Tenecteplase for the Treatment of Pulmonary Embolism

Caitlyn Patton, PharmD
PGY-1 Pharmacy Resident
SSM Health St. Louis University Hospital
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Learning Objectives

1. Describe the classifications of pulmonary embolism
2. Compare and contrast studies investigating the efficacy and safety of tenecteplase for the treatment of pulmonary embolism
3. Select an appropriate treatment for a patient presenting with pulmonary embolism

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Background

Pulmonary Embolism (PE) Pathophysiology[1,2]

- Interferes with circulation and gas exchange
- Increased pulmonary vascular pressure
- Abnormal gas exchange

Clot Formation[3,4]

- Thrombus composition
  - PE/Deep vein thrombosis: Venous clot of fibrin and platelets (red clot)
  - MI: Arterial clot of atherosclerotic plaque contents surrounded by platelets (white clot)
- Spectrum of coagulopathy in PE
  - Ranges from decreased platelets and subclinical prolongation of clotting times to development of disseminated intravascular coagulation (DIC)

Diagnosis of PE[5,6]

- Computed tomographic (CT) – gold standard imaging to assess blood flow
- Echocardiography (ECHO) – assess right ventricle (RV) function
- Electrocardiogram (ECG) – helps indicated RV dilation
- Elevated cardiac markers
  - Troponin I: >0.04 ng/ml or Troponin T: >0.01 ng/ml
  - Brain natriuretic peptide (BNP): >100 pg/ml
  - N-terminal pro-BNP: > 500 pg/ml
- D-Dimer <1000 ng/ml can be used to help exclude PE

Classifications[7,8]

Low Risk PE	Submassive PE (intermediate risk)	Massive PE (high risk)

• Normotensive
• Normal biomarker levels
• No RV dysfunction on imaging
	• SBP > 90 mmHg
	and either of the following
	• RV dysfunction confirmed by imaging
	  • CT or ECHO with RV/LV diameter ratio ≥ 0.9 associated RV dilation and dysfunction
	• Elevated cardiac markers
	  • Troponin I: >0.04 ng/ml
	  • Troponin T: >0.01 ng/ml
	  • Brain natriuretic peptide (BNP): >100 pg/ml
	  • N-terminal pro-BNP: > 500 pg/ml
		• SBP < 90 mmHg for 15 minutes
		• SBP drop ≥ 40 mmHg from baseline for 15 minutes
		• Vasopressors required to maintain blood pressure
		• Cardiac arrest

Treatment Options[9,10]

- Low risk: systemic anticoagulation
- Submassive: systemic anticoagulation
- Massive: systemic anticoagulation and one of the following
    - Percutaneous mechanical thrombectomy
    - Surgical thrombectomy
    - Catheter directed thrombolysis
    - Systemic thrombolysis
        - Work by dissolving blood clots through assisting the activation of plasminogen to plasmin which is then ultimately used to degrade fibrin from clot formation

Thrombolytic Guideline-Directed Therapy for PE [1,8,9,11]

American Heart Association 2011
• Anticoagulation for objectively confirmed PE • Fibrinolysis reasonable for massive PE • **Alteplase: 100mg over 2 hours** • Fibrinolysis may be considered with submassive PE with clinical judgement
European Society of Cardiology 2019
• High or intermediate clinical probability of PE begin anticoagulation • Systemic thrombolytic for high-risk PE • **Alteplase: 100mg over 2 hours** • Unclear evidence of thrombolytics in intermediate-risk
American Society of Hematology 2020
• Low-risk for complications suggest home treatment over hospital management • **Recommend thrombolytic followed by anticoagulation for patients with PE and hemodynamic compromised** • Suggest anticoagulation alone over thrombolysis for patients with submassive PE
CHEST 2021
• Low-risk PE treat with anticoagulation • **Suggest thrombolytics over no therapy in PE associated with hypotension and not high bleed risk** • Recommend against thrombolytics in PE not associated with hypotension

Alteplase Literature[12,13]

MAPPET-3	MOPETT
• Compare heparin + alteplase (100 mg over 2 hours) to heparin + placebo on submassive PE • In-hospital death or clinical deterioration lower with heparin + alteplase than heparin + placebo (11% vs 25%, p=0.006) • Major bleed: 1/118 (0.8%) heparin + alteplase vs 5/138 (3.6%) heparin + placebo (p=0.29)	• Effects of heparin + low-dose alteplase (10 mg bolus followed by 40 mg over 2 hours) compared to heparin + placebo on submassive PE • 16% of thrombolysis group and 57% of control group had pulmonary hypertension at 28 month follow-up (p<0.001) • No bleeding in either group

Comparison of Alteplase and Tenecteplase[14]

Alteplase

- Initial half-life: 5 min
- Administration: given over 2 hours
- Cost: $10,560.43 AWP for 100 mg vial
- FDA approved for acute PE
  - 100 mg over 2 hours

Tenecteplase

- Initial half-life: ~20 min
- Administration: given over 5-10 seconds
- Cost: $8,313.53 AWP for 50 mg vial
- Structurally differs in 3 areas from alteplase
  - Contribute to a longer half life
  - Stronger fibrin selectivity→ thought to contribute to less bleed risk
- FDA approved for myocardial infarction

Weight	Dose
<60 kg	30 mg
≥60 to <70 kg	35 mg
≥70 to <80 kg	40 mg
≥80 to <90 kg	45 mg
≥90 kg	50 mg

Clinical Question: What literature prompted the broadening of guideline recommendations regarding the use of thrombolytics to treat pulmonary embolism?

Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost.* 2014;12(4):459-68.

Objective: Assess if tenecteplase increases the probability of favorable composite outcomes after a submassive PE

Design: Multicenter, double-blinded, intention-to-treat, placebo-controlled, randomized trial

Eligibility Criteria

Inclusion	Exclusion
• Age > 17 years • PE diagnosed on CT within 24 hours • Normal arterial systolic blood pressure with RV strain	• Systolic hypotension < 90 mmHg • Inability to walk • Contraindication to fibrinolysis • End-stage conditions

Comparators

- LMWH 1 mg/kg or dalteparin 200 units/kg followed by weight-based tenecteplase or placebo

Outcomes

- **Primary**
  - 5-day adverse event from PE: Death, circulatory shock or need for intubation
  - 5-day adverse event from treatment: Death from hemorrhage, active bleeding, any bleeding requiring surgery or intravascular treatment
  - 90-day ADR outcomes: VTE recurrence, poor functional capacity outcome, poor physical health-related quality of life

Results

Primary Outcome

- 5-day adverse outcomes: 3 in placebo compared to 1 in tenecteplase

Measurement	Death	Shock
Placebo (n=3)	1	2
Tenecteplase (n=1)	1	0

- 90-day follow-up adverse outcomes: 13 (30%) in placebo compared to 5 (12.5%) in tenecteplase

Measurement	Recurrent PE	Poor functional capacity	Poor Perception of wellness	Recurrent PE, poor functional capacity and wellness	Poor functional capacity and wellness	Recurrent PE and poor wellness
Placebo (n=13)	1	2	2	1	5	2
Tenecteplase (n=5)	1	3	0	0	1	0

- Total adverse outcomes: 16/43 (37%) in placebo compared to 6/40 (15%) in tenecteplase (p-value = 0.017)

Secondary Outcome

Measurement	RV dilation or hypokinesis (n)	SF-36 Mental Component (mean)	Self assessment overall health (n)	Overall health assessment (n) 1 worst; 10 best
Placebo (n=39)	13	53	29	2.4
Tenecteplase (n=37)	14	53	30	3.3
P-value	0.64	0.670	0.43	0.036

Assessment

Strengths	Limitations
• Assess quality of life outcomes • Included high bleed risk population • US population	• Composite endpoint • Underpowered • Lack of data • Low risk populations • Short term follow-up of 5 days

Conclusion

- Composite outcome that includes death, circulatory shock, respiratory distress, and measurements of quality of life
- Study found the use of tenecteplase in submassive PE to reduce adverse outcomes. However, the study was small, underpowered, and the composite outcome was weighed by self-assessment results. Further studies are warranted to assess tenecteplase in PE treatment

Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med.* 2014;370(15):1402-11.

Objective: Investigate the clinical efficacy and safety of fibrinolytic therapy with a single-bolus injection of tenecteplase

Design: Multicenter, double-blind, placebo-controlled randomized trial from Nov 2007 to July 2012

Eligibility

Inclusion	Exclusion
• Age ≥ 18 • Acute PE with an onset of symptoms 15 days or less before randomization • RV dysfunction confirmed by ECHO or CT • Myocardial injury	• Hemodynamic collapse • Coagulopathy/significant bleeding risk • Thrombolytics in prior 4 days • Uncontrolled hypertension

Comparators

- Heparin bolus immediately after randomization
- Randomized to receive weight-based tenecteplase or placebo

Outcomes

- Primary efficacy: composite of death or hemodynamic decompensation within 7 days
- Secondary:
  - 7 days: Death, hemodynamic decompensation, or recurrence of PE
  - 30 days: Death, major adverse events
- Safety:
  - 7 days: ischemic or hemorrhagic stroke, major bleed
  - 30 days: adverse events

Results

- **Baseline**

Characteristic	PE by CT N (%)	RV dysfunction by ECHO N (%)	RV dysfunction by CT N (%)	Elevated troponin I N (%)	Elevated troponin T N (%)	Either troponin I or T elevated N (%)
Placebo (n=499)	472 (94.6)	255 (51.1)	72 (14.4)	361 (72.3)	164 (32.9)	494 (99.0)
Tenecteplase (n=506)	480 (94.9)	278 (54.9)	74 (14.6)	364 (71.9)	164 (32.4)	502 (99.2)

- **Outcomes**
  - Primary
    - Death or hemodynamic decompensation within 7 days – significantly lower in tenecteplase group
    - Tenecteplase 13 (2.6%) vs. placebo 28 (5.6%), p=0.02
  - Secondary
    - Mortality
      - 7 days: tenecteplase 6 (1.2%) vs. placebo 9 (1.8%), P=0.42
      - 30 days: tenecteplase 12 (2.4%) vs. placebo 16 (3.2%), P=0.42
    - Hemodynamic decompensation: Tenecteplase 8 (1.6%) vs. placebo 25 (5%), P=0.002
    - Major extracranial bleed: Tenecteplase 32 (6.3%) vs. placebo 6 (1.2%), P<0.001
    - Hemorrhagic stroke: Tenecteplase 10 (2%) vs. placebo 1 (0.2%), P=0.003

Assessment

Strengths	Limitations
• Large sample size • Powered for primary outcome analysis • Included large submassive population compared to previous study • Safety outcomes assessing bleed risk • Inclusion of high bleed risk populations • Composite outcome driven by clinical outcome	• Bleeding risk assessed as secondary outcome • Not powered to analyze • Lack of detail surrounding bleeding events • Short bleed risk follow-up

Conclusion

- Primary efficacy outcome driven by hemodynamic decompensation results
- The risk of hemorrhagic stroke was significantly higher in the tenecteplase group compared to placebo
- Weight-based dose of tenecteplase in patients with submassive PE prevented hemodynamic decompensation but increased the risk of bleeding and stroke

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Javaudin F, Lascarrou JB, Le Bastard Q. et al. Thrombolysis During Resuscitation for Out-of-Hospital Cardiac Arrest Caused by Pulmonary Embolism Increases 30-Day Survival: Findings From the French National Cardiac Arrest Registry. *Chest.* 2019;156(6):1167-1175.

Objective: Analyzed whether a thrombolytic during resuscitation improved 30-day survival in PE-related out-of-hospital cardiac arrest (OHCA)

Design: Retrospective cohort study based on data extracted from French National OHCA Registry from July 2011 to March 2018

Eligibility

Inclusion	Exclusion
• Age ≥ 18 years • Managed by mobile ICU and diagnosis of PE on hospital admission	• All other causes of OHCA and patients who had ROSC prior to mobile ICU management

Comparators

- Patients that received thrombolytic therapy during cardiac arrest vs no thrombolytic therapy
    - Thrombolytics received:
        - Tenecteplase: median dose 45 mg (min. 35 mg and max. 50 mg)
        - Alteplase: median dose 50 mg (min. 50 mg and max. 80 mg)

Outcomes

- Primary: 30-day survival
- Secondary: Survival at 24hr, length of stay in ICU, neurologic outcomes

Results

Primary Outcome

- 30-day survival seen in 21 (9%) patients (p=0.055)
    - Thrombolytic group: 9 patients
        - Tenecteplase: 5 patients
        - Alteplase: 4 patients
    - No thrombolytic group: 12 patients
- When adjusted on propensity score variables higher survival in thrombolytic group (p=0.005)

Secondary Outcomes

- Survival at 24 hours
    - Thrombolysis group was 66% vs 63% in control group (p=0.76)
- Median length of stay in ICU
    - Thrombolysis group length of stay was 1 day vs 1 day in control group (p=0.23)
- Positive neurological outcomes
    - Thrombolysis group was 10% vs 5% in control (RR 1.97; 95% CI 0.70 – 5.56)
- Death due to hemorrhage
    - Thrombolysis group 6% vs 5% in control (p=0.73)

Assessment

Strengths	Limitations
• Small sample size allowed for focused variables in the propensity score • Tenecteplase was most utilized thrombolytic • Examined massive PE	• Alteplase dosing • Lack of sub-analysis of bleed risk • Non-standardized management after initial treatment • Mobile ICU

Conclusion

- Evaluated the use of thrombolytics in very high-risk massive PE population
- Utilized tenecteplase more frequently than alteplase
- Significantly higher 30-day survival in patients who received thrombolytics during cardiac arrest compared with patients who did not receive it
- Thrombolytic therapy (with tenecteplase most utilized) was associated with a higher 30-day survival compared to patients who did not receive a thrombolytic

Meta-Analysis Review: Zhang Z, Xi L, Zhang S, et al. Tenecteplase in Pulmonary Embolism Patients: A Meta-Analysis and Systematic Review. *Front Med (Lausanne).* 2022;9:860565

Objective: To assess the efficacy and safety of tenecteplase in patients with PE

Methods

- Literature search utilized PubMed, EMBASE and the Web of Science
- Inclusion criteria
    - Assess the efficacy and safety of tenecteplase on PE
    - Included information on sample size, outcomes and statistical measures
    - Age >17
    - Randomized controlled trials or cohort studies

Results

Tenecteplase in massive PE	Tenecteplase in submassive PE

• Thrombolytic during cardiac arrest had higher 30-day survival rate
  ○ 16% vs 6% (p=0.005)
• No increase mortality rate due to hemorrhage
  ○ 6% vs 5% (p=0.73)
	• Reduced RV dysfunction at 24 hours
	  ○ P= 0.04
	• Reduced hemodynamic decompensation but risk of bleed
	  ○ P= 0.002
	• All-cause mortality: 17% less likely in tenecteplase group compared to placebo with < 30-day follow-up
	• Major bleeding: 79% more likely in tenecteplase group compared to placebo with < 30-day follow-up

Conclusion

- Largest meta-analysis assessing efficacy and safety of tenecteplase on PE
- Tenecteplase may be suitable for massive PE patients because of beneficial 30-day survival rate without increasing hemorrhagic incidents. However, tenecteplase is not recommended with submassive PE because of high bleed risk.

Systemic Review – Marti and Colleagues[15]

- Systematic review of 15 studies compared thrombolytic therapy + anticoagulation to anticoagulation alone
    - Major bleeding (based on ISTH definition) was reported in 12 studies
        - Occurred in 9.9% (96/974) of thrombolytic group vs 3.6% (35/961) of control group (p<0.0001)

	All studies		Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	P-value	OR (95% CI)	OR (95% CI)	OR (95% CI)	P-value
Major bleeding	2.91 (1.95 - 4.36)	<0.001	1.07 (0.43 - 2.62)	5.02 (2.72 - 9.26)	2.16 (1.03 - 4.54)	0.02
Fatal/intracranial hemorrhage	3.18 (1.25 - 8.11)	0.008	1.09 (0.27 - 4.40)	7.32 (1.64 - 32.63)	N/A	0.07

Conclusion

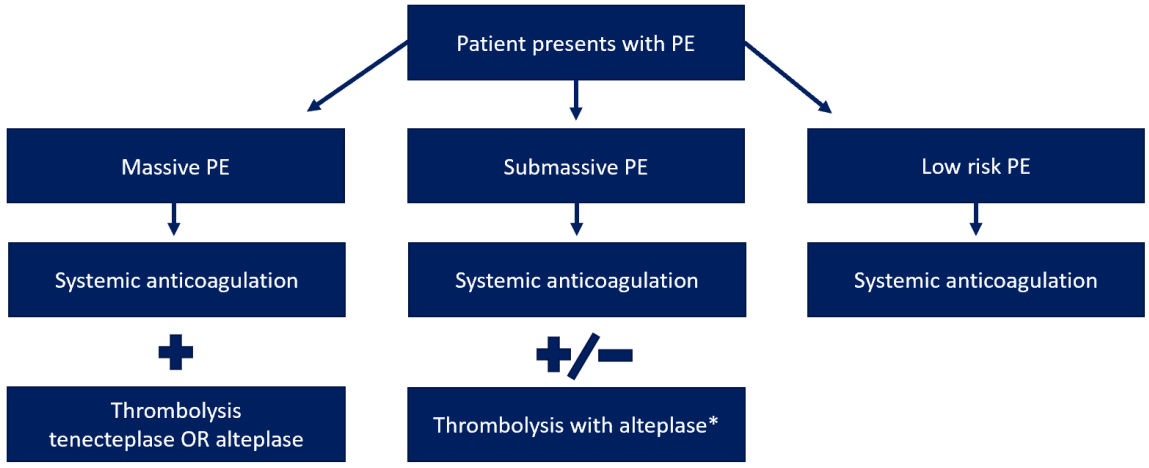
Literature Summary[16-19]

TOPCOAT Kline et al.	PEITHO Meyer et al.	Javaudin et al.	Meta-analysis Zhang et al.
• In submassive PE, **weight-based tenecteplase** improved function outcomes	• In submassive PE, **weight-based tenecteplase** reduced hemodynamic decompensation • Increase risk of bleed and stroke, mainly hemorrhagic	• In massive PE and OHCA, thrombolytic therapy is associated with higher 30-day survival • No increase death due to hemorrhage compared to placebo	• 4 RCT and 2 cohort trials • 1 focused on massive PE • Massive PE: tenecteplase had higher 30-day survival • Submassive PE: tenecteplase reduced RV dysfunction and hemodynamic decompensation, but associated with risk of bleeding

Takeaway

- Historical guidelines recommended the use of alteplase for massive PE, but more recent guidelines recommend any thrombolytic agent
    - Support for thrombolytic in massive PE is largely extrapolated from studies utilizing submassive PE populations
    - Large proportion of PE literature utilized tenecteplase
- Tenecteplase for pulmonary embolism
    - Weight-based dosing improved functional outcomes and reduced hemodynamic decompensation but increased risk of bleeding in submassive PE
    - When utilized in cardiac arrest secondary to PE, tenecteplase improved survival rate without increasing bleeding risk
- Operational benefit of tenecteplase compared to alteplase
    - Lower cost
    - Easier administration – bolus compared to infusion

Algorithm



*Carefully consider bleed risk, alternative dosing, and catheter-directed therapy

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Appendix A[20-22]

Author	n	Inclusion Criteria	Population	Intervention	Results

Kline et al. (2007)	22	• Review case reports including search terms pulmonary embolism and tenecteplase	• 14 case reports published as of 2006
			  ○ 10 of 14 patients had SBP < 90 mmHg
			• 8 additional patients treated at Carolinas Medical Center
			  ○ 7 of 8 patients had SBP > 90 mmHg
				• Varied dosing but mean dose from case reports was 0.52 ± 0.15 mg/kg and 0.58 ± 0.15 mg/kg in the Carolinas group	• No major bleeding in Carolinas group
					• Sufficient data to serve as phase I evidence and warrants a rationale for phase II trial

TIPES (2009)	51	• Age 18 – 85 years • Onset within 10 days, SBP ≥ 100 mmHg, and RV dysfunction on CT within 24 hr of diagnosis of PE	• Acute PE with RV dysfunction without hypotension	• Dose of tenecteplase ranging from 30 to 50 mg, with a 5 mg step every 10 kg from <60 to ≥ 90kg	• Tenecteplase more effective than placebo in early reduction of RV dysfunction in hemodynamically stable patients • 1 tenecteplase and 1 placebo patient with recurrent PE • 1 death in placebo group • 3 major non-fatal bleeding – 2 in tenecteplase and 1 in placebo
Shukla et al. (2014)	30	• Age 18 and older • Confirmed acute PE by CT	3 Groups • Acute PE complicated by shock stage and/or persistent hypotension (12 patients) • RV dilatation and/or dysfunction without hypotension (14 patients) • Severe hypoxemia without hypotension and RV dysfunction (4 patients)	• Dose of tenecteplase ranging from 30 to 50 mg, with a 5 mg step every 10 kg from <60 to ≥ 90kg	• All patients survived • Resolution of PE on follow up CT documented in 26 patients • No major bleeding • Reduction in RV dysfunction