EFFICACY AND SAFETY OUTCOMES OF RECANALIZATION PROCEDURES IN PATIENTS WITH ACUTE SYMPTOMATIC PULMONARY EMBOLISM: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Authors:
Jimenez D[1*], Martín-Saborido C[2*], Muriel A[3], Zamora J[3], Morillo R[1], Barrios D[1], Klok FA[4], Huisman MV[4], Tapson V[5], Yusen RD[6].

Affiliation:
[1] Respiratory Department, Hospital Ramón y Cajal, Medicine Department, Universidad de Alcala (IRYCIS), Madrid, Spain
[2] Faculty of Health Sciences, Universidad Francisco de Vitoria, Madrid, Spain
[3] Biostatistics Department, Ramón y Cajal Hospital, IRYCIS, CIBERESP, Madrid, Spain
[4] Department of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, the Netherlands
[5] Cedars-Sinai Medical Center, Los Angeles, CA, USA
[6] Divisions of Pulmonary and Critical Care Medicine and General Medical Sciences, Washington University School of Medicine, St. Louis, Missouri, USA

*Contributed equally

Correspondence and reprints:
David Jiménez
Respiratory Department
Ramón y Cajal Hospital
28034 Madrid, SPAIN
Phone: 34 913368314

e-mail: **djimenez.hrc@gmail.com**

Running head: Thrombolysis for PE
Keywords: Pulmonary embolism; mortality; bleeding; thrombolysis; meta-analysis.

Tables: 2
eTables: 2
Figures: 3
eFigures: 12
Word count: 2,809

KEY MESSAGES

What is the key question?

For treatment of acute pulmonary embolism (**PE**), the benefits and risks of the different recanalization procedures (i.e., full-dose systemic thrombolysis, reduced-dose systemic thrombolysis, or catheter-directed thrombolysis) vs. each other lack clarity.

What is the bottom line?

Compared with standard anticoagulation, recanalization procedures had a similar risk of all-cause mortality, and full-dose thrombolysis was associated with an increased risk of major bleeding.

Why read on?

Low-dose thrombolysis was associated with the lowest probability of dying and bleeding.

ABSTRACT

Background: We aimed to review the efficacy and safety of recanalization procedures for the treatment of pulmonary embolism (**PE**).

Methods: We searched PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from inception through July 31, 2015, and included randomized clinical trials that compared the effect of a recanalization procedure vs. each other or anticoagulant therapy in patients diagnosed with PE. We used network meta-analysis and multivariate random-effects meta-regression to estimate pooled differences between each intervention, and meta-regression to assess the association between trial characteristics and the reported effects of recanalization procedures vs. anticoagulation.

Results: For all-cause mortality, there were no significant differences in event rates between any of the recanalization procedures and anticoagulant treatment (full-dose thrombolysis: odds ratio, 0.60; 95% confidence interval [**CI**], 0.36-1.01; low-dose thrombolysis: 0.47; 95% CI, 0.14-1.59; and catheter-associated thrombolysis: 0.31; 95% CI, 0.01-7.96). Full-dose thrombolysis increased the risk of major bleeding (2.00; 95% CI, 1.06-3.78) compared with anticoagulation. Catheter-directed thrombolysis was associated with the lowest probability of dying (surface under the cumulative ranking curve [**SUCRA**], 0.67), followed by low-dose thrombolysis (SUCRA, 0.66), and full-dose thrombolysis (SUCRA, 0.55). Similarly, low-dose thrombolysis was associated with the lowest probability of major bleeding (SUCRA, 0.61), followed by catheter-directed thrombolysis (SUCRA, 0.54), and full-dose thrombolysis (SUCRA, 0.17). The results were similar in sensitivity analyses based on restricting only to studies in hemodynamically stable PE patients.

Conclusions: In the treatment of PE, recanalization procedures do not seem to offer a clear advantage compared with standard anticoagulation. Low-dose thrombolysis was associated with the lowest probability of dying and bleeding.

Trial registration: PROSPERO CRD42015024670.

Abstract word count: 260

INTRODUCTION

Although most patients with acute pulmonary embolism (**PE**) have an uncomplicated clinical course while undergoing standard anticoagulation treatment, the overall short-term mortality rate is still significant (1, 2). Death from acute PE usually occurs before or soon after hospital admission (3, 4).

There have been two main treatments for acute PE, anticoagulant therapy alone or systemic thrombolytic therapy (5). Most patients presenting to the hospital with PE have normal blood pressure, normal right ventricular function, and a low clinical severity score and therefore have a very low short-term mortality with prompt initiation of anticoagulation. Although systemic thrombolysis has angiographic and haemodynamic benefits for patients with acute PE, compared to standard therapy, it markedly increases major bleeding, including intracranial and fatal bleeding (6). Consequently, systemic thrombolytic therapy is usually reserved for PE patients with hemodynamic instability (7). The ability to actively remove emboli in patients with acute PE without increasing bleeding would be an important advance. Low-dose systemic thrombolysis and catheter-based thrombolytic therapy require only a fraction of the systemic fibrinolytic dose, and this dose reduction might improve the safety of thrombolysis for PE. A common problem in evaluating the efficacy of these interventions is the lack of trials (or a paucity of available trials) that directly compare these interventions. As a result, no meta-analysis has comprehensively compared the effect of a recanalization procedure vs. each other in patients diagnosed with acute symptomatic PE.

The primary aim of our study was to perform a network meta-analysis of randomised controlled trials (**RCT**) for treatment of acute PE to obtain a better estimate of the benefits and risks of the different recanalization procedures (i.e., full-dose systemic thrombolysis, reduced-dose systemic thrombolysis, or catheter-directed thrombolysis) vs. each other or anticoagulant therapy.

METHODS

Data sources and searches

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (**PRISMA**) statement extension for network meta-analysis and was conducted following an a priori–established protocol registered with PROSPERO (8). We searched PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases. Each database was searched from its inception date to 31 July 2015. Conference abstracts were included in our search. The retrieved articles were examined to eliminate potential duplicates or overlapping data. No limits or language restriction were applied during the search. The RCTs were identified using the Cochrane Collaboration highly sensitive search strategy (sensitivity-maximizing and precision-maximizing version) (9). The search string was: #1. pulmonary embolis*; #2. thrombolysis OR thrombolytic therapy OR streptokinase OR urokinase OR tenecteplase OR alteplase OR desmoteplase OR tissue plasminogen activator OR clot-dissolving medication; #3. #1 AND #2. We also hand searched the references of relevant articles for additional clinical trials not identified by the electronic search and contacted experts. Finally we searched clinicaltrials.gov for information on clinical trials that were terminated but unpublished. The planned analysis was registered at the PROSPERO international prospective register of systematic reviews on July 20, 2015 (CRD42015024670).

Study selection

One reviewer (DJ) performed the database search and initial screening of titles and abstracts. Two investigators (DJ, RM) independently carried out full text screening of all eligible articles. We included a study if participants were patients with acute symptomatic PE objectively diagnosed with standard imaging techniques and received anticoagulant therapy; the intervention was treatment with a recanalization procedure (i.e., full-dose systemic thrombolysis, reduced-dose systemic thrombolysis, or catheter-directed thrombolysis); the comparison group was either treatment with a different recanalization procedure or no recanalization treatment (i.e., the patients received standard anticoagulation); it was a randomised controlled trial; and it reported mortality

outcomes. Observational studies, and trials without a control group were excluded.

Data extraction and quality assessment

Two reviewers (DJ and RM) independently extracted data onto a computer spreadsheet, with discrepancies resolved by consensus. Extracted data included first author, year of publication, type of intervention and control group, number of patients, patient characteristics, and duration of follow-up. The primary outcomes were all-cause mortality and major bleeding, as defined by the study protocol. Secondary outcomes were risk of intracranial hemorrhage (**ICH**) and recurrent embolism. The occurrence of these outcomes was abstracted according to the intention-to-treat population for individual trials. The outcomes data from the first available time point identified as a primary end point from each trial were incorporated into our primary analysis. Each study was graded for potential bias into low, high, and unclear according to the Cochrane Collaboration handbook (10).

Data synthesis and analysis

Separate meta-analyses of direct evidence only (pairwise meta-analyses) were performed using DerSimonian and Laird random-effects model to estimate pooled odds ratios (**ORs**) and 95% confidence intervals (**CIs**) (11). Forest plots were created for each outcome. When there were no events in one treatment group, we used a 0.5 continuity correction. Heterogeneity was assessed using the estimated between-study variance (τ^2), Cochran χ^2 test, and the I^2 statistic (12).

Because there are few trials making head to head comparisons between recanalization procedures, we performed a network metaanalysis. Unlike traditional meta-analyses, this method has the advantage of allowing trials comparing recanalization procedures with some other common treatment (e.g., placebo) to be incorporated into the analysis, thus increasing power and enabling a better comparison of recanalization therapies to be made (13). We used multivariate, random-effects meta-regressions to perform each analysis using the network family of commands in Stata (14). We evaluated

inconsistency between direct and indirect sources of evidence by comparison of the fit and parsimony of consistency and inconsistency models and by calculation of the difference between direct and indirect estimates of a specific treatment effect ('loop-specific approach'). The relative ranking of recanalization interventions on primary and secondary outcomes was presented as their surface under the cumulative ranking (**SUCRA**) probabilities, which represent their likelihood of being ranked best (15). In this study, higher SUCRA scores reflect lower associated all-cause mortality and bleeding events. We estimated the probability of each treatment being the best by averaging 10,000 Monte Carlo replications. The level of statistical significance was set at $P < 0.05$ and all statistical tests were 2-sided.

We performed some sensitivity analyses to assess the robustness of the findings. These were based on (1) restricting only to studies in patients with hemodynamically stable PE; (2) restricting only to trials where the mean age of participants in the thrombolytic group was > 65 years; and (3) alternative statistical model (frequentist approach using a random-effects inconsistency model).

RESULTS

From a total of 930 unique studies identified using the search strategy, 22 RCTs (2,494 patients) were included in the network meta-analysis (**eFigure 1**). These included 16 trials comparing full-dose thrombolysis to no thrombolysis (2,016 patients) (6, 16-30), 1 comparing low-dose thrombolysis to no thrombolysis (121 patients) (31), 1 comparing ultrasound-assisted catheter-directed thrombolysis with no thrombolysis (59 patients) (32), and 4 comparing full-dose thrombolysis with low-dose thrombolysis (298 patients) (33-36). The available direct comparisons and network of trials is shown in **Figure 1** and **eFigures 2-4** in the Supplement.

Characteristics of included studies

The RCTs included in the network meta-analysis are summarized in **Table 1.** Overall, these 22 trials were reported between 1970 and 2014 and included 2,494 participants. The mean study sample size was 113 participants, ranging from 8 to 1,005 patients. The baseline characteristics of patients included in these trials are described in **Table 1**. The primary outcome (all-cause mortality) was reported in all studies.

Direct meta-analysis

Results of direct pairwise meta-analysis are summarized in **Table 2** and **eFigures 5-8** in the Supplement. All interventions were associated with a nonsignificant reduction of all-cause mortality (full-dose thrombolysis: odds ratio [**OR**], 0.64; 95% CI, 0.37 to 1.09; low-dose thrombolysis: 0.32, 0.03 to 3.13; catheter-directed thrombolysis: 0.31, 0.01 to 7.96); full-dose thrombolysis was not superior to low-dose thrombolysis (1.04, 0.24 to 4.41). Full-dose thrombolytic therapy was significantly associated with a greater risk of major bleeding (2.39, 1.44 to 3.95) and intracranial haemorrhage (**ICH**) (3.66, 1.13 to 11.86) compared with anticoagulant therapy (**eFigures 6 and 7** in the Supplement), whereas low-dose thrombolysis showed a nonsignificant benefit in terms of major bleeding and ICH compared with full-dose thrombolysis (**Table 2**). All outcomes were associated with negligible heterogeneity ($I^2 < 12\%$).

Network meta-analysis –primary outcomes

In network meta-analysis, compared with anticoagulation alone, full-dose thrombolysis was associated with an OR of 0.60 (95% CI, 0.36-1.01), low-dose thrombolysis with an OR of 0.47 (95% CI, 0.14-1.59), and catheter-directed thrombolysis with an OR of 0.31 (95% CI, 0.01-7.96) for dying (**Figure 2**). When recanalization treatments were compared, none of comparisons reached conventional level of statistical significance (**Figure 2**). In network meta-analysis, compared with anticoagulation alone, full-dose thrombolysis was associated with an OR of 2.00 (95% CI, 1.06-3.78), low-dose thrombolysis with an OR of 0.90 (95% CI, 0.25-3.21), and catheter-directed thrombolysis with an OR of 0.97 (95% CI, 0.02-56.03) for bleeding (**Figure 2**). Again, when recanalization treatments were compared for bleeding, none of comparisons reached conventional level of statistical significance (**Figure 2**).

Network meta-analysis suggested that catheter-directed thrombolysis was associated with the lowest probability of dying (SUCRA, 0.67), followed by low-dose thrombolysis (SUCRA, 0.66), and full-dose thrombolysis (SUCRA, 0.55) (**Figure 3**). Similarly, low-dose thrombolysis was associated with the lowest probability of major bleeding (SUCRA, 0.61), followed by catheter-directed thrombolysis (SUCRA, 0.54), and full-dose thrombolysis (SUCRA, 0.17) (**Figure 3**).

Network meta-analysis –secondary outcomes

In network meta-analysis, compared with anticoagulation, all procedures had 0.48 to 2.07 odds of being associated with ICH (**eFigure 9**). Compared with anticoagulant therapy, low-dose thrombolysis was associated with the lowest odds of ICH (OR, 0.48; 95% CI, 0.07-3.14; SUCRA, 0.78), whereas full-dose thrombolysis (OR, 2.07; 95% CI, 0.86-5.02; SUCRA, 0.16) was associated with the highest odds of ICH (**eFigure 10**).

Compared with anticoagulation, all procedures had 0.34 to 0.97 lower odds of being associated with recurrent embolism (**eFigure 9**). Compared with anticoagulant therapy, low-dose thrombolysis was associated with the lowest odds of recurrent embolism (OR, 0.34; 95% CI, 0.09-1.25; SUCRA, 0.81), whereas catheter-directed thrombolysis (OR, 0.97; 95% CI, 0.02-50.36; SUCRA, 0.40) was associated with the highest odds of recurrent embolism (**eFigure 10**).

Sensitivity analysis

Results from sensitivity analyses are reported in **eTable 1** in the Supplement. Overall, the results were similar to the main analysis for the primary outcome in sensitivity analyses based on (1) restricting only to studies in patients with hemodynamically stable PE; (2) restricting only to trials where the mean age of participants in the thrombolytic group was > 65 years; and (3) alternative statistical model (frequentist approach using a random-effects inconsistency model).

Publication bias and network consistency

There was no evidence of publication bias, either qualitatively based on funnel-plot asymmetry (**eFigure 11** in the Supplement) or quantitatively (Egger regression test, P > 0.05 for all comparisons), although the number of studies included in each comparison was small. There were significant differences between direct and indirect estimates in the only closed loop that allowed assessment of network consistency (anticoagulation-full-dose thrombolysis-low-dose thrombolysis).

Quality of evidence

The risk of bias summary and figure for included studies are listed in **eFigure 12** and **eTable 2** in the Supplement. Some studies did not present details for randomization, allocation concealment, and blinding. No more than 4 of the included trials (< 20%) were deemed to be at high risk of bias in only 3 domains (randomization, allocation concealment, blinding) of the Cochrane Collaboration risk of bias tool. In most domains, the majority of trials were at low risk, except for the allocation concealment and blinding categories in which most trials were at an unclear risk due to inadequate reporting of methods.

DISCUSSION

To our knowledge, this is the first network meta-analysis comparing full-dose thrombolysis, low-dose thrombolysis, catheter-directed thrombolysis and inactive controls on mortality and other adverse outcomes in patients with acute symptomatic PE. The study has several key findings. First, full-dose thrombolysis, low-dose thrombolysis, and catheter-directed thrombolysis showed a non-significant trend toward lower risk of all-cause death compared with anticoagulation. Second, full-dose thrombolysis was associated with higher odds of major bleeding compared with anticoagulant treatment, with moderate confidence in estimates, but was associated with lower odds of recurrences. Third, low-dose thrombolysis was the treatment that performed best in terms of efficacy (all-cause mortality) and safety (major bleeding). However, the clinical interpretation of these findings is limited not only by the uncertainty around

these estimates, but also by the potential bias due to the small number of trials in each node.

Traditional pairwise meta-analyses are limited in helping to summarise the most effective treatment among different kinds of recanalization procedures. Other than comparisons between full-dose thrombolysis and anticoagulant therapy (37, 38), the number of studies that analysed each particular pair of treatments is still relatively small. Furthermore, for some procedures (i.e., full-dose vs. catheter-directed thrombolysis) there was no direct comparative research. The ability to estimate effectiveness in this work using network meta-analysis allows for more comprehensive assessment of treatment options than has been previously possible. Additionally, in contrast to separate pairwise analyses, we have been able to rank each treatment based on the strength of its association with mortality and bleeding. Even though the results of the pairwise and network meta-analyses were mostly similar, the biggest difference was seen in the comparison of full-dose with anticoagulation on intracranial haemorrhage with the pairwise meta-analysis estimating a larger association than the network model. This was most likely because to the large amount of between-study variation observed in the indirect comparisons being incorporated into the analysis.

Some previous pairwise meta-analyses showed significantly lower associated mortality with full-dose systemic thrombolytic use in PE (37, 38). In our study, we did not find a significant reduction in all-cause mortality with full-dose thrombolytic therapy. This discrepancy between the studies may be explained at least in part by the use of different methodological and statistical techniques. For low-dose systemic thrombolysis and catheter-directed thrombolysis, lack of statistical power might account for the nonsignificant results, as suggested by the wider confidence intervals. Alternatively, full-dose systemic thrombolysis showed a significant association with major bleeding, a finding consistent with previous meta-analyses (37-39). While low-dose and catheter-directed thrombolysis have the potential to offer benefits of full-dose systemic thrombolysis while minimizing bleeding risk attributable to a lower dose of the thrombolytic agent, limited randomized clinical trial data might be the main

obstacle for providing a definitive conclusion on the comparison of the effect of different reperfusion therapies on major bleeding and ICH. On balance, our results show that low-dose and catheter-directed thrombolysis seem the most highly ranked treatment across the two primary outcomes. Since catheter-directed thrombolysis requires rapid access to the cardiac catheterization or interventional radiology laboratory (5), low-dose thrombolysis is appealing for PE patients when early recanalization procedures are indicated. However, it should be kept in mind that in patients with such presentations, particularly when PE is associated with hemodynamic instability, there are relatively few data for any approaches other than standard-dose systemic thrombolysis.

Ultimately, given the differences in safety, efficacy, and response to therapy, from a clinical perspective, the clinician should always consider the overall clinical picture, and patient management plans need to balance the risks and benefits. There is also a need for randomized trials that compare low-dose thrombolytic therapy in with anticoagulation alone in stable patients who have intermediate-high risk PE. Evidence from such studies would place the role of this procedure for PE on a firmer footing.

This study has limitations. First, there was a paucity of head-to-head trials. Second, the biggest threat to validity of the results of any meta-analysis is conceptual heterogeneity (i.e., considerable differences among trials in patient characteristics, studied interventions, outcome assessment, or study design), which can limit the comparability of trials. Strategies to limit the effect of conceptual heterogeneity included strict inclusion and exclusion criteria and the use of various sensitivity analyses to assess the robustness of the results. Third, we found inconsistency for efficacy, which was mainly determined by the loop of anticoagulation-full-dose thrombolysis-low-dose thrombolysis. Since some evidence suggests that quality of thrombolytic clinical trials has substantially changed in the past 30 years, we believe that this inconsistency might be a consequence of a cohort effect that relates to different methods used in the older studies compared with those done more recently (40). Fourth, ranking probabilities may be affected by unequal numbers of trials per comparison, sample size of individual studies, network configuration, and effect

sizes among treatments and should be interpreted with caution. Finally, some included trials had an unclear or high rate of selection and performance bias, and there are unaddressed concerns regarding the effect of recanalization procedures in a clinical setting.

In conclusion, compared with standard anticoagulation, recanalization procedures had a similar risk of all-cause mortality, though full-dose thrombolysis was associated with an increased risk of major bleeding. This network metaanalysis did not identify a statistically significant difference between the outcomes associated with these therapies, but low-dose thrombolysis was associated with the lowest probability of dying and bleeding. The current body of evidence is limited and further conclusive studies are needed to establish the role of each of the recanalization procedures.

Funding sources

This study (PII11/00246) was supported by the Instituto de Salud Carlos III (Plan Estatal de I+D+i 2013-2016) and cofinanced by the European Development Regional Fund ‘‘A way to achieve Europe’’ (ERDF)

Conflict of interest statement

The authors declared no conflicts of interest.

Author contributions

Study concept and design: Jiménez, Huisman, Tapson, Yusen

Acquisition of data; analysis and interpretation of data; statistical analysis: Jimenez, Martín-Saborido, Muriel, Zamora, Morillo, Barrios, Klok, Huisman, Tapson, Yusen

Drafting of the manuscript: Jimenez, Klok, Huisman, Tapson, Yusen

Critical revision of the manuscript for important intellectual content: Jimenez, Martín-Saborido, Muriel, Zamora, Morillo, Barrios, Klok, Huisman, Tapson, Yusen

Study supervision: Jimenez, Yusen

The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figure 1. Network of included studies with available direct comparisons for all-cause mortality

Figure 2. Network meta-analysis estimates of all-cause mortality (upper triangle) and major bleeding (lower triangle) for each comparison

Figure 3. Clustered ranking plot based on cluster analysis of surface under the cumulative ranking curve (SUCRA) for benefit (all-cause mortality) and safety (major bleeding). Treatments lying in the upper right corner are more effective and safe than the other treatments

eFigure 1. Study identification and selection

eFigure 2. Network of included studies with available direct comparisons for major bleeding

eFigure 3. Network of included studies with available direct comparisons for intracranial haemorrhage

eFigure 4. Network of included studies with available direct comparisons for recurrent venous thromboembolism

eFigure 5. Odds of mortality in patients with pulmonary embolism treated with different recanalization procedures

eFigure 6. Odds of major bleeding in patients with pulmonary embolism treated with different recanalization procedures

eFigure 7. Odds of intracranial haemorrhage in patients with pulmonary embolism treated with different recanalization procedures

eFigure 8. Odds of recurrent venous thromboembolism in patients with pulmonary embolism treated with different recanalization procedures

eFigure 9. Network meta-analysis estimates of recurrent venous thromboembolism (upper triangle) and intracranial haemorrhage (lower triangle) for each comparison

eFigure 10. Clustered ranking plot based on cluster analysis of surface under the cumulative ranking curve (SUCRA) for benefit (recurrent venous thromboembolism) and safety (intracranial haemorrhage). Treatments lying in the upper right corner are more effective and safe than the other treatments

eFigure 11. Publication bias assessed via funnel plots assessed for the primary outcomes.

eFigure 12. Quality assessment of 22 RCTs included in the analysis

Table 1. Characteristics of included randomized clinical trials

Source	*Number of patients*	*Intervention*[a]	*Control*[a]	*High-risk PE included*	*Age, Mean (range or SD), y*	*Follow-up, d*	*Male, Nº (%)*	*All-cause mortality*	*Major bleeding*	*ICH*	*Recurrent VTE*
Meyer et al (6), 2014	1005	Tenecteplase (30-50 mg)	Placebo	No	66.2 (15.3)	30	473 (47%)	Yes	Yes	Yes	Yes
Kline et al (16), 2014	83	Tenecteplase	Placebo	No	55.4 (14)	5	49 (59.0)	Yes	Yes	Yes	Yes
Becattini et al (17), 2010	58	Tenecteplase (30-50 mg)	Placebo	No	68.1 (1.9)	7	13 (22.4)	Yes	Yes	Yes	Yes
Konstantinides et al (18), 2002	256	Alteplase (100 mg)	Placebo	No	62.1 (10.5)	30	122 (47.6)	Yes	Yes	Yes	Yes
Goldhaber et al (19), 1993	101	rt-PA (100 mg)	Placebo	No	58.5 (17)	14	44 (44.0)	Yes	Yes	Yes	Yes
Dalla-Volta et al (20), 1992	36	Alteplase (100 mg)	Placebo	No	64.7 (12.5)	30	12 (33.0)	Yes	Yes	Yes	Yes

Levine et al (21), 1990	58	Alteplase (0.6 mg/Kg of ideal body weight)	Placebo	No	61.5 (2.7)	10	29 (54.5)	Yes	Yes	Yes	Yes
PIOPED (22), 1990	13	Alteplase (40-80 mg)	Placebo	No	58.5 (15.8)	7	9 (55.6)	Yes	Yes	Yes	No
Marini et al (23), 1988	30	Urokinase (800 000 IU for 12h/d for 3d or 3 300 000 IU for 12h)	Placebo	No	53 (23-72)		11 (44)	Yes	Yes	Yes	Yes
Ly et al (24), 1978	25	Streptokinase (250 000 IU loading dose, then 100 000 IU/h for 72h)	Placebo	Yes	53.2 (23-70)	10	11 (44.0)	Yes	Yes	No	No
Tibbutt et al (25), 1974	30	Streptokinase (600 000 IU over 30m through PA catheter followed by 100 000U/h IV for 72h)	Placebo	Yes	48.7 (25-71)	3	15 (50.0)	Yes	Yes	No	No
UPET (26), 1970	160	Urokinase (2 000 U/lb, then 2 000 U/lb/h for 12h)	Placebo	Yes	[b]	14	92 (57.3)	Yes	Yes	Yes	Yes
Fasullo et al (27), 2011	72	Alteplase (100 mg)	Placebo	No	56.0 (16.1)	180	41 (56.9)	Yes	Yes	Yes	Yes

Jerjes et al (28), 1995	8	Streptokinase (1 500 000 IU)	Placebo	Yes	51 (22.9)	1-3	5 (63.0)	Yes	Yes	Yes	No
Dotter et al (29), 1979	31	Streptokinse (2 000 000 to 11 000 000 IU)	Placebo	Yes	Yes	14	[c]	Yes	Yes	Yes	Yes
Taherkahni et al (30), 2014	50	Alteplase (100 mg) or streptokinase (1 500 000 IU)	Placebo	No	55.7 (12.4)	7	20 (40.0)	Yes	Yes	Yes	No
Sharifi et al (31), 2012	121	t-PA (50 mg)	Placebo	No	Intervention: 58 (9) Control: 59 (10)	840	55 (45.5)	Yes	Yes	Yes	Yes
Kucher et al (32), 2014	59	rt-PA (10 to 20 mg through PA catheter)	Placebo	No	63 (14)	90	28 (47.5)	Yes	Yes	Yes	Yes
Goldhaber et al (33), 1994	90	rt-PA (100 mg)	rt-PA (0.6 mg/Kg with a maximum dose of 50 mg)	Yes	Intervention: 53 (17) Control: 58 (16)	14	46 (51.1)	Yes	Yes	Yes	Yes
Sors et al (34), 1994	53	Alteplase (100 mg)	Alteplase (0.6 mg/Kg with a maximum dose of 50 mg)	Yes	Intervention: 69 (12) Control: 67 (17)	Hospital stay	23 (43.4)	Yes	Yes	Yes	Yes
Wang et al (35), 2010	118	rt-PA (100 mg)	rt-PA (50 mg)	Yes	Intervention: 51.9 (13.5) Control: 55.3 (14.1)		69 (58.5)	Yes	Yes	Yes	Yes

Abdelsamad et al (36), 2011	40	Streptokinase (1 000 000 IU over 1 hour)	Streptokinase (250 000 IU over 30 min, then 100 000 IU/h over 24 h)	No	NA	NA	Yes	Yes	No	No

[a] Patients also received standard anticoagulation.
[b] Precise ages of patients not provided; 50.6%of patients were younger than 50 years and 49.4% of patients 50 years or older.
[c] Unspecified.

Abbreviations: PE, pulmonary embolism; ICH, intracraneal haemorrhage; VTE, venous thromboembolism; rt-PA, recombinant tissue plasminogen activator; IU, international units.

Table 2. Summary of direct meta-analysis for all-cause mortality and adverse event outcomes

		Active intervention[a]		*Control (Placebo unless otherwise noted)*[a]		
Intervention	***No. of studies***	***No. with event***	***Total No.***	***No. with event***	***Total No.***	***OR (95% CI)***
All-cause mortality						
Full-dose thrombolysis	16	23	1,010	42	1,006	0.64 (0.37-1.09)
Low-dose thrombolysis	1	1	61	3	60	0.32 (0.03-3.13)
Catheter-directed thrombolysis	1	0	30	1	29	0.31 (0.01-7.96)
Full-dose thrombolysis vs. low-dose thrombolysis	4	4	112	7	186	1.04 (0.24-4.41)
Major bleeding						
Full-dose thrombolysis	16	99	1,010	38	1,006	2.39 (1.44-3.95)
Low-dose thrombolysis	1	0	61	0	60	Not estimable
Catheter-directed thrombolysis	1	0	30	0	29	Not estimable
Full-dose thrombolysis vs. low-dose thrombolysis	4	9	112	7	186	2.26 (0.78-6.58)
Intracranial haemorrhage						
Full-dose thrombolysis	14 2	15	983	2	978	3.66 (1.13-11.86)
Low-dose thrombolysis	1	0	61	0	60	Not estimable
Catheter-directed thrombolysis	1	0	30	0	29	Not estimable
Full-dose thrombolysis vs. low-dose thrombolysis	3	3	97	0	161	6.85 (0.74-63.24)
Recurrent VTE						
Full-dose thrombolysis	11	19	945	37	945	0.57 (0.32-1.03)
Low-dose thrombolysis	1	0	61	3	60	0.13 (0.01-2.64)
Catheter-directed thrombolysis	1	0	30	0	29	Not estimable
Full-dose thrombolysis vs. low-dose thrombolysis	3	4	97	6	161	1.35 (0.36-5.00)

[a] Patients also received standard anticoagulation

Abbreviations: OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism.