

Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism

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Purpose: The aim of this systematic review was to evaluate the efficacy and safety of thrombolytic treatment in patients with submassive pulmonary embolism (PE).

Methods: An electronic search was carried out based on the databases from MEDLINE, Embase, Science Citation Index (SCI), and the Cochrane Library. We included prospective, randomized, and clinical trials in thrombolysis with heparin alone in adults who had evidence of right ventricular dysfunction and normotension. The main endpoints consist of mortality, recurrent PE, and bleeding risk. The relative risk (RR) and the relevant 95% confidence intervals were determined by the dichotomous variable.

Results: Only seven studies involving 594 patients met the inclusion criteria for further review. The cumulative effect of thrombolysis, compared with intravenous heparin, demonstrated no statistically significant difference in mortality (2.7% versus 4.3%; RR = 0.64 [0.29–1.40]; $P=0.27$) or recurrent PE (2% versus 5%; RR = 0.44 [0.19–1.05]; $P=0.06$). Thrombolytic therapy did not increase major hemorrhage compared with intravenous heparin (4.5% versus 3.3%; RR = 1.16 [0.51–2.60]; $P=0.73$), but it was associated with an increased minor hemorrhage (41% versus 9%; RR = 3.91 [1.46–10.48]; $P=0.007$).

Conclusion: Compared with heparin alone, neither mortality nor recurrent PE is reduced by thrombolysis in patients with submassive PE, and it does not reveal an increasing risk of major bleeding. In addition, thrombolysis also produces the increased risk of minor bleeding; however, no sufficient evidence verifies the thrombolytic benefit in this review, because the number of patients enrolled in the trials is limited. Therefore, a large, double-blind clinical trial is required to prove the outcomes of this meta-analysis.

Keywords: thrombolysis treatment, submassive pulmonary embolism, pulmonary embolism, heparin, warfarin

Introduction

Acute pulmonary embolism (PE) is one of the most common, life-threatening cardiovascular events. In the past few years, the proportion of hospitalized PE patients has been gradually increasing.¹ The fatality rate varies with regard to the hemodynamic status.^{2–4} At present, an understanding of the role of thrombolysis in the management of PE is not perfect. Guidelines from the American College of Chest Physicians report that for patients with acute massive PE who do not have a high bleeding risk, systemically thrombolytic therapy is suggested (grade 2C).⁵ Nevertheless, right ventricular dysfunction (RVD) is seen as the main pathophysiological change of acute PE, which is associated with the prognosis of patients. Studies of RV function in PE demonstrate that 50% of patients with PE discover RVD by echocardiogram; submassive PE comprises

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almost half of the nonmassive group.⁶ As the report indicated, the acute PE patients who are hemodynamically stable with RVD have higher mortality than those with normal right ventricular function.^{7,8} Regardless of the higher mortality in patients with RVD, the application of thrombolysis in submassive PE is still controversial.^{9–11} Hence, we conducted an advanced meta-analysis to evaluate the efficacy and safety of thrombolysis in submassive PE patients.

Materials and methods

Evidence retrieval

All randomized clinical trials for thrombolytic therapy in patients with hemodynamically stable PE were reviewed. We widely searched the following databases: MEDLINE, Embase, Science Citation Index (SCI), and the Cochrane Library 1964–2012. The keywords were “pulmonary embolism” or “thromboembolism” and “thrombolysis” or “fibrinolysis,” “randomized controlled trial,” “controlled clinical trial,” combined with approved thrombolytic drugs – “rt-PA or alteplase or recombinant tissue plasminogen activator” and “streptokinase” and “urokinase or Abbokinase® or prourokinase.” In addition, we searched again for a reference of possible included studies. Languages were not restricted to prevent the bias to publications.

Study selection

Two independent investigators executed the trial selection independently. Disagreements were settled by a consensus or by seeking an independent third viewpoint.

All enrolled studies met the following criteria: 1) the PICO question format was set up as: P = patient; I = intervention; C = comparison; and O = outcome. (Other factors included: patients [acute, submassive, pulmonary, embolism, and thromboembolism]; intervention [systemic thrombolysis and intravenous thrombolysis]; comparison [intravenous heparin, coagulation, and placebo control]; and outcome [mortality, recurrence of PE, or bleeding risk]); 2) design was defined as prospective, randomized controlled trials; and 3) PE with RVD or which was hemodynamically stable and had to be objectively confirmed by multidetector computer tomography, pulmonary angiography, or lung scanning. Those trials were excluded as follows: nonrandomized or quasirandomized, retrospective study, and comparison between thrombolytic regimens.

Validity assessment and data extraction

Two of the authors used universal criteria from the *Cochrane Library Handbook 5.0.1* (*Cochrane Handbook*

for *Systematic Review of Interventions, Version 5.0.1*, The Cochrane Collaboration, Oxford, UK), which includes random sequence generation, concealment of allocation, usage of blinding, incomplete outcome data, selective outcome reporting, and other potential factors.

The same author independently extracted the essential information and the endpoint from each trial. The recurrent PE was taken into consideration when it was mentioned in the presence of at least one of the following criteria in the original articles: 1) a new filling defect demonstrated by computed tomography or pulmonary angiography, or a new high probability perfusion defect revealed by ventilation–perfusion lung scan; 2) sudden, otherwise unexplained death; and 3) proven by autopsy. Safety outcomes included major and minor hemorrhage. The former was described as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or was associated with a fall in hemoglobin level of at least 2 g per dL, or leading to the transfusion of two or more units of whole blood or red cells.¹² Adversely, it was seen in the latter.

Statistical analysis

All statistical calculations were implemented with RevMan 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark). We used the pooled relative risk (RR) to assess the efficacy and safety of thrombolytic therapy with 95% confidence interval (CI); $P < 0.05$ was considered statistically significant. Individual trials in this meta-analysis were primarily performed by the heterogeneity test. If no significant heterogeneity was examined ($P \geq 0.1$, by the chi-square test), the fixed-effect model and corresponding method of Mantel–Haenszel (M–H) were used. On the contrary, if $P < 0.1$, the random-effect model was used. $I^2 < 50\%$ was acceptable in the *Cochrane Handbook for Systematic Review of Interventions*, which measured the degree of heterogeneity in the research results.

Results

Study screening, essential characteristics in enrolled trials

Our search yielded 34 randomized controlled trials that described thrombolysis in acute PE (Figure 1). After their titles and abstracts were scanned, 27 trials were not eligible for this present meta-analysis. Also, 24 trials were excluded as they were a comparison between two regions or different protocols, or enrolled patients with massive PE among them.^{13–36} One study was excluded as patients were

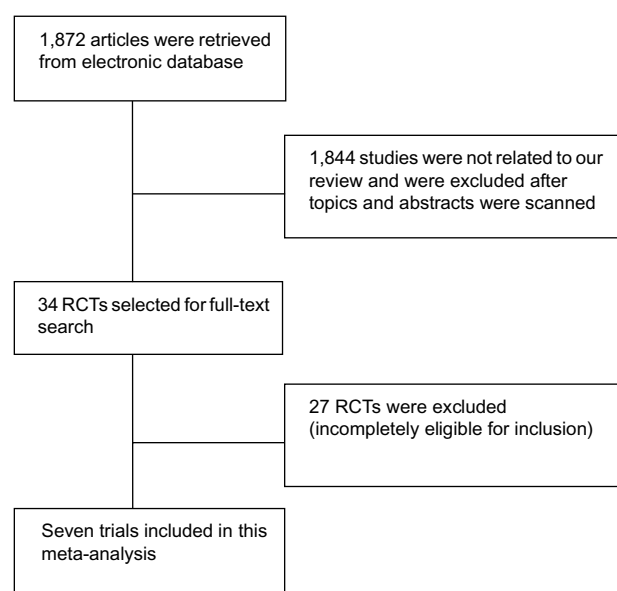


Figure 1 Flow chart of literature screening.
Abbreviation: RCT, randomized controlled trial.

presented with acute proximal venous thrombosis.³⁷ The other two studies were excluded because of low quality and irrelevant outcomes, respectively.^{38,39} Finally, seven clinical trials involving 594 patients with submassive PE were included; 291 patients were randomized to thrombolysis treatment while 303 patients were treated with heparin only.

In addition, seven trials included patients with an onset of symptoms within thrombolytic time window for acute PE before enrollment. All studies excluded the patients with a contraindication to thrombolysis or coagulation, as well as hemodynamic instability or shock (shock was interpreted as systolic blood pressure within 90 mmHg).

Alteplase was used as a thrombolysis agent in six trials while tenecteplase was used in one trial, which was administered through a peripheral vein. The heparin dose was adjusted to maintain the activated partial thromboplastin time at 2.0–2.5 times the normal. The follow-up period ranged from 7–180 days. After randomization, all enrolled patients were kept on an overlapping oral warfarin course, but only warfarin was continued after discharge and during follow-up. (Table 1).

Methodological quality

All enrolled studies were reported to be randomized, but specific random methods were mentioned in four trials. Among them, three trials reported the literature validity, while another one did not describe the allocation concealment.

The application of blind selection was relatively satisfied because double-blind selections were reported in five trials. The loss of follow-up was nonexistent in the patients in six trials (Table 2).

Curative effect of thrombolysis

Mortality and recurrence of PE were reported in all trials (Figures 2 and 3). The mean mortality in the thrombolytic group (2.7%) was slightly lower than that in the heparin treatment alone (4.3%), but the pooled effects were not statistically significant ($RR = 0.64$ [0.29 – 1.40]; $P = 0.27$). No statistical heterogeneity was found for this endpoint (chi-square test = 5.73; $P = 0.45$; $I^2 = 0\%$). The occurrence of recurrent PE in the thrombolytic and heparin groups was 2% and 5%, respectively, which showed no statistical difference ($RR = 0.44$ [0.19 – 1.05]; $P = 0.06$). Moreover, there was no heterogeneity among trials (chi-square test = 4.73; $P = 0.32$; $I^2 = 15\%$).

Safety outcomes

All trials did not demonstrate an increase in major hemorrhage after thrombolysis or heparin treatment (4.5% versus 3.3%; $RR = 1.16$ [0.51 – 2.60]; $P = 0.73$) (Figure 4). In addition, only four of all the trials showed significant minor hemorrhagic risk after thrombolysis treatment compared with heparin treatment (41% versus 9%; $RR = 3.91$ [1.46 – 10.48]; $P = 0.007$) (Figure 5). However, there was a certain heterogeneity for the latter (chi-square test = 6.15; $P = 0.10$; $I^2 = 51\%$) (Figure 5).

Funnel plot analysis

A point on behalf of each trial on mortality was symmetrically distributed in the CI of the funnel plot (Figure 6). The symmetry of the plot did not indicate the absence of major publication bias.

Discussion

Previous meta-analyses did not provide evidence for the benefits of thrombolysis compared with heparin alone in unselected patients with acute PE.^{46,47} However, a mix of patients with and without shock were enrolled in randomized controlled trials of systematic reviews. No further research focused on the subset of patients with PE. Earlier studies explored the safety of thrombolytic drugs when an invasive imaging technology for PE management was universally utilized.⁴⁸ The pooled estimates of presently available clinical trials indicated that either mortality or recurrence of PE was not decreased by thrombolysis when compared with heparin. Simultaneously, it was not associated with the increased risk

Table 1 Characteristics of included trials in this meta-analysis

Trial	Country	Number (thrombolysis/heparin)	Study patients		Study design	Followed by anticoagulation			Follow-up
			Inclusion	Exclusion [#]		Comparison	Thrombolysis	Heparin	
Levine ⁴⁰	Canada	33/25	Outset <15 days	Shock	Alteplase 0.6 mg/kg IV over 2 minutes	Saline solution placebo	Heparin, warfarin	Heparin, warfarin	10 days
PIOPED ⁴¹	USA	9/4	Outset <7 days	Shock	Alteplase 40–80 IV over 90 minutes	Heparin	Heparin, warfarin	Heparin, warfarin	7 days
PAIMS 2 ⁴²	Italy	20/16	Outset <10 days	Shock	2-hour infusion of alteplase (10 mg bolus plus 50 mg in 1 hour, plus 40 mg in 2 hours)	Heparin 1,750 IU/hour IV	Heparin, warfarin	Heparin, warfarin	7 days
Goldhaber	USA	46/55	Outset <14 days	Shock	Alteplase 100 mg IV over 2 hours	Heparin 5,000 units as initial dosage, followed by 1,000 units/hour	Heparin, warfarin	Heparin, warfarin	14 days
Konstantinides ⁴³	Germany	118/138	Outset <5 days	Hemodynamic instability	Alteplase 10 mg bolus, followed by 90 mg IV over 2 hours	Placebo	Heparin 1,000 units/hour, warfarin	Heparin 1,000 units/hour, warfarin	30 days
Becattini ⁴⁴	Italy	28/30	Outset <10 days	Hemodynamic disorder	Tenecteplase 30–50 mg for 5 seconds, followed by 5 mg/10 kg IV over 6 hours	Placebo	Heparin 80 IU/kg IV bolus, followed by 18 IU/kg/hour warfarin	Heparin 80 IU/kg IV bolus, followed by 18 IU/kg/hour warfarin	7 days
Fasullo ⁴⁵	Italy	37/35	Outset <6 hours	Hemodynamic disorder	Alteplase 10 mg bolus, followed by 90 mg IV over 2 hours	Placebo	Heparin 1,000 units/hour, warfarin	Heparin 1,000 units/hour, warfarin	180 days

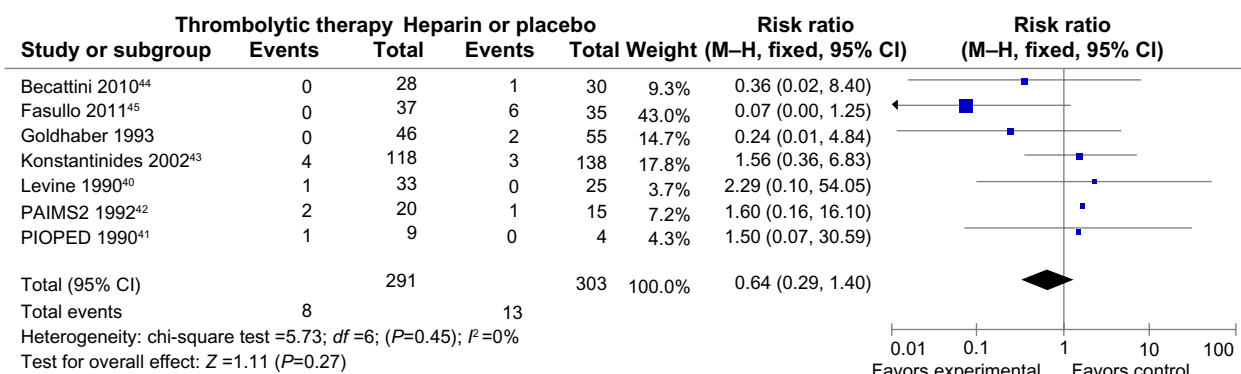
Note: # the patients with contraindications to thrombolytic drugs were excluded.

Abbreviations: IV, intravenous; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2.

Table 2 Methodological quality of included trials

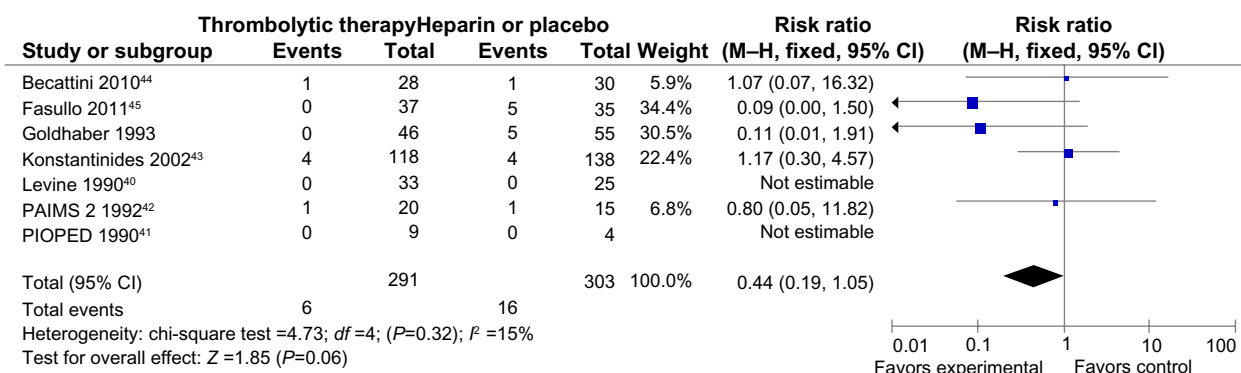
Study	Randomized method	Allocation concealment	Blinding of participants	Incomplete outcome data	Selective reporting	Other potential factors	Description of withdrawal
Levine ⁴⁰	Unclear	Unclear	Yes	No	Unclear	Unclear	No losses
PIOPED ⁴¹	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No losses
PAIMS 2 ⁴²	Unclear	Unclear	No	No	Unclear	Unclear	No losses
Goldhaber	Yes	Yes	No	Yes	Unclear	Unclear	Yes
Konstantinides ⁴³	Yes	Yes	Yes	Yes	Unclear	Unclear	No losses
Becattini ⁴⁴	Yes	Yes	Yes	No	Unclear	Unclear	No losses
Fasullo ⁴⁵	Yes	Unclear	Yes	No	Unclear	Unclear	No losses

Abbreviations: PIOPED, Prospective Investigation Of Pulmonary Embolism Diagnosis; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2.

**Figure 2** Forest plot of the mortality compared to the thrombolysis with heparin for the patients with acute submassive PE.

Notes: The horizontal line represents 95% confidence interval of relative risk (RR), its central blue square is the position of RR, and the black diamond represents overall effect size.

Abbreviations: M-H, Mantel-Haenszel test; CI, confidence interval; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

**Figure 3** Forest plot of recurrent PE compared to the thrombolysis with heparin for the patients with acute submassive PE.

Notes: The horizontal line represents 95% confidence interval of relative risk (RR), its central blue square is the position of RR, and the black diamond represents overall effect size.

Abbreviations: M-H, Mantel-Haenszel test; CI, confidence interval; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

of major bleeding, but the thrombolytic therapy in PE brought significant minor hemorrhagic risk.

Thrombolytic agents have been shown to dissolve the clot rapidly and resolve the deteriorative RVD.⁴⁹ However, the thrombolytic benefits in acute submassive PE have not been demonstrated in our study. In a retrospective cohort study from 392 patients, 73% of these patients were nonmassive while 27%

of the patients were massive PE and were administered subcutaneously with low molecular weight heparin only, or subcutaneously with low molecular weight heparin plus thrombolytics. The mortality rate was 16.8% in patients who were massive and 3.5% for those who were nonmassive;⁵⁰ the latter rate was close to the mortality (4.3%) detected in our study. Conversely, this assumption was refuted by the Registro Informatizado de la

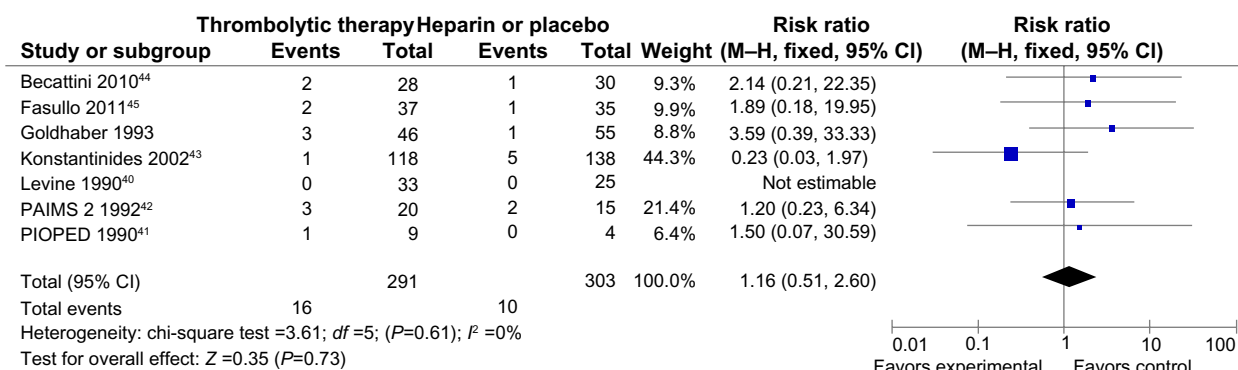


Figure 4 Forest plot of major bleeding compared the thrombolysis with heparin for the patients with acute submassive PE.

Notes: The horizontal line represents 95% confidence interval of relative risk (RR), its central blue square is the position of RR, and the black diamond represents overall effect size.

Abbreviations: M-H, Mantel-Haenszel test; CI, confidence interval; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

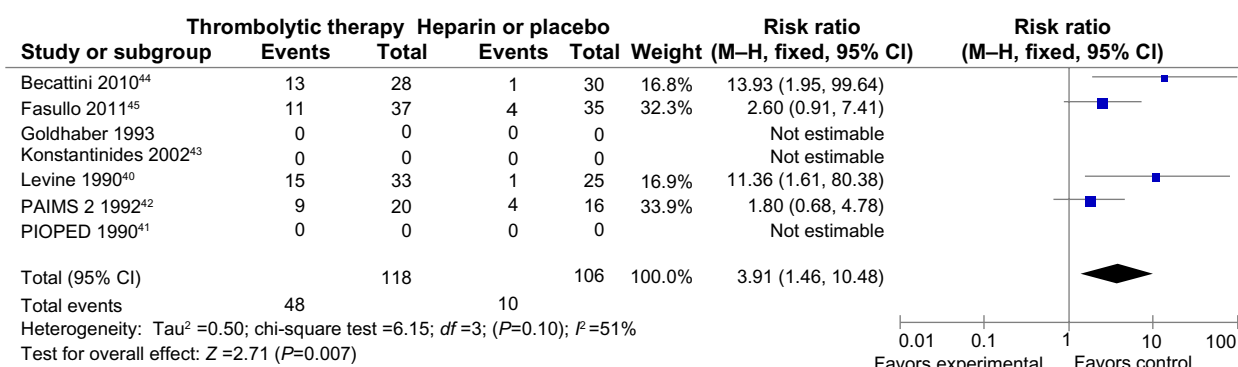


Figure 5 Forest map of minor bleeding compared the thrombolysis with heparin for the patients of acute submassive PE.

Notes: The horizontal line represents 95% confidence interval of relative risk (RR), its central blue square is the position of RR, and the black diamond represents overall effect size.

Abbreviations: M-H, Mantel-Haenszel test; CI, confidence interval; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

Enfermedad TromboEmbólica (RIETE Registry) that included 15,944 patients with symptomatic acute PE. In the normotensive subgroup, thrombolysis brought a more significant risk of death than no thrombolysis during the 3-month follow-up.⁵¹

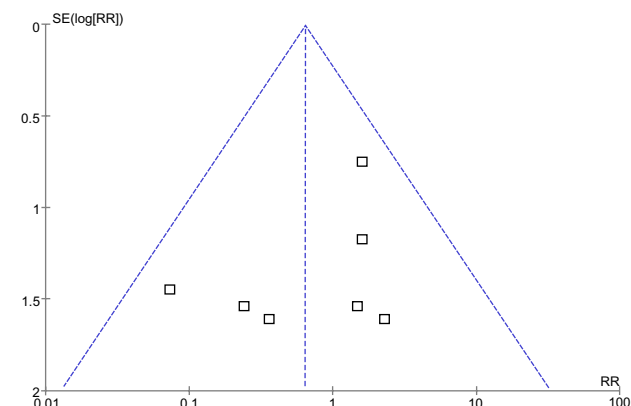


Figure 6 Funnel plot of overall effect for mortality versus study precision.

Abbreviations: SE, standard error; RR, relative risk.

In addition, the recurrent PE was the leading cause of death in patients with submassive PE; therefore, the mortality was close to the PE recurrence rate from this meta-analysis. This outcome was in accordance with the result of the retrospective cohort study reported by Hamel et al.⁵²

The 13% cumulative rate of major hemorrhage was reported in the pooled data,⁵³ including clinical trials that compared thrombolysis with heparin alone or different thrombolytic regimens with each other. This incidence was apparently higher than the rate in our review (4.5%). Nevertheless, major bleeding has been seldom seen in the largest trials as a result of an advanced noninvasive imaging technique in recent years.⁴³ The safety of thrombolytic therapy in our study was not influenced by an overdose of warfarin in the follow-up period.

There are some limitations in our meta-analysis. The number of patients with hemodynamically stable or RVD confirmed by echocardiography was flat, so that the relevant statistical power was confined. The endpoint of our systematic

review remains debatable, because the small sample capacity precludes us making reliable conclusions. The Pulmonary Embolism Thrombolysis trial (PEITHO) has been planned as a prospective, multicenter, randomized, double-blind, placebo-controlled trial in patients with submassive PE. This trial is expected to enroll approximately 1,000 patients who have evidence of RVD and normotension, with a view to evaluate the superiority of tenecteplase.⁵⁴ Data collection for the primary outcome measure of this trial has been completed. The primary efficacy outcome is composed of death from any cause or hemodynamic collapse, which is different from a previous large trial included in the present meta-analysis. Another outcome is to assess ischemic or hemorrhagic stroke with regards to the safety outcomes; moderate and severe bleeding are included and specified. The estimated study completion date is in July 2014. However, the conclusion of the PEITHO trial is to only account for the clinical benefit of a new agent while our study covers all approved thrombolytic drugs.

In conclusion, this systematic review did not demonstrate the clinical benefits of thrombolytic treatment in patients with an acute submassive pulmonary embolism. Thrombolysis could be beneficial to the patients with severe RVD or emerging hemodynamically instability (selected high risk patients).

With the application of a noninvasive diagnostic device in the modern management of PE, major bleeding is significantly less frequent in the largest trials compared with earlier ones.^{6,43} A large, double-blind, randomized controlled trial is required to prove the outcomes of this meta-analysis because the number of patients enrolled in the trials is limited.

Disclosure

The authors report no conflicts of interest in this work.

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