Penn Medicine

VEITH SYMPOSIUM 2024

Intravenous Thrombolytic Therapy For PE: Why, When and At What Dose

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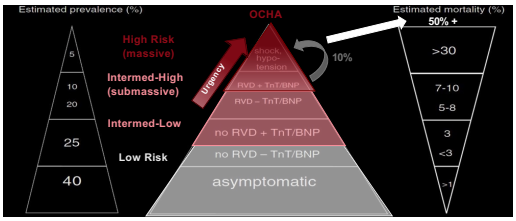
Disclosures

NONE

Learning Objectives

- HOW TO MAKE THE DECISION
- DOSING AND OTHER CONSIDERATIONS
- CONTEMPORARY PRACTICE PATTERNS & FUTURE DIRECTIONS

Risk Stratification



Insights Imaging 2011;2:705; EHJ 2014;35:3033.
Thromb Haemost. 2008;100:747.
Circulation 2000;101:2817 & 2011;123:1788

6.6 Recommendations for acute-phase treatment of high-risk pulmonary embolism[1]

Recommendations	Class[a]	Level[b]
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. [182]	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[c] [185]	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[c]	IIa	C
Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.	IIa	C
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.[d] [352]	IIb	C

ESC European Society of Cardiology

Guidelines

Class I LOE B recommendations in high risk PE

Widely available, easy administration

Only recommendation with a LOE B designation
- Single RCT, 8 patients
- Extrapolated from intermediate risk patients

Risk Factors for Bleeding – When not to use

Major Contraindications	Relative Contraindications
Structural intracranial disease	SBP > 180, DBP > 110
Prior ICH	Recent non-intracranial bleeding
Recent ischemic stroke (3 mo)	Recent surgery/ invasive procedure
Active bleeding/ bleeding diathesis	Ischemic stroke > 3 mo
Recent brain/ spine surgery	Traumatic CPR
Recent head trauma	Pregnancy
	Age > 75, low body weight (< 60 kg)

Figure 2. Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

Source	Thrombolytics No. of Events	Thrombolytics No. of Patients	Anticoagulants No. of Events	Anticoagulants No. of Patients	OR (95% CI)	Weight, %
UPETSG,[28] 1970	6	82	7	78	0.80 (0.26-2.49)	20.2
Tibbutt et al,[26] 1974	0	13	1	17	0.17 (0.00-8.94)	1.6
Ly et al,[29] 1978	1	14	2	11	0.37 (0.03-3.96)	4.5
Martin et al,[30] 1988	0	20	0	10	Not estimable	
Levine et al,[22] 1990	1	33	0	25	5.80 (0.11-303.49)	1.6
PIOPED,[27] 1990	1	9	0	4	4.24 (0.06-296.20)	1.4
Dalla-Volta et al,[23] 1992	2	20	1	16	1.61 (0.15-16.82)	4.7
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)	3.3
Jerges-Sanchez et al,[24] 1995	0	4	4	4	0.03 (0.00-0.40)	3.8
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)	11.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)	1.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)	9.3
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)	6.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)	1.7
TOPCOAT,[7] 2014	1	40	1	43	1.08 (0.07-17.53)	3.3
PEITHO,[6] 2014	6	506	9	499	0.66 (0.24-1.82)	24.8
Total	23	1061	41	1054	0.53 (0.32-0.88)	100.0

Heterogeneity: $\chi^2_{14} = 16.51$; $P = .28$; $I^2 = 15\%$
Overall effect: $z = 2.45$; $P = .01$

Favors Thrombolytics | Favors Anticoagulants
0.005 0.1 1.0 10 200
OR (95% CI)

Chatterjee, et al. JAMA 2014

Figure 3. Odds of Mortality in Patients With Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

Source	Thrombolytics No. of Events	Thrombolytics No. of Patients	Anticoagulants No. of Events	Anticoagulants No. of Patients	OR (95% CI)	Weight, %
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)	5.3
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)	18.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)	2.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)	15.1
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)	10.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)	2.7
TOPCOAT,[7] 2014						
PE(THO),[6] 2014						
Total	1					

Favors Thrombolytics | Favors Anticoagulants

Heterogeneity: $\chi^2_{8} = 7.63$; $P = .37$; $I^2 = 8$
Overall effect: $z = 2.22$; $P = .03$

First Author/ Study	Year	Lytic Agent	No. Given Lytic	No. Given Placebo	Timing of Second Measurement, h	Fibrinolytic Treatment, mm Hg: Mean PAP (Pre)	Fibrinolytic Treatment, mm Hg: Mean PAP (Post)	Placebo, mm Hg: Mean PAP (Pre)	Placebo, mm Hg: Mean PAP (Post)
Tibbut[126]	1974	SK	11	12	72	30.8	18.5	34.3	29.6
PIOPED[127]	1990	tPA	9	4	1.5	28	25	33	33
Konstantinides[128]	1998	tPA	27	13	12	34	22	29	27
NHLBI[129]	1973	UK	82	78	24	26.2	20	26.1	25
Dalla-Volta[124]	1992	tPA	20	16	2	30.2	21.4	22.3	24.8
Mean (SD)						29.8 (3.0)	21.4 (2.4)	28.9 (4.9)	27.9 (3.5)

Chatterjee, et al. JAMA 2014
Jaff MR, et al. Circulation. 2011; 123: 1788-1830.

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 (%): Thrombolytic Group	Anticoagulant Group	No. Needed to Treat or Harm	*P* Value
★ 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

Chatterjee, et al. JAMA 2014

PERT TEAM

Multidisciplinary approach

Facilitate decision making

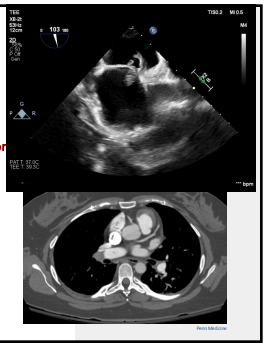
Reduces 30 day mortality
- Intermediate/ high risk

Lower rates of major bleeding

Patient selection

High risk presentation
- **Hemodynamic instability**
  - RV dysfunction & RV injury, **shock +/- vasopressor**
  - Hypoxemia (< 90%)
  - Respiratory distress (>30/min)
- Clot in transit
- High global clot burden + poor reserve

Consideration to lysis: intermediate risk
- Evolving decompensation (hypoxemia, shock)



High Risk Patients

- **Recombinant tPA most commonly used**
  - IV continuous infusion vs bolus dosing
  - Immediate vs delayed

Alteplase 100mg over 2 hours → **Bolus 100mg over 15 minutes OR 50mg bolus followed by infusion of 50mg over 2 hours**

- Establish and secure line access before therapy start
- Monitor closely for bleeding complications
  - Neuro checks
  - Frequent vitals
  - Line checks

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Authors: 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., +38 , for the PEITHO Investigators* Author Info & Affiliations

Published April 10, 2014 | N Engl J Med 2014;370:1402-1411 | DOI: 10.1056/NEJMoa1302097

Reduced-Dose Intravenous Thrombolysis for Acute Intermediate–High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial

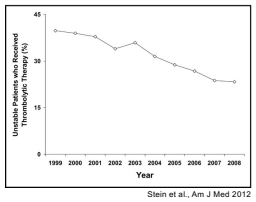
Olivier Sanchez[1,2,3,4] Anais Charles-Nelson[5,6] Walter Ageno[7] Stefano Barco[8,9,10] Harald Binder[10] Gilles Chatellier[2,5,6] Daniel Duerschmied[11] Klaus Empen[12] Melanie Ferreira[13] Philippe Girard[4,14] Menno V. Huisman[15] David Jiménez[16] Sandrine Katsahian[5,6,17] Matija Kozak[18] Mareike Lankeit[8,19,20] Nicolas Meneveau[4,21,22] Piotr Pruszczyk[23] Antoniu Petris[24] Marc Righini[25] Stephan Rosenkranz[26] Sebastian Schellong[27] Branislav Stefanovic[28] Peter Verhamme[29,30] Kerstin de Wit[31] Eric Vicaut[13] Andreas Zirlik[32] Stavros V. Konstantinides[8,33,0] Guy Meyer[1,3,4,†] for the PEITHO-3 Investigators

Other considerations

- CPR/ cardiac arrest > 10 minutes/ traumatic arrest
  - Case by case basis
  - Modest success
- Clot in transit
  - Limited data to recommend AC vs reperfusion therapy
- Failed systemic thrombolysis
  - Try, try again? - full or half dose vs AC

Drawbacks and Limitations

- Safety concerns
  - ~10% major bleeding risk
  - 4% intracranial hemorrhage risk
- Unclear efficacy data in high risk patients
  - Limited RCTs in high risk pts
  - Effect on long term sequelae (Post PE syndrome, CTED, CTEPH)
- Poor utilization
  - Nearly 30% have a contraindication
  - < 25% high risk patients receive thrombolytics



Stein et al., Am J Med 2012

28.5% in-hospital mortality with current practice

Silver, et al, JSCAI, 2023

Contemporary Practice

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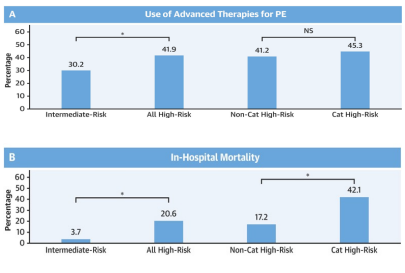
Contemporary Management and Outcomes of Patients With High-Risk Pulmonary Embolism

Taisei Kobayashi, MD,[1,2] Steven Pugliese, MD,[1] Sanjum S. Sethi, MD, MPH,[3] Sahil A. Parikh, MD,[4] Joshua Goldberg, MD,[4] Fahad Alkhafan, MD, MPH,[1] Clara Vitarello, MPH,[1] Kenneth Rosenfield, MD,[4] Robert Lookstein, MD,[5] Brent Keeling, MD,[1] Andrew Klein, MD,[1] C. Michael Gibson, MS, MD,[1,6] Lauren Glassmoyer, MD,[1] Sameer Khandhar, MD,[1] Eric Secemsky, MD,[1] Jay Giri, MD, MPH[1,6]



Future Directions

- ROLE FOR CATHETER BASED THERAPIES IN INTERMEDIATE-HIGH AND HIGH RISK PATIENTS
  - QUALITY OF LIFE, MORTALITY, CLINICAL DETERIORATION EVENTS
- HOW INCREASED UTILIZATION OF CATHETER BASED THERAPIES IMPACTS SYSTEMIC THROMBOLYTIC USE
- VA ECMO AS A BRIDGE TO CATHETER BASED OPTIONS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