.0)	9 (1.8)
Estrogen use — no. (%)	30 (5.9)	33 (6.6)
Missing data	7 (1.4)	5 (1.0)

DIAGNOSTIC EVALUATION AND INITIAL MANAGEMENT

Characteristic	Tenecteplase (N=506)	Placebo (N=499)
	no. (%)	
Confirmation of pulmonary embolism		
CT	480 (94.9)	472 (94.6)
Ventilation–perfusion lung scanning	31 (6.1)	35 (7.0)
Pulmonary angiography	6 (1.2)	8 (1.6)
Confirmation of right ventricular dysfunction		
Echocardiography	278 (54.9)	255 (51.1)
CT	74 (14.6)	72 (14.4)
Both echocardiography and CT	154 (30.4)	172 (34.5)
Confirmation of myocardial injury		
Elevated cardiac troponin I	364 (71.9)	361 (72.3)
Elevated cardiac troponin T	164 (32.4)	164 (32.9)
Either troponin I or troponin T elevation	502 (99.2)	494 (99.0)
Low-molecular-weight heparin or fondaparinux given before randomization	170 (33.6)	133 (26.6)

EFFICACY OUTCOME

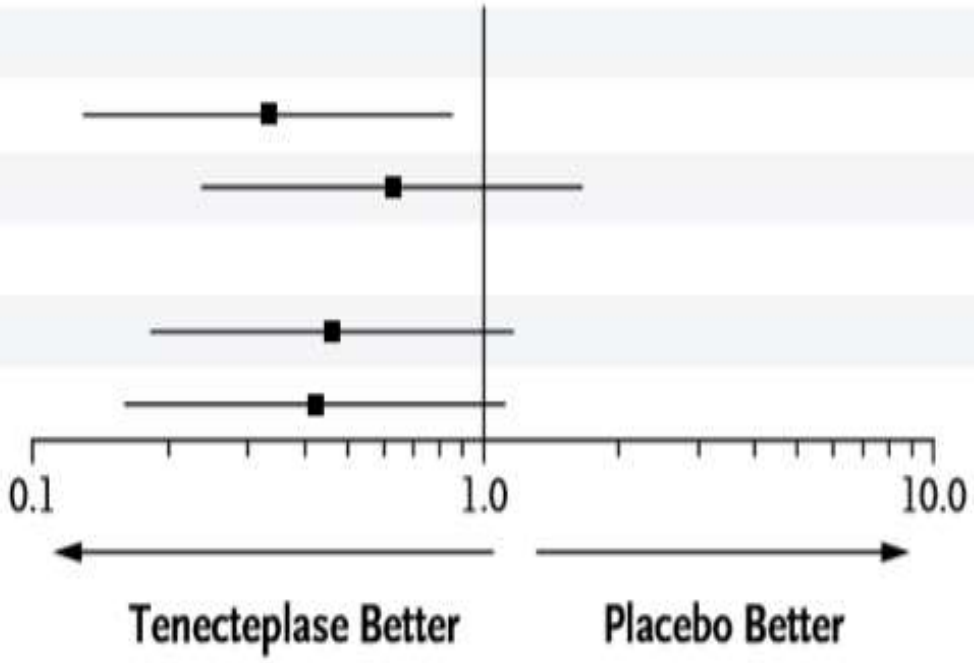
23 patients in placebo group underwent open label rescue fibrinolytics and 2 in tenecteplase

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

SUBGROUP ANALYSIS OF PRIMARY OUTCOME

Death or Hemodynamic Decompensation

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.36
≤75 yr	6/344 (1.7)	17/335 (5.1)	0.33 (0.13–0.85)	
>75 yr	7/162 (4.3)	11/164 (6.7)	0.63 (0.24–1.66)	
Sex				0.90
Male	7/242 (2.9)	14/231 (6.1)	0.46 (0.18–1.16)	
Female	6/264 (2.3)	14/268 (5.2)	0.42 (0.16–1.12)	



THE PEITHO trial. N Engl J Med 2014;370:1402-11

CONCLUSION

- Prompt fibrinolysis reduce risk of hemodynamic decompensation or death in normotensive patients with RV dysfunction as indicated by ECHO or CT and MI (positive cardiac troponin)

PE AND CTEPH

- ALL COMERS - All patients with symptomatic PE
- SURVIVORS - Patients with symptomatic PE alive after initial treatment period of 6 months
- SURVIVORS WITHOUT MAJOR COMORBIDITY - Patients with symptomatic PE who were alive after initial treatment period of 6 months and did not have predefined significant cardiopulmonary, oncologic or rheumatologic comorbidities

PE AND CTEPH

- Incidence – 0.1% - 11.8%

Physiologic abnormality	Percentage of outflow obstruction
Widened A-a gradient	10
Pulmonary hypertension	30
Compromised cardiac output	50
Shock, cardiovascular collapse	75

Dieck et al. Thrombolysis in Pulmonary Embolism.Texas Heart Institute Journal 1989;16:19-26

EVIDENCE

STUDIES	POPULATION	STUDY TYPE/	FOLLOW UP	OUTCOME
ALL COMERS				
Miniati et al	320	Prospective Single	0-4.8 years	PE with vascular obstruction >50% is strong predictor of short term survival
Klok et al	866	Prospective Multiple	34 months	Incidence – 0.57% (all cause PE) Unprovoked PE – 1.5%
SURVIVORS				
Held et al	130	Prospective/ Single	3-6 mths	37.7%, 25.5% and 29.3% patients symptomatic after 3, 6, and 12 months. 20.4%, 11.5% and 18.8% of patients at 3, 6 and 12 mths echocardiography of PH

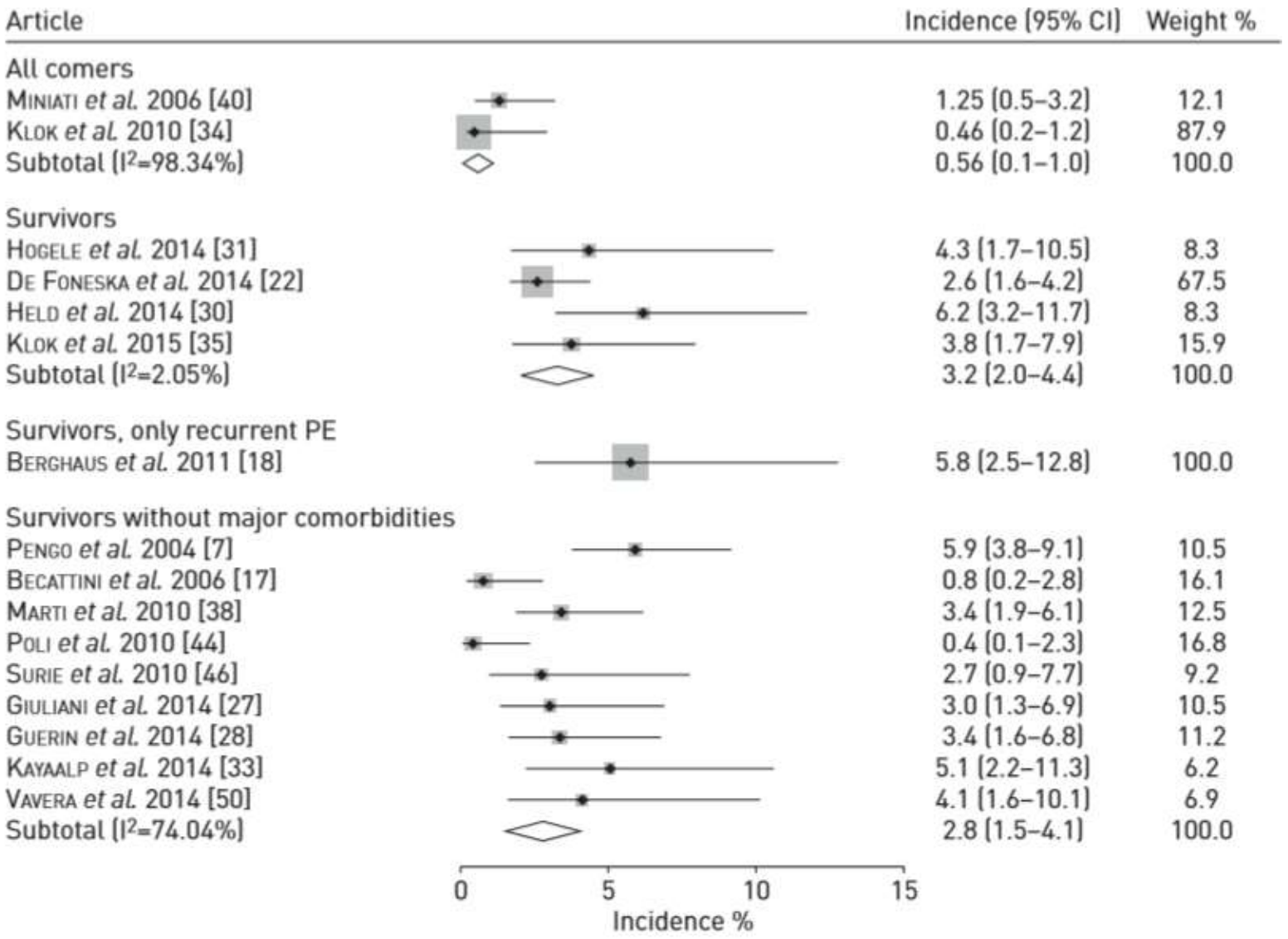
Minniati et al. Long-Term Survival After Acute Pulmonary Embolism. Medicine 2006;85:253–262
Klok et al. The incidence of CTEPH after acute PE. Haematologica 2010; 95
Held et al. BMC Pulmonary Medicine 2014, 14:141

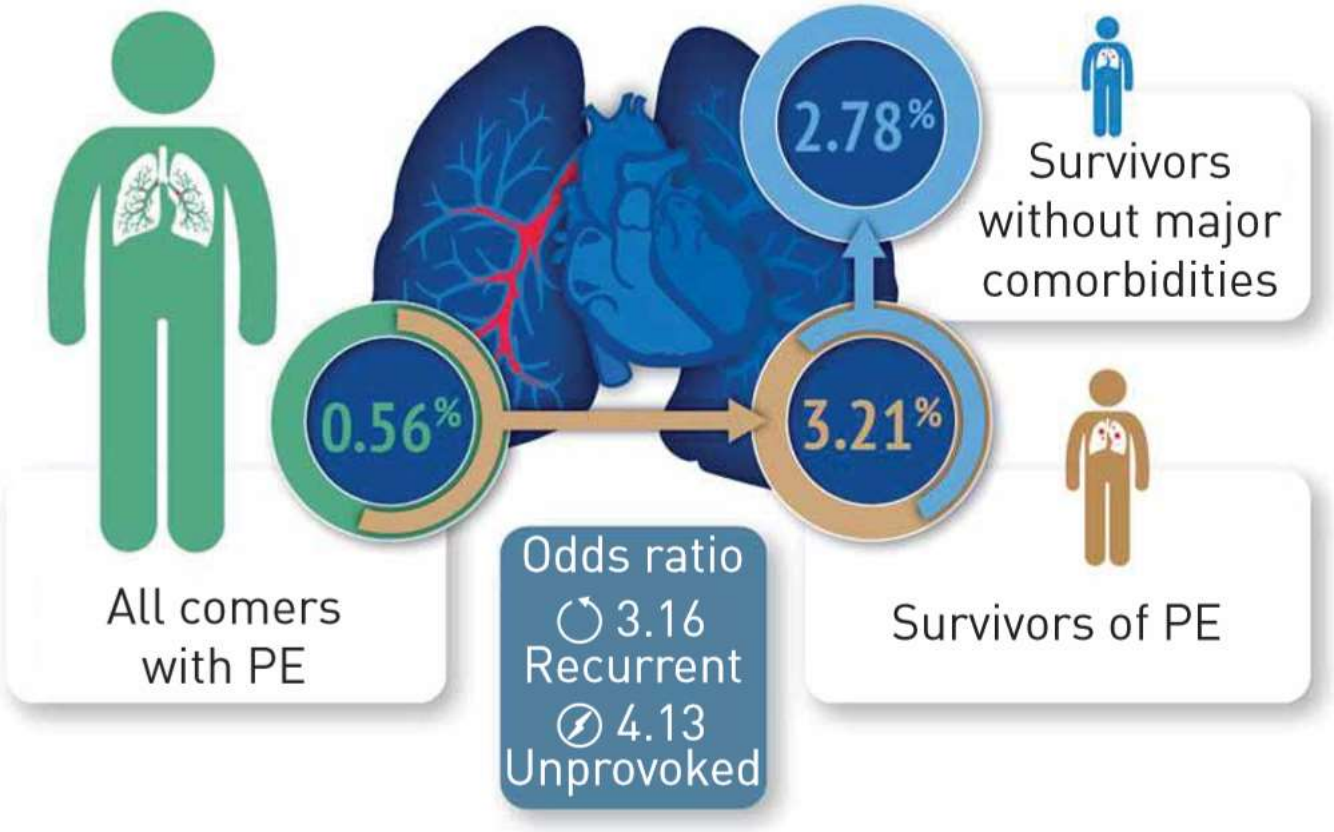
EVIDENCE

STUDIES	POPULATION	STUDY TYPE/	FOLLOW UP	OUTCOME
Klok et al	160	Prospective/ Single	7 mths	ECHO based CTEPH rule out criteria – high sensitivity
De Foneska et al	616	Retrospective/ Single	3 years	Overall diagnostic rate – 2.6%
SURVIVORS WITHOUT MAJOR COMORBIDITIES				
Becattini et al	259	Prospective Multi	46 mths	Incidence of CTEPH – 1%
Guerin et al	208	Prospective Multiple	26 months	Incidence of CTEPH – 4.8%
Marti et al	294	Prospective/ Single	24 mths	Incidence of 9.4%

Klok et al. External validation of CTEPH rule out criteria. Thrombosis Research 2014
Becattini, Incidence of CTEPH. CHEST 2006; 130:172–175
Guérin et al. Prevalence of CTEPH after PE. Thromb Haemost 2014; 112: 598–605
D. Martí et al / Arch Bronconeumol. 2010;46(12):628-633

METAANALYSIS OF INCIDENCE OF CTEPH BY RIGHT HEART CATHETERISATION





Overall pooled incidence of CTEPH - 2.3%

Unprovoked PE and recurrent VTE - strong risk factors for development of CTEPH

Long-term benefit of thrombolytic therapy in patients with pulmonary embolism

Multicentre, randomized study of 40 patients

Hemodynamic studies done in 23 patients

(Heparin -11 and thrombolytics – 12)

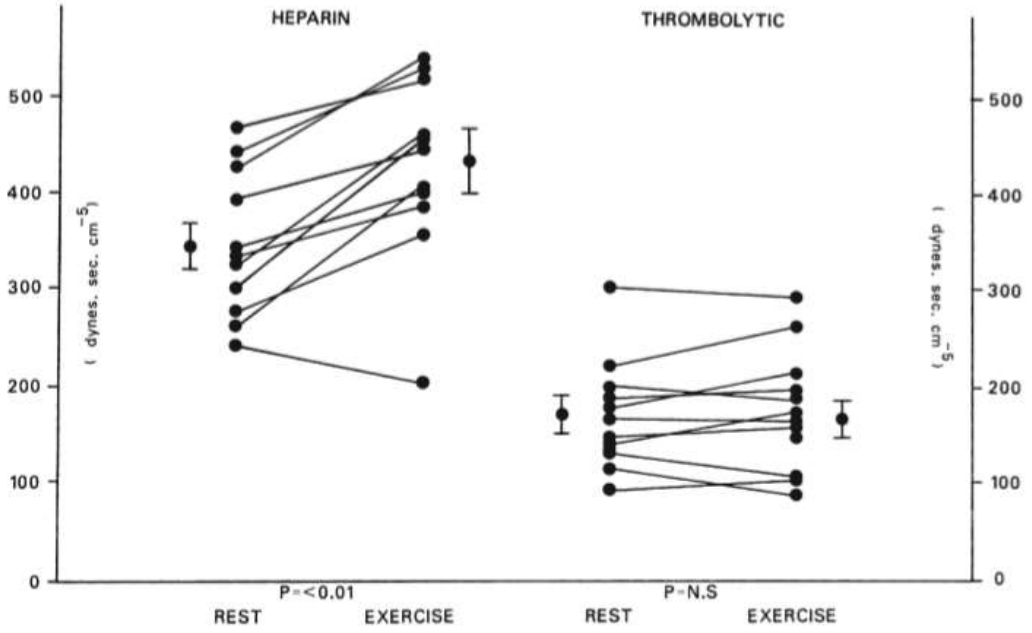
Event	Anticoagulation (n = 21)	Lytic therapy (n = 19)
Deep vein thrombosis	8/21 (38.1%)	3/19 (15.8%)*
Recurrent PE	4/21 (19.0%)	2/19 (10.5%)*
Death from recurrence	2/7 (28.6%)	0/3 (0%)
IVC	6/21 (28.6%)	2/19 (10.5%)*
Symptoms (NYHA class II or greater)	8/11 (72.7%)	4/12 (33.3%)*

In 12 patients -received urokinase or streptokinase, mean pulmonary artery pressure decreased from 28 to 17 mm of Hg in 7.5yrs

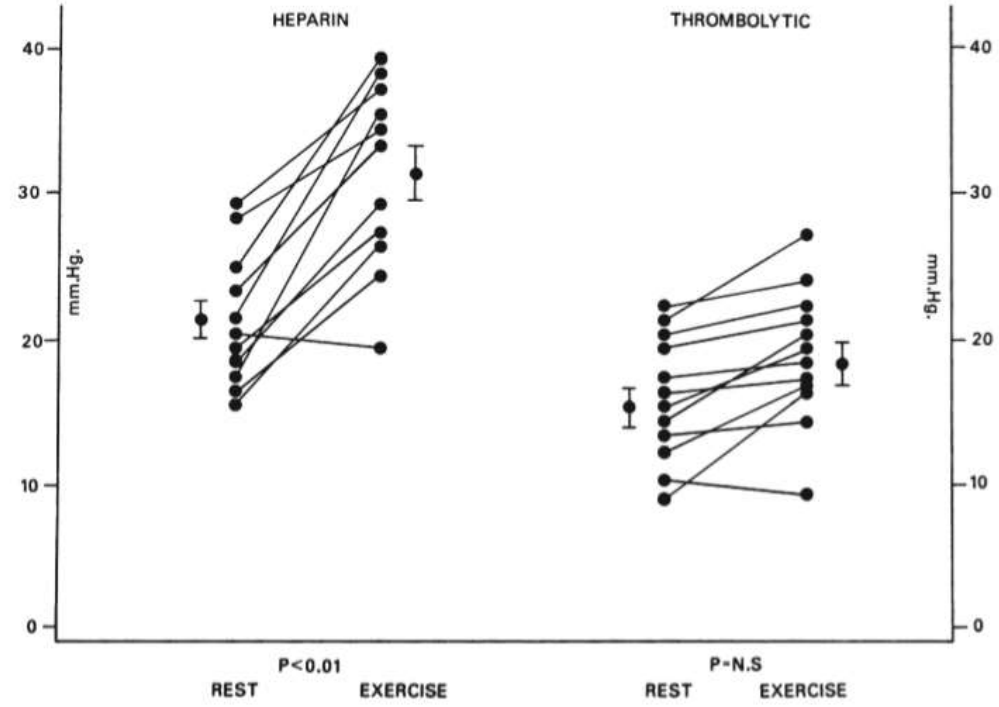
In 11 patients – Heparin group – 26 to 22 mm of Hg in 7.3yrs

GVRK Sharma et al. Vascular Medicine

Long-term benefit of thrombolytic therapy in patients with pulmonary embolism



Effect of exercise on pulmonary vascular resistance



Effect of exercise on pulmonary artery mean pressure

GVRK Sharma et al. Vascular Medicine 2000

CHEST Original Research
PULMONARY HYPERTENSION

Prospective Evaluation of Right Ventricular Function and Functional Status 6 Months After Acute Submassive Pulmonary Embolism

Frequency of Persistent or Subsequent Elevation in Estimated Pulmonary Artery Pressure

PROSPECTIVE STUDY

Cohort -162 Normotensive, CT proven PE patients

Heparin group – 144

Heparin plus alteplase – 18 patients

In Heparin group, RVSP at follow up was higher than baseline in 27% patients with 46% having NHYA score ≥ 3 and 6MWD < 330 mts

In Heparin and alteplase patients, only 11% had RVSP ≥ 40 mm of Hg and none of them had pressure higher than baseline

Kline et al. CHEST 2009

MOPPET

- MOPPET – Moderate Pulmonary Embolism Treated with Thrombolysis
- Prospective, randomized, single center open study
- Introduced concept of low dose thrombolysis
- Dose < 50% of standard dose (100 mg)

RATIONALE: Exquisitely favourable pulmonary response as lungs receive entire cardiac output

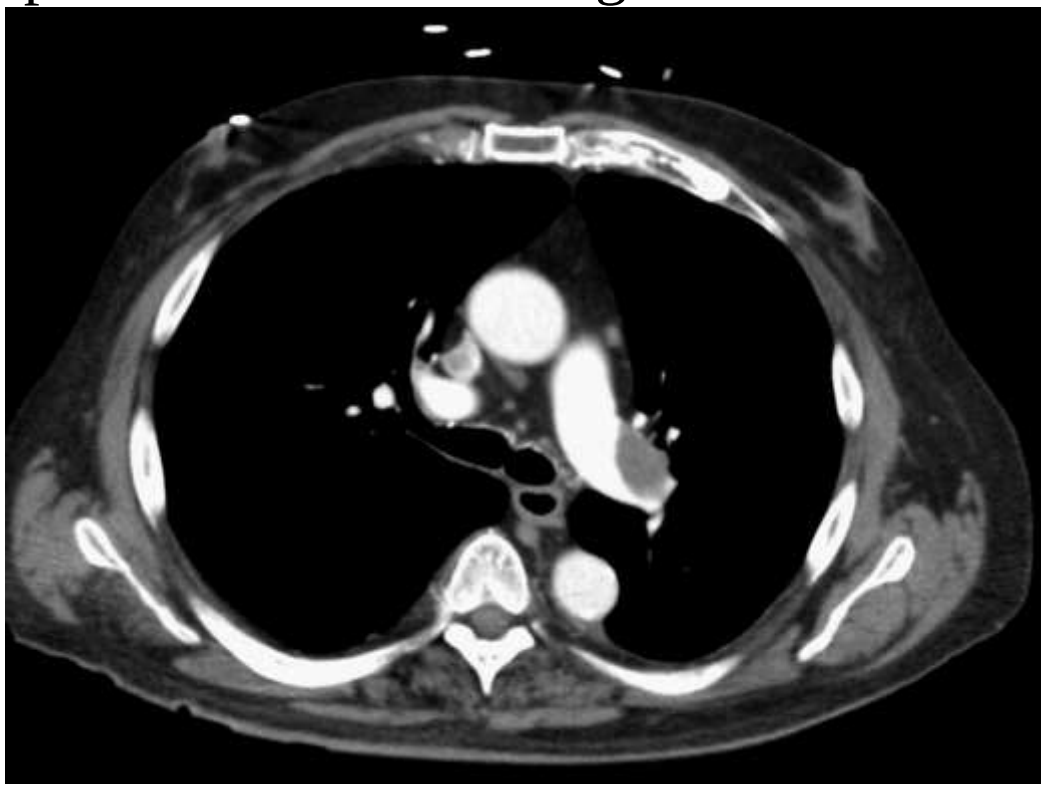
MOPPET TRIAL

Evidence derived from existing guidelines, tPA dose is same as for systemic arterial circulation

- Coronary thrombus – 100mg of tPA – 5% of cardiac output } ROUTE
- Ischemic stroke – 0.9mg/kg of tPA – 15% of cardiac output } ATTRITION

MODERATE PE

- Defined as presence of signs and symptoms of PE plus CT pulmonary angiographic involvement of >70% involvement of thrombus in ≥ 2 lobar or left or right main pulmonary arteries or by high probability ventilation/perfusion scan showing ventilation perfusion mismatch in ≥ 2 lobes



The “MOPETT” Trial. Am J Cardiol 2013

INCLUSION CRITERIA

Minimum of ≥2 new signs and symptoms :

- Chest pain
- Tachypnea (RR at rest ≥22 breaths/min)
- Tachycardia (heart rate at rest ≥90 beats/min)
- Dyspnea
- Cough
- Oxygen desaturation (oxygen partial pressure <95%)
- Elevated jugular venous pressure ≥12 cm H2O
- RV enlargement or hypokinesia and elevation of biomarkers of RV injury -troponin I and brain natriuretic peptide not a requirement for enrollment

The “MOPETT” Trial. Am J Cardiol 2013

EXCLUSION CRITERIA

- Onset of symptoms >10 days
- More 8 hours since the start of parenteral anticoagulation
- SBP <95 or >200/100 mm Hg
- Eligibility for full-dose thrombolysis
- Contraindication to UFH or LMWH
- Severe thrombocytopenia (platelet count <50,000/mm3)

The “MOPETT” Trial. Am J Cardiol 2013

EXCLUSION CRITERIA

- Major bleeding within <2 months requiring transfusion
- Surgery or major trauma within <2 weeks
- Brain mass; neurologic surgery, intracerebral hemorrhage, or subdural hematoma within <1 year
- End-stage illness
- Inability to perform echocardiography because of chest deformities, bandages, or catheters

The “MOPETT” Trial. Am J Cardiol 2013

Echocardiography within 2hrs of randomization and before tPA administration
Repeated at 24 to 48hrs after and at 6 months interval

↓

Pulmonary artery systolic pressure (PASP) estimated from Tricuspid valve regurgitant jet velocity
Cut off - ≥ 40mm of Hg

↓

Using modified Bernoulli equation – 4v2 + RAP (Right atrial pressure)

Right atrial enlargement	Right atrial pressure	4 chamber view RA/LA (max. diameter)
	5mm of Hg	RA < LA
Mild	10mm of Hg	1-1.2
Moderate	15mm of Hg	1.3-1.5
Severe	18mm of Hg	>1.5 Diameter of IVC ≥2.5 cms – 18mm of Hg

The “MOPETT” Trial. Am J Cardiol 2013

DOSE OF ANTICOAGULANTS

TENECTEPLASE GROUP

- Either UFH or enoxaparin (preferred)
- Enoxaparin – 48 of 61 (79%)
- Dose – 1mg/kg s/c BD
- Initial dose – 80 mg

HEPARIN ONLY GROUP

- UFH in case of renal insufficiency or patient preference
- Enoxaparin – 49 of 60 (81%)
- Dose – 1mg/kg s/c BD
- Initial dose – 80 mg

The “MOPETT” Trial. Am J Cardiol 2013

DOSE OF ANTICOAGULANTS

TENECTEPLASE GROUP

- UFH – 70U/kg as bolus (not exceeding 6000U) with subsequent dose adjustment for aPTT – 1.5-2 of baseline
- Infusion rate – 10U/kg/hr

HEPARIN ONLY GROUP

- UFH – 80U/kg as bolus (not exceeding 6000U) with subsequent dose adjustment for aPTT – 1.5-2 of baseline
- Infusion rate – 18U/kg/hr

The “MOPETT” Trial. Am J Cardiol 2013

USUAL PROTOCOL OF UFH

Initial dose	80 units/kg bolus, then 18 units/kg per hour*	
aPTT result	**Action**	**Next aPTT Δ**
aPTT <35 seconds (<1.2 x control)	80 units/kg bolus, then increase infusion rate by 4 units/kg per hour	6 hours
aPTT 35 to 45 seconds (1.2 to 1.5 x control)	40 units/kg bolus, then increase infusion rate by 2 units/kg per hour	6 hours
aPTT 46 to 70 seconds ¶ (1.5 to 2.3 x control)	No change (therapeutic range)	6 hours (when two consecutive values are within therapeutic range, then next aPTT in morning)
aPTT 71 to 90 seconds (2.3 to 3.0 x control)	Decrease infusion rate by 2 units/kg per hour	6 hours
aPTT >90 seconds (>3.0 x control)	Hold infusion 1 hour, then decrease infusion rate by 3 units/kg per hour	6 hours

SAFE DOSE THROMBOLYSIS

Weight ≥ 50kgs – Total dose – 50 mg

Bolus – 10 mg (IV bolus in 1min)

followed by 40 mg infusion over 2 hrs

Weight < 50kgs – Total dose – 0.5mg/kg

WARFARIN STARTED IN ALL PATIENTS AT ADMISSION

The “MOPETT” Trial. Am J Cardiol 2013

BASELINE CHARACTERISTICS

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Men	28 (46%)	27 (45%)	0.92
Age (yrs)	58 ± 9	59 ± 10	0.56
Weight (kg)	84 ± 14	83 ± 13	0.68
Previous or concomitant disease			
Hypertension	32 (52%)	31 (52%)	0.93
Diabetes mellitus	23 (38%)	25 (40%)	0.66
Cardiovascular	35 (57%)	37 (62%)	0.80
Hypercholesterolemia*	27 (33%)	25 (30%)	0.77
Pulmonary	22 (36%)	25 (42%)	0.53
Renal	8 (13%)	9 (15%)	0.77
Current smoker	12 (20%)	15 (25%)	0.48
Unprovoked pulmonary embolism	28 (46%)	27 (45%)	0.92
Estrogen therapy	6 (10%)	7 (12%)	0.75
Cancer			
Active	8 (13%)	9 (15%)	0.77
History	3 (5%)	3 (5%)	0.98
Known prothrombotic state	6 (10%)	5 (8%)	0.77
Previous venous thromboembolism	13 (21%)	12 (20%)	0.86
Concomitant deep venous thrombosis	35 (57%)	33 (55%)	0.79

END RESULTS

PRIMARY END POINTS (at 28± 5 mths follow up)	Tenecteplase group (n = 58, 100%)	Control group (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

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END RESULTS

SECONDARY END POINTS	Tenecteplase group (n = 61, 100%)	Control group (n = 60, 100%)	p value
Recurrent Pulmonary embolism	0	3 (5%)	0.08
Total mortality	1 (1.6%)	3 (5%)	0.3
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	

The “MOPETT” Trial. Am J Cardiol 2013

DIFFERENCE IN PASP

TIMING	Pulmonary artery systolic pressure (mm Hg)				p value
	Tenecteplase group		Control group		
On admission	50±6		51± 7		0.4
Within 48 hrs	34±7		41± 4		<0.001
6 months	31 ± 6		49± 8		<0.001
28 ± 5 mths	28±7		43±6		<0.001

The “MOPETT” Trial. Am J Cardiol 2013

SIDE EFFECTS OF THROMBOLYSIS

STUDIES	POPULATION	INTERVENTION	COMPARATOR	OUTCOME
Konstantinides *et al* Multicenter registry	Normotensive - 719 patients with major PE	Thrombolytics	Heparin alone	Major bleeding rate of 21.9% as compared to 7.8%
Konstantinides *et al* Randomized trial	Submassive PE - 256	Thrombolytics (Alteplase)	Heparin alone	Major bleeding in thrombolysis group – 0.8% with no intracerebral haemorrhage or fatal bleeding Treatment with heparin plus placebo was associated with 3 times risk of death or treatment escalation
ICOPER registry Prospective	PE	-	-	Incidence of intracerebral haemorrhage – 3%
Kanter *et al* Retrospective	Hospitalised PE - 312	-	-	Frequency of ICH – 1.9%
Dalen *et al* Literature review	559 PE patients	-	-	Frequency of ICH 2.1%

DATA FROM PEITHO

	Tenecteplase (n-502)	Placebo	Odds ratio	P value
BLEEDING BETWEEN RANDOMIZATION AND DAY 7				
Major bleeding	31 (6.2)	5 (1.0)	6.5 (2.51-16.86)	<0.001
ISTH major bleeding	57 (11.4)	11 (2.2)		
STROKE BETWEEN RANDOMIZATION AND DAY 7	12 (2.4)	1 (0.2)	12.17 (1.58-93.96)	0.002
Ischemic stroke	2	0		
Hemorrhagic stroke	10	1		

THE PEITHO TRIAL. N Engl J Med 2014;370:1402-11

DATA FROM MOPPET

- No major or minor bleeding in any patient
- Likely Reason:

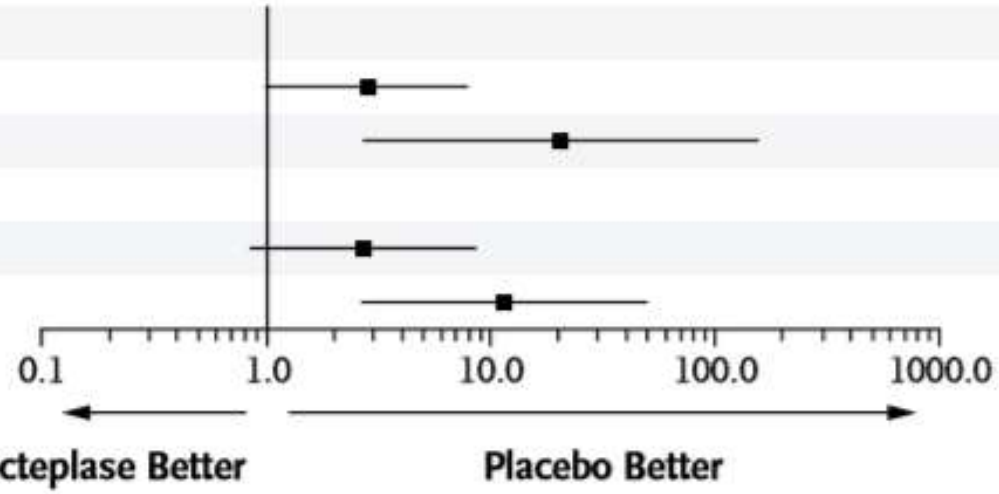
- Modification of parenteral anticoagulation
- Targetted lower aPTT of 1.5-2 times baseline
- Safe dose thrombolysis

EFFECT – Intense fluctuations in aPTT which is noted during first 1 to 2 days is eliminated

SUBGROUP ANALYSIS

B Major Extracranial Bleeding

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.09
≤75 yr	14/344 (4.1)	5/335 (1.5)	2.80 (1.00–7.86)	
>75 yr	18/162 (11.1)	1/164 (0.6)	20.38 (2.69–154.53)	
Sex				0.13
Male	11/242 (4.5)	4/231 (1.7)	2.70 (0.85–8.61)	
Female	21/264 (8.0)	2/268 (0.7)	11.49 (2.67–49.53)	



THE PEITHO trial. N Engl J Med 2014;370:1402-11

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

Event	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value
	no./total no. (%)		
Total strokes	15/939 (1.6)	5/946 (0.5)	0.03
Intracranial hemorrhage			
Any	9/939 (1.0)	2/946 (0.2)	0.04
After protocol amendment*	4/747 (0.5)	2/758 (0.3)	0.45
Primary ischemic stroke			
Without hemorrhagic conversion	5/939 (0.5)	3/946 (0.3)	0.51
With hemorrhagic conversion	1/939 (0.1)	0/946	0.50
Nonintracranial bleeding			
Major	61/939 (6.5)	45/944 (4.8)	0.11
Minor	205/939 (21.8)	191/944 (20.2)	0.40
Blood transfusion	27/937 (2.9)	22/943 (2.3)	0.47

CONCLUSION

- RV dysfunction in PE is associated with increased incidence of mortality
- Low dose thrombolysis should be considered in patients with intermediate risk PE
- CTEPH is an important complication of PE which should be adequately addressed