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A systematic review for the role of systemic thrombolysis in intermediate-risk (submassive) pulmonary embolism

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ABSTRACT

Background: Pulmonary emboli (PE) represents an extended spectrum of diseases. 10% of submassive PE progress to massive PE, and while overall mortality is around 5%, it can reach 30%,[1] highlighting the potential severity of submassive PE. Treatment of low and high-risk PE is rather straightforward. However, treating intermediate risk PE is challenging due to the potential risks associated with aggressive therapy. We assessed the effect of adding thrombolytic therapy to standard treatment with heparin on short-term mortality, clinical deterioration, and bleeding in intermediate-risk PE cases. Intermediate-risk PE in this systematic review is objectively confirmed PE either by computer tomography (CT) or ventilation/perfusion (V/Q) scan in normotensive patients (systolic blood pressure ≥ 90 mmHg) with evidence of right ventricular strain by echocardiography or CT with or without evidence of myocardial injury by raised cardiac biomarkers.[2]
Methods: A literature search was conducted using PubMed, OvidSP Platform, Google Scholar, BestBETs, The Cochrane

Library - Databases, American College of Chest Physicians (ACCP), American Heart Association (AHA), European Society of Cardiology (ESC), American College of Emergency Physicians (ACEP), and NICE guidelines from 1946 to the 21st March 2018. References of retrieved articles were reviewed for other possibly related citations. The randomized controlled trials (RCTs) were studied and appraised using the Cochrane risk-of-bias tool (Table 1).
Results: From 66 potentially relevant studies, six RCTs were published between 2002 and 2017 and included in this systematic review (Table 2). A total of 1568 patients were enrolled: 747 received thrombolytic therapy with alteplase (two trials, 155 patients) or tenecteplase (four trials, 592 patients), and 821 were treated with heparin only. None of these RCTs proved that adding thrombolytic therapy to standard anticoagulant treatment statistically decreased early mortality. The five studies looking at clinical deterioration proved that thrombolysis was beneficial. Five out of six RCTs resulted in a non-significant difference in major bleeding prevalence. Only the PEITHO[3] trial proved the opposite. The incidence of minor bleeding was significantly higher in the four studies in which it was measured (Table 3).
Conclusions: Currently, there is inadequate evidence to support the use of systematic thrombolysis for patients with acute intermediate-risk PE. Although it may prevent clinical deterioration which necessitates escalation of treatment in the short term, it comes with increased risk of bleeding. Individual risk-benefit patient assessment and shared decision making may be wise until better evidence to proceed otherwise is demonstrated. Larger clinical trials concerning reduced thrombolytic doses and prolonged infusion rate is essential.

Keywords: pulmonary embolism, thrombolysis, submassive PE, intermediate-risk PE, bleeding, mortality

Table 1. Quality assessment of selected RCTs according to the Cochrane Risk of Bias Assessment.

	MAPPET (Konstantinides, 2002)	TIPES (Becattini, 2010)	Fasullo (Fasullo S, 2011)	TOPCOAT (Kline JA, 2014)	PEITHO (Meyer, 2014)	Sinha (Sinha SK, 2017)
Sequence generation	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear risk
Allocation concealment	Unclear risk	Unclear	Unclear	Low risk	Low risk	Unclear risk
Blinding	Low risk	Unclear risk	Low-risk	Low risk	Low risk	High risk
Incomplete outcome data	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 2. Summary of selected studies.

Study & reference	Design & Size	Inclusion criteria	Intervention & control
1. MAPPET Konstantinides, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347(15):1143-50.	- RCT - Double-blind - 275	- Symptoms less than 96 hours & SBP ≥90 mmHg - RVD based on echo or ECG or PH on right side catheterization	Thrombolysis: Alteplase100 mg IV (10 mg bolus followed by 90 mg over 2 hours) Control: placebo
2. TIPES Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi L, Enea I, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010;125(3):e82-6.	- RCT - Double-blind - 58	- Symptoms within 10 days & SBP ≥100 mmHg - RVD at echocardiography	Thrombolysis: Tenecteplase 30–50 mg (weight adjusted) Control: placebo
3. Fasullo Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Terrazzino G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. Am J Med Sci. 2011;341(1):33-9.	- RCT - Double-blind - 78	- Symptoms within 6 hours & SBP ≥100 mmHg - RVD at echocardiography	Thrombolysis: Alteplase 10 mg bolus, plus 90 mg over 2 hours Control: placebo
4. TOPCOAT Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, 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.	- RCT - Double-blind - 83	- Symptoms within 24 hours & SBP ≥100 mmHg - Hypokinesis on echo, elevated troponin or BNP	Thrombolysis: Tenecteplase 30–50 mg (weight adjusted) Control: placebo
5. PEITHO Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Eng J Med. 2014;370(15):1402-11.	- RCT - Double-blind - 1006	- Symptoms within 15 days & SBP ≥100 mmHg - RVD confirmed by echo or CT and or positive troponin test	Thrombolysis: Tenecteplase 30–50 mg (weight adjusted) Control: placebo
6. Sinha Sinha SK, Sachan M, Goel A, Singh K, Mishra V, Jha MJ, et al. Efficacy and Safety of Thrombolytic Therapy in Acute Submassive Pulmonary Embolism: Follow-Up Study. J Cli Med Res. 2017;9(2):163-169.	- RCT - Unblinded - 87	- Symptoms within 15 days & SBP ≥90 mmHg - RVD confirmed by echo or CT and or positive troponin test	Thrombolysis: Tenecteplase 30–50 mg (weight adjusted) Control: placebo

Table 3. Results of the pulmonary emboli studies.

	Mortality outcomes	Major bleeding outcomes	Minor bleeding outcomes	Clinical deterioration outcomes
MAPPET	Thrombolysis 4/118 (3.4%) vs. placebo 3/138 (2.2%), (p = 0.71)	Thrombolysis 1/118(0.8%) vs. placebo 5/138 (3.6%), (p = 0.29)	Not evaluated	Thrombolysis 12/118 (10.2%) vs. placebo 34/138 (24.6%), (p = 0.004)
TIPES	Thrombolysis 0/28 (0%) vs. placebo 1/30 (3.33%)	Thrombolysis 2/28 (7.14%) vs. heparin 1/30 (3.33%)	Thrombolysis 13/28 (46.42%) vs. placebo 1/30 (2.5%)	Thrombolysis 0/28(0%) vs. placebo 1/30 (3.3%)
Fasullo	Thrombolysis 0/37 vs. placebo 5/35 (14.2%) (p = 0.055)	Thrombolysis 2/37 (5.4%) vs. heparin 1/35 (2.85%) (p: NS)	Thrombolysis 11/37 (29.7%) vs. placebo 4/35 (11.4%), (p = 0.20)	Not evaluated
TOPCOAT	Thrombolysis 1/40 (2.5%) vs. placebo 1/43 (2.32%)	Thrombolysis 1/40 (2.5%) vs. placebo 0/43(0%)	Not evaluated	Thrombolysis 0/40(0%) vs. placebo 2/43 (4.65%)
PEITHO	Thrombolysis 12/506 (2.4%) vs. placebo 16/499 (3.2%), (p = 0.42)	Thrombolysis 58/506 (11.5%) vs. placebo 12/499 (2.4%)	Thrombolysis165/506 (32.6%) vs. placebo 43/499 (8.6%)	Thrombolysis 8/506 (1.6) vs. placebo 25/499 (5.0), (p = 0.002)
Sinha	Thrombolysis 2/45 (4.5%) vs. placebo 2/41 (5%), (p = 0.3)	Thrombolysis 1/45 (2%) vs. placebo 1/41 (2%), (p = 0.45)	Thrombolysis 7/45 (16%) vs. placebo 5/41 (12%), (p = 0.04)	Thrombolysis 2/45 (4.5%) vs. placebo 8/41 (20%), (p = 0.04)

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