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Thrombolytic therapy for pulmonary embolism (Review)

Hao Q, Dong BR, Yue J, Wu T, Liu GJ

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[Intervention Review]

Thrombolytic therapy for pulmonary embolism

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ABSTRACT

Background

Thrombolytic therapy is usually reserved for patients with clinically serious or massive pulmonary embolism (PE). Evidence suggests that thrombolytic agents may dissolve blood clots more rapidly than heparin and may reduce the death rate associated with PE. However, there are still concerns about the possible risk of adverse effects of thrombolytic therapy, such as major or minor haemorrhage. This is the third update of the Cochrane review first published in 2006.

Objectives

To assess the effects of thrombolytic therapy for acute pulmonary embolism.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 16 April 2018. We undertook reference checking to identify additional studies.

Selection criteria

We included randomised controlled trials (RCTs) that compared thrombolytic therapy followed by heparin versus heparin alone, heparin plus placebo, or surgical intervention for patients with acute PE. We did not include trials comparing two different thrombolytic agents or different doses of the same thrombolytic drug.

Data collection and analysis

Two review authors (JY, QH) assessed the eligibility and quality of trials and extracted data. We calculated effect estimates using the odds ratio (OR) with 95% confidence interval (CI) or the mean difference (MD) with 95% CI. We assessed the quality of the evidence using GRADE criteria.

Main results

We identified no new studies for inclusion in this 2018 update. We included in the review 18 trials with a total of 2197 participants. We were not able to include one study in the meta-analysis because it provided no data that we could extract. Most of the studies carried a high risk of bias because of high or unclear risk related to randomisation and blinding. Meta-analysis showed that, compared with heparin alone, or heparin plus placebo, thrombolytics plus heparin can reduce the odds of death (OR 0.57, 95% CI 0.37 to 0.87, 2167 participants, P = 0.01, low-quality evidence) and recurrence of PE (OR 0.51, 95% CI 0.29 to 0.89, 1898 participants, P = 0.02, low-quality evidence). Effects on mortality weakened when we excluded from analysis four studies at high risk of bias (OR 0.66, 95% CI 0.42 to

1.06, 2054 participants, P = 0.08). The incidence of major and minor haemorrhagic events was higher in the thrombolytics group than in the control group (OR 2.90, 95% CI 1.95 to 4.31, 1897 participants, P < 0.001, low-quality evidence; OR 3.09, 95% CI 1.58 to 6.06, 1553 participants, P = 0.001, very low-quality evidence, respectively). We downgraded the quality of the evidence to low or very low because of design limitations, potential influence of pharmaceutical companies, and small sample sizes. Length of hospital stay (mean difference (MD) -0.89, 95% CI -3.13 to 1.34) and quality of life were similar between the two treatment groups. Limited information from a small number of trials indicated that thrombolytics may improve haemodynamic outcomes, perfusion lung scanning, pulmonary angiogram assessment, echocardiograms, pulmonary hypertension, coagulation parameters, clinical outcomes, and survival time to a greater extent than heparin alone. However, the heterogeneity of the studies and the small number of participants involved warrant caution when results are interpreted. Similarily, fewer participants from the thrombolytics group required escalation of treatment. None of the included studies reported on post-thrombotic syndrome or compared the costs of different treatments.

Authors' conclusions

Low-quality evidence suggests that thrombolytics reduce death following acute pulmonary embolism compared with heparin. The included studies used a variety of thrombolytic drugs. Thrombolytic therapy may be helpful in reducing the recurrence of pulmonary emboli but may cause major and minor haemorrhagic events and stroke. More high-quality, blinded randomised controlled trials assessing safety and cost-effectiveness of therapies for pulmonary embolism are required.

PLAIN LANGUAGE SUMMARY

Drugs to dissolve pulmonary embolism (blood clot in the lungs)

Background

A pulmonary embolus is a potentially fatal blood clot that lodges in the main artery of the lungs, straining the right side of the heart and affecting blood circulation. Patients with this condition are at risk for new emboli forming (recurrence). In the case of a massive pulmonary embolism, treatment to restore blood flow is urgently required. Heparin thins the blood, but newer drugs that actively break up the clots (thrombolytics) may act more quickly and may be more effective. These newer drugs include streptokinase, urokinase, and recombinant tissue-type plasminogen activator. The major complication of this treatment is bleeding.

Key results

Review authors searched the literature and included 18 studies in this update (evidence current to 16 April 2018). These trials involved 2197 adult participants with pulmonary embolism, who were randomly assigned to a thrombolytic agent followed by heparin versus heparin alone or heparin plus placebo or surgical procedure. We were able to combine data from 17 clinical trials with a total of 2167 patients. Thrombolytics seemed to lower the likelihood of death or recurrence of blood clots over heparin. However, after exclusion of four very low-quality studies, this benefit disappeared. On the other hand, thrombolytics caused more side effects, including major and minor bleeding events (haemorrhagic events) and stroke, than heparin alone. Limited information from five trials shows that thrombolytics were better at improving blood flow through the lungs; seven included studies show that they can improve heart function.

Quality of the evidence

The quality of the evidence is low because of several important design limitations, potential influence of pharmaceutical companies, and small sample sizes. We need more large and rigorous trials to examine whether thrombolytic therapy is truly beneficial for pulmonary embolism.

Summary of findings for the main comparison. Thrombolytic therapy versus heparin: primary outcome measures for pulmonary embolism

Thrombolytic therapy versus heparin: primary outcome measures for pulmonary embolism

Patient or population: patients with acute pulmonary embolism
Setting: hospital
Intervention: thrombolytic therapy
Comparison: heparin

Outcomes (duration of follow-up: from 7 days to 12 months)	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Heparin	Thrombolytic therapy			
Death from all causes	**Study population**		**OR 0.57** (0.37 to 0.87)	2167 (17)	⊕⊕⊖⊖ low[a]
	49 per 1000	**28 per 1000** (19 to 43)			
	Moderate				
	50 per 1000	**29 per 1000** (19 to 44)			
Recurrence of pulmonary emboli	**Study population**		**OR 0.51** (0.29 to 0.89)	1898 (10)	⊕⊕⊖⊖ low[a]
	39 per 1000	**20 per 1000** (12 to 35)			
	Moderate				
	42 per 1000	**22 per 1000** (13 to 38)			
Major haemorrhagic events	**Study population**		**OR 2.9** (1.95 to 4.31)	1897 (12)	⊕⊕⊖⊖ low[a]
	38 per 1000	**102 per 1000** (71 to 145)			
	Moderate				

	31 per 1000	**85 per 1000** (59 to 121)			
Minor haemorrhagic events	**Study population**		**OR 3.03** (1.60 to 5.73)	1553 (10)	⊕⊖⊖⊖ very low[a,b]
	101 per 1000	**253 per 1000** (152 to 391)			
	Moderate				
	107 per 1000	**266 per 1000** (161 to 407)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels for very serious risk of bias (due to high risk of selection, performance, and detection bias in most included studies).
[b]Downgraded by one level for serious inconsistency (due to substantial heterogeneity; I^2 = 57%).

BACKGROUND

Description of the condition

A pulmonary embolus, or a blood clot in the artery of the lungs, is a life-threatening condition known as 'pulmonary embolism (PE)' that is accompanied by significant morbidity and mortality. Massive and submassive PEs are subtypes of PE that are often encountered in the literature, even though the definitions of these subtypes are often vague and can lead to ambiguity (Goldhaber 2002). Because the severity and prognosis of PE vary widely, risk stratification after PE diagnosis is essential. The American Heart Association defines massive PE, submassive PE, and low-risk PE based on associated clinical deterioration and short-term mortality (Table 1; Jaff 2011; Sista 2017). Submassive or massive PE has been used interchangeably with the term intermediate-risk or high-risk PE, respectively (Gupta 2018).

Several options are available for the management of PE. Anticoagulation therapy forms the foundation of PE management (Hepburn-Brown 2018). In massive or high-risk PE, where restoration of pulmonary arterial flow is urgently required due to right ventricular failure, prompt therapeutic intervention is imperative. In such cases, thrombolysis (peripheral or catheter-directed) or surgical embolectomy should be considered (Hepburn-Brown 2018; Tapson 2017).

Description of the intervention

Although the thrombotic origin of PE has been well documented for almost two centuries, anticoagulation (anti-clotting drugs) as treatment for venous thromboembolism (VTE) dates back less than a century, and thrombolysis was initiated only relatively recently. In 1962, Browse and James reported that streptokinase could lyse (break up) pulmonary emboli in dogs and humans. Four patients treated with different dosage regimens experienced striking clinical improvement (Browse 1962). Additional studies show that patients who had hypotension (low blood pressure) responded quickly to streptokinase therapy, and their lung scans returned almost completely to normal (Bottiger 1994; Browse 1962; Chesterman 1969). However, improvement was less marked in those with associated cardiopulmonary disease and recurrent emboli (Hirsh 1971; Meneveau 2006).

The findings of four clinical studies of urokinase for PE indicate that improvement with urokinase was more dramatic than with heparin alone (Genton 1968; Sasahara 1967; Sautter 1967; Tow 1967). Based on this promising experience, the National Heart and Lung Institute organised a multi-institutional randomised controlled trial (RCT) to evaluate thrombolytic agents for treatment of PE. Results of Phase I (the Urokinase Pulmonary Embolism Trial - UPET) show that a 12-hour infusion of urokinase followed by heparin and oral anticoagulants, compared to heparin and oral anticoagulants alone, increased the resolution rate of pulmonary thromboemboli (Hyers 1970). Phase II (the Urokinase-Streptokinase Pulmonary Embolism Trial - USPET), completed in 1973, shows comparable results for two additional thrombolytic regimens - 24 hours of streptokinase and 24 hours of urokinase. Increasing the duration of urokinase administration to 24 hours conferred little benefit, and the distinction between 24 hours of urokinase and 24 hours of streptokinase was not clear (UPET Study Group 1974). These trials did not document actual improvement in survival; however, patients with massive embolism did derive major physiological benefit. Therefore, thrombolytic agents may be useful for severely ill patients with massive embolism or submassive embolism, especially when accompanied by shock.

In the late 1980s, recombinant tissue-type plasminogen activator (rt-PA) was introduced for treatment of acute PE, and an RCT reported its faster action and greater safety in comparison with urokinase (Goldhaber 1988). One multi-centre study shows that rt-PA decreased mean pulmonary arterial pressure (Meyer 1992). Effects of intravenous rt-PA on arterial blood gases and right ventricular function were compared with the effect of heparin treatment in acute PE. Results show that rt-PA is more effective for acute PE than heparin alone, and that a high dose of rt-PA leads to rapid improvement in arterial blood gases and lung perfusion images with no clinical episodes of recurrent PE (Goldhaber 1993; Yamasawa 1992). The collaborative PIOPED study suggested that rt-PA given over two hours has little effect on angiographic clot burden but may produce some improvement in haemodynamics. However, this treatment is not without risk (Tapson 2017). Until now, the effectiveness of thrombolytic therapy in PE remains under discussion (Eberle 2018; Hepburn-Brown 2018).

Why it is important to do this review

Although good evidence shows that thrombolytic agents are superior to heparin alone in accelerating the lysis of pulmonary emboli, restoring normal pulmonary circulation, and decreasing strain on the right side of the heart, few data are available on their long-term benefits for PE (Chatterjee 2014). Studies of long-term benefit of thrombolytic therapy for patients with PE suggest that thrombolytic therapy preserves the normal haemodynamic response to exercise and maintains cardiac output during long-term follow-up, possibly preventing recurrence of VTE and development of pulmonary hypertension (Sharma 2000).

Although it is difficult to prove that thrombolytic agents decrease mortality from pulmonary emboli, one large registry shows that thrombolytic treatment was associated with a 50% reduction in death risk among clinically stable patients with right ventricular enlargement (Konstantinides 1999), and another prospective RCT shows that thrombolytic therapy reduced the mortality rate of massive acute PE (Jerjes-Sánchez 1995).

Different thrombolytic agents - rt-PA, alteplase, streptokinase, and urokinase - are almost equally efficacious in dissolving clots. However, these agents are not without risk, sometimes leading to frequent massive bleeding, including intracranial haemorrhage (Chatterjee 2014; Dalla-Volta 1992). Other studies show that bleeding and fever were increased in streptokinase-treated patients, but both were generally controllable, with most bleeding occurring at the puncture site (Goldhaber 1993; Sasahara 1973). Several recent meta-analyses conducted to assess the efficacy and safety of thrombolytic therapy for treatment of PE show no obvious differences in mortality nor in risk of PE relapse between the group of patients receiving thrombolytic agents and the group not receiving them (Cao 2014; Gao 2015; Liu 2014; Marti 2014; Nakamura 2014). However, they reveal substantial differences between these two groups with regard to the risk of bleeding events (Chatterjee 2014; Gao 2015).

Although most studies agree that thrombolytic agents are superior to heparin alone in accelerating the lysis of pulmonary thromboemboli, their benefits in terms of reduced death rate from

PE and influence on survival and risks of associated haemorrhagic complications remain unclear, especially for patients with submassive, or intermediate-risk, PE. This review will attempt to ascertain the efficacy of thrombolytic agents for treatment of PE. This is the third update of a review first published in 2006.

OBJECTIVES

To assess the effects of thrombolytic therapy for acute pulmonary embolism.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) that compared thrombolytic therapy (e.g. streptokinase, urokinase, recombinant tissue plasminogen activator (rt-PA), alteplase) followed by heparin versus heparin alone, heparin plus placebo, or surgical intervention (e.g. embolectomy) for people with acute pulmonary embolism (PE). We did not include trials that compared two different thrombolytic agents or different doses of the same thrombolytic drug.

Types of participants

We included participants who had symptoms or signs of PE, confirmed by pulmonary angiography, ventilation/perfusion lung scan, or another validated measurement.

Types of interventions

We included any type of thrombolytic drug (e.g. streptokinase, urokinase, rt-PA, alteplase) followed by heparin versus heparin alone, heparin plus placebo, or surgical intervention (e.g. embolectomy).

Types of outcome measures

We analysed the following clinical outcome measures on an intention-to-treat (ITT) basis.

Primary outcomes

- Death from all causes
- Recurrence of pulmonary emboli
- Haemorrhagic events
  - Major haemorrhagic events: a decreased haemoglobin concentration > 2 g/dL; retroperitoneal or intracranial bleeding; transfusion of two or more units of blood, which may or may not lead to discontinuation of anticoagulant treatment
  - Minor haemorrhagic events: other bleeding events not meeting the criteria for major bleeding

Secondary outcomes

- Haemodynamic improvement and thrombolysis: immediate clinical, haemodynamic, angiographic, perfusion lung scanning, or echocardiographic outcomes or the rapidity of resolution of PE as judged by the change in total pulmonary resistance (TPR) over the initial hours
- Chronic thromboembolic pulmonary hypertension after three months, six months, and one year, and at the end of the follow-up period
- Differences in coagulation parameters over time
- Post-thrombotic syndrome (PTS): complications after deep vein thrombosis (DVT) may include persistent oedema (swelling), pain, purpura (bleeding into the skin), increased skin pigmentation, eczematoid (eczema-like) dermatitis, pruritus (itchiness), ulceration, and cellulitis (bacterial infection just below the skin). All of these complications result from impaired return of blood through the veins of the lower leg to the heart. This is determined by using any validated measurement for PTS
- Escalation of treatment
- Hospital stay
- Survival time
- Composite clinical outcome: sum per participant of mortality, recurrent PE, and major and minor haemorrhagic events
- Quality of life (QoL)
- Healthcare cost comparison

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for randomised controlled trials and controlled clinical trials without language, publication year, or publication status restrictions.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web, searched on 16 April 2018).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, and Cochrane Register of Studies Online (CRSO; 2018, Issue 3).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, and Ovid MEDLINE®) (searched from 1 January 2017 to 16 April 2018).
- Embase Ovid (searched from 1 January 2017 to 16 April 2018).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Ebsco (searched from 1 January 2017 to 16 April 2018).
- Allied and Complementary Medicine Database (AMED) Ovid (searched from 1 January 2017 to 16 April 2018).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. When appropriate, we combined these strategies with adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6; Lefebvre 2011). We have provided the search strategies used for major databases in Appendix 1.

The Information Specialist searched the following trials registries on 16 April 2018.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

For this update, review authors searched all references from included studies.

Data collection and analysis

Selection of studies

Two review authors (JY, QH) independently assessed the titles and abstracts of all trial reports identified by the searches. Whenever possible, we obtained the full-text hard copies for studies that appeared to fulfil the selection criteria. Each review author had a list of selected papers and duplicate sets of the papers for independent analyses. To ascertain that the study met the inclusion criteria, we used a standard form to collect information concerning type of study, types of participants, and types of interventions, and we resolved disagreements through discussion.

Data extraction and management

Two review authors (JY, QH) independently extracted information on participants, methods, interventions, outcomes, and results using a pre-tested form, resolving disagreements through discussion.

Assessment of risk of bias in included studies

We recorded data regarding the methodological criteria employed by investigators in all included studies. We have presented in the review a narrative summary in the 'Risk of bias' tables and have discussed these details in the text where relevant. Two review authors (JY, QH) independently assessed trials for risk of bias with regard to adequate sequence generation; allocation concealment; blinding of participants, personnel, and outcomes assessors; attrition bias (i.e. whether all participants were accounted for in the analysis (intention-to-treat, or ITT)); selective reporting; and other types of bias. We graded each domain as 'low risk of bias', 'high risk of bias', or 'unclear risk of bias' according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Sequence generation

Examples of randomisation methods falling into each risk of bias category for generation of the allocation sequence include the following.

- Low risk of bias: adequate generation of allocation sequence encompasses randomisation methods such as computer-generated numbers, a table of random numbers, shuffling of cards or envelopes, coin or dice tossing, and drawing of lots.
- High risk of bias: inadequate generation of allocation sequence refers to group allocations by case record number; date of birth; day, month, or year of admission; judgement of the clinician or the participant; laboratory test or series of tests; and availability of the intervention.
- Unclear risk of bias: study authors reported generation of the allocation sequence unclearly.

Allocation concealment

Examples of methods used for allocation concealment that fall into each category include the following.

- Low risk of bias: adequate allocation concealment was achieved through central randomisation (including telephone, web-based, and pharmacy-controlled randomisation; sealed opaque containers administered serially to participants).
- High risk of bias: inadequate allocation concealment occurred via any procedure that was transparent before allocation.
- Unclear risk of bias: trials provided insufficient information to allow a judgement on risk of bias.

Blinding

Double-blinding methods include masking the clinician (person delivering treatment), the participant, and the outcomes assessor to treatment allocation. We determined risk of bias in line with the following examples.

- Low risk of bias: we considered masking of both participants and the results assessor as carrying low risk of performance and detection bias. We did not consider blinding necessary for mortality or other outcomes not influenced by blinding.
- High risk of bias: non-blinded assessment outcomes such as quality of life (QoL) carry high risk of bias; for objective outcomes (e.g. death), we did not consider this necessary.
- Unclear risk of bias: studies did not provide sufficient information for a judgement of 'yes' or 'no'. We considered single-blinding of the results assessor to carry moderate risk of performance bias, detection bias, or both. If single-blinding was performed on participants but not on the results assessor, we considered the outcomes to carry high risk of detection bias.

Incomplete outcome data

'Incomplete outcome data' refers to a mismatch between the number of randomised participants and the number included in the main analysis. Examples of the three risk categories include the following.

- Low risk of bias: trials are not missing outcome data or note few exclusions and attrition; an ITT analysis is possible.
- High risk of bias: the rate of exclusion, attrition, or both is higher than 15%, or there are wide differences in exclusions between intervention group and control group, whichever ITT analysis is used.
- Unclear risk of bias or moderate risk of bias: trials report the rate of exclusion or attrition (or both) as higher than 10%, whichever ITT analysis is used.

Selective reporting

If the protocol of the included study was available, we compared outcomes in the protocol versus those in the published report. If the protocol was not available, we compared outcomes listed in the Methods section of the study against those presented in the Results.

Other bias

We assessed potential factors affecting the precision of an estimate of included studies.

- All quality criteria met: low risk of bias.
- One or more of the quality criteria met in part: unclear risk of bias.
- One or more criteria not met: high risk of bias.

We resolved disagreements about whether or not a trial fulfilled certain quality criteria through discussion with a third review author (BD). We have detailed all quality criteria ratings and supporting information in the 'Risk of bias' tables (see Characteristics of included studies).

Measures of treatment effect

We analysed the data using RevMan 5.3 (Review Manager 2014). We summarised dichotomous data as odds ratio (OR) and continuous data as mean difference (MD), using 95% confidence intervals (CIs) throughout.

Unit of analysis issues

For multiple-arm trials, we included the intervention group of interest according to the objective in our review. We took care to avoid double-counting of participants when we included multiple-arm trials. For cross-over trials, we planned to include the first period of the trial and to exclude the subsequent period to prevent interference with previous drugs, even if the trial reported a washout period. For cluster RCTs, we planned to calculate the effective sample size both in the intervention group and in the control group based on the numbers of clusters and participants, and then, when necessary, to use the generic inverse variance method to pool this type of data according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted trial authors for missing data. For this review, we analysed outcome measures on an ITT basis.

Assessment of heterogeneity

For detecting heterogeneity across studies, we used the Chi^2 test with a 10% level of statistical significance, establishing a P value of 0.1 as the cutoff value to determine statistical significance. We used the I^2 statistic to estimate total variation across studies. We considered an I^2 value less than 40% to represent low-level heterogeneity, 40% to 50% as representing a moderate level of heterogeneity, 50% to 90% as showing a substantial level of heterogeneity, and 75% to 100% as indicating considerable heterogeneity (Higgins 2011).

Within each subgroup, we used Chi^2 analyses to test for statistical evidence of heterogeneity among studies, and we used I^2 to measure the degree of inconsistency across studies. When Chi^2 analysis was significant and I^2 values were in excess of 50%, we analysed differences in participant selection, baseline values, risk of bias, design, and methods that could possibly explain the heterogeneity.

Assessment of reporting biases

Funnel plots have a limited role when used with small numbers of studies (< 10) in a meta-analysis. Our review included only a few studies (< 10) in each subgroup, so we did not use this approach to assess reporting bias. In the future, if we can include more studies in a subgroup, we will use a funnel plot to assess the presence of publication bias. However, we did attempt to access the protocols of the included studies to assess selective reporting bias.

Data synthesis

We used a random-effects model for pooled analysis of heterogeneous data (I^2 = 40% to 100%) and a fixed-effect model for individual study data and pooled analyses of homogeneous data (I^2 < 40%). We used the Mantel-Haenszel method to synthesise dichotomous data and the inverse variance method to synthesise continuous data. We summarised dichotomous data as odds ratio (OR) and continuous data as mean difference (MD) and used 95% confidence intervals (CIs) throughout. When it was not possible to undertake meta-analyses, we described a systematic approach to synthesising the findings of multiple studies.

Subgroup analysis and investigation of heterogeneity

We analysed subgroups according to the different types of interventions included in the review. We also performed a subgroup analysis according to different types of PE (massive/submassive) for the primary outcomes. We analysed studies of submassive PE that used an ultrasound-assisted, catheter-directed thrombolysis system (USAT (rt-PA)) separately from other studies investigating submassive PE because USAT (rt-PA) is a new and different intervention from traditional thrombolytic therapy. For studies that included both massive and other unknown PE types, we categorised participants as 'type of PE unknown'. We used the interaction test (whereby an I^2 statistic is computed for heterogeneity across subgroup results) for subgroup differences in Review Manager 2014 as the basis for interpreting subgroup analyses. For future updates, and if the necessary data become available, we plan to analyse subgroups according to different doses and durations of intervention.

Sensitivity analysis

We performed a sensitivity analysis according to the methodological quality of included studies. We excluded very low-quality studies from the pooled meta-analysis. In this review, we defined very low-quality studies as having high risk in two or more risk of bias domains.

'Summary of findings' table

In this review, we included only RCTs. We used the GRADE profiler to help us create Summary of findings for the main comparison and reported the primary outcomes of death from all causes; recurrence of pulmonary emboli; and major and minor haemorrhagic events based on an ITT population (GRADEpro GDT 2015). We downgraded the evidence from 'high quality' by one or two levels for serious or very serious study limitations (risk of bias), indirectness and inconsistency of evidence, imprecision of effect estimates, or potential publication bias according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

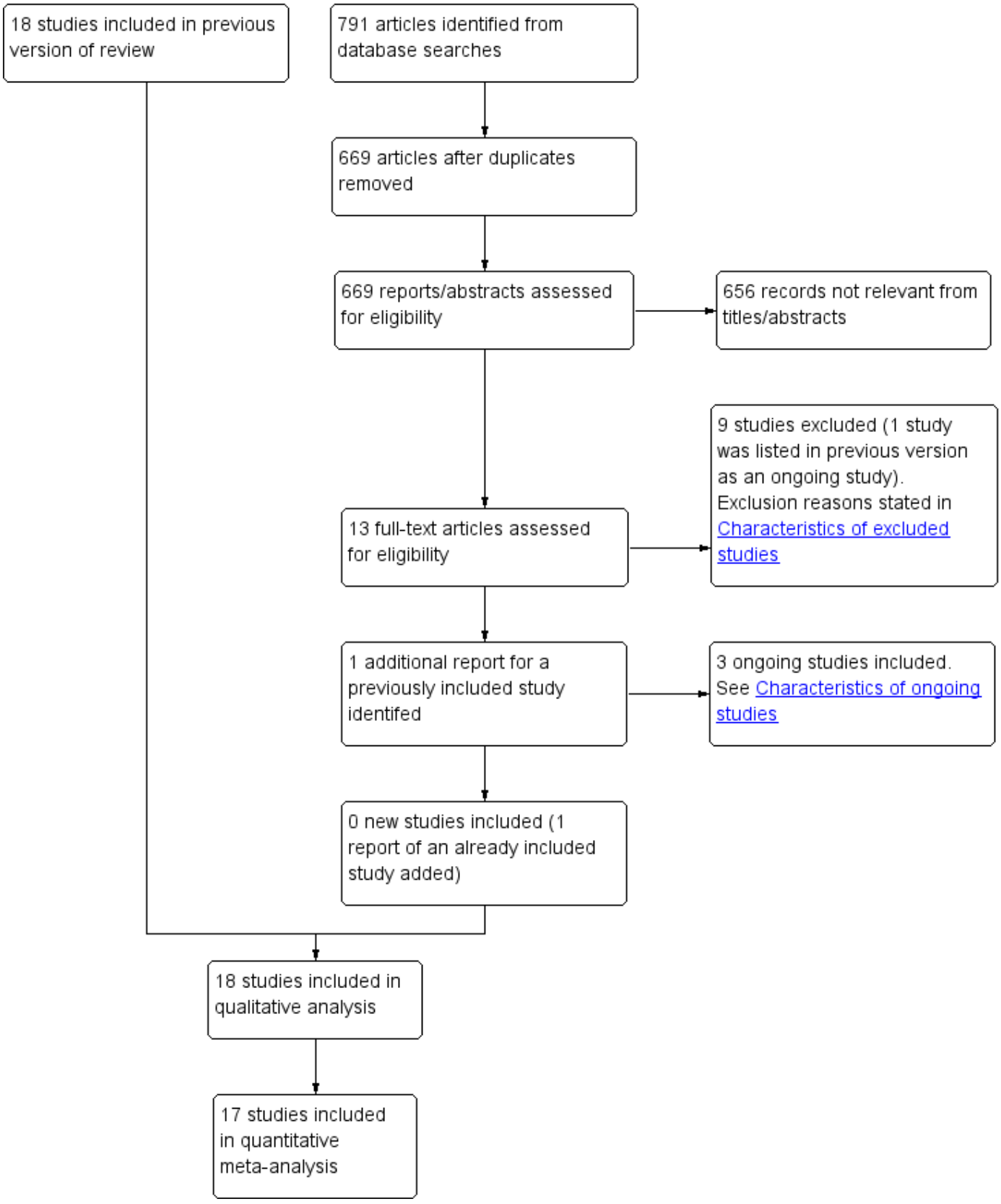
Description of studies

Results of the search

We included no new studies in this 2018 update. We identified one additional report for an already included study (Meyer 2014). We excluded nine new additional studies (Alexandru Ion 2017; Barrios 2017; Carroll 2018; Jing 2018; Lehnert 2017; NCT00680628; NCT00968929; Xu 2016; Yilmazel 2018). We had previously listed one

study as ongoing (NCT00680628). We identified three new ongoing studies (EUCTR2017-005075-91-DK; NCT02604238; NCT03218410). See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included a total of 18 studies with 2197 participants (Becattini 2010; Dalla-Volta 1992; Dotter 1979; Fasullo 2011; Goldhaber 1993; Jerjes-Sánchez 1995; Kline 2014; Konstantinides 2002; Kucher 2014; Levine 1990; Ly 1978; Marini 1988; Meyer 2014; PIOPED 1990; Sharifi 2013; Taherkhani 2014; Tibbutt 1974; UPETSG 1970). We were able to use 17 of the included trials (2167 participants) in the meta-analysis; the other study lacked outcome data (Marini 1988).

Design

All included RCTs used a parallel design and included two study arms (apart from Marini 1988, which had three arms). Nine were multi-centre RCTs (Becattini 2010; Dalla-Volta 1992; Kline 2014; Konstantinides 2002; Kucher 2014; Levine 1990; Meyer 2014; PIOPED 1990; UPETSG 1970); one was a two-centre study (Tibbutt 1974); and the remainder were single-centre studies (Dotter 1979; Fasullo 2011; Goldhaber 1993; Jerjes-Sánchez 1995; Ly 1978; Marini 1988; Sharifi 2013; Taherkhani 2014).

Participants

All trials focussed on adults aged 18 or over. Trials took place in Italy (Becattini 2010; Dalla-Volta 1992; Fasullo 2011), the United States (Dotter 1979; Goldhaber 1993; Kline 2014; PIOPED 1990; UPETSG 1970), Canada (Levine 1990), Norway (Ly 1978), Germany (Konstantinides 2002), Germany and other European countries (Kucher 2014; Meyer 2014), Iran (Taherkhani 2014), and the United Kingdom (Tibbutt 1974). Three studies did not describe the study setting or country (Jerjes-Sánchez 1995; Marini 1988; Sharifi 2013). All trials stated baseline data and analysed comparability. Eleven trials included participants with submassive PE (Becattini 2010; Dalla-Volta 1992; Fasullo 2011; Goldhaber 1993; Kline 2014; Konstantinides 2002; Kucher 2014; Levine 1990; Meyer 2014; Sharifi 2013; Taherkhani 2014), and only one study included only participants with massive PE (Jerjes-Sánchez 1995). We were unable to identify the type of PE in six studies (Dotter 1979; Ly 1978; Marini 1988; PIOPED 1990; Tibbutt 1974; UPETSG 1970).

Interventions

Studies involved different types of thrombolytics, including alteplase, urokinase, streptokinase, rt-PA, ultrasound-assisted catheter-directed thrombolysis system, and tenecteplase, usually followed by heparin. The control intervention was heparin alone in 11 included trials (Dalla-Volta 1992; Dotter 1979; Goldhaber 1993; Jerjes-Sánchez 1995; Kucher 2014; Ly 1978; Marini 1988; Sharifi 2013; Taherkhani 2014; Tibbutt 1974; UPETSG 1970). The remaining seven trials used placebo plus heparin (Becattini 2010; Fasullo 2011; Kline 2014; Konstantinides 2002; Levine 1990; Meyer 2014; PIOPED 1990). No studies compared thrombolytics versus surgical intervention.

Outcome measures

Investigators reported a variety of outcome measures. Most trials reported overall mortality, recurrence of PE, and haemorrhagic events. Main outcome measures also included perfusion lung scanning, haemodynamic outcomes, and angiographic score. Two trials that performed perfusion lung scanning reported data at several time points (first, third, and seventh days post treatment) (Levine 1990; UPETSG 1970). Three trials reported haemodynamic outcomes in nine subgroups (PIOPED 1990; Tibbutt 1974; UPETSG 1970). Four other trials reported length of hospital stay or hospitalised status of the participant, including rate of rehospitalisation (Kucher 2014; Meyer 2014; Sharifi 2013; Taherkhani 2014). Kline 2014 reported on functional capacity and quality of life (using the Venous Insufficiency Epidemiological and Economic Study, or VEINES, questionnaire and score). None of the trials assessed healthcare costs.

See the Characteristics of included studies table for further details.

Ongoing studies

We identified three new ongoing studies for this update (EUCTR2017-005075-91-DK; NCT02604238; NCT03218410), bringing the total number of ongoing studies to six (EUCTR2017-005075-91-DK; EudraCT: 2005-001070-27; NCT01531829; NCT02604238; NCT03218410). See Characteristics of ongoing studies for further details.

Excluded studies

For this 2018 update, we identified and excluded nine additional studies (Alexandru Ion 2017; Barrios 2017; Carroll 2018; Jing 2018; Lehnert 2017; NCT00680628; NCT00968929; Xu 2016; Yilmazel 2018). One study was previously listed as ongoing, but we excluded it from this update because the study was terminated (NCT00680628), bringing the total to 56 excluded studies (Abdelsamad 2011; Agnelli 1997; Alexandru Ion 2017; Barrios 2017; Bell 1974; Bell 1976; Bell 1977; Bhardwaj 2010; Carroll 2018; Charbonnier 1984; Chen 2009; Comerota 2009; De Takats 1973; Erkan 2002; Francois 1986; Goldhaber 1989; Goldhaber 1992; Goldhaber 1994; IRCT201104245625N2; Jin 2012; Jing 2018; Konstantinides 1998; Lehnert 2017; Liu 2012; Marder 1978; Meneveau 1997; Meneveau 1998; Meyer 1992; Miller 1971; Muhl 2007; NCT00968929; NCT00680628; NCT01956955; Ohayon 1986; Palla 1997; Pang 2007; Prandoni 1985; Research Group on Urokinase and PE 1984; Saponjski 2002; Sasahara 1975; Sharma 2000; Sors 1994; Tebbe 1999; Tebbe 2009; UKEP Study Group 1987; UPET Study Group 1974; Verstraete 1988; Wang 2006; Wang 2009; Wang 2010; Wu 2010; Xu 2016; Yang 2007; Yang 2011; Yilmazel 2018; Zhu 2008). See the Characteristics of excluded studies table for further details.

Risk of bias in included studies

We deemed all included studies to be at low or unclear risk for allocation and reporting bias. Two studies each were at high risk of selection bias (Jerjes-Sánchez 1995; Ly 1978), performance and detection bias (Goldhaber 1993; Taherkhani 2014), and attrition bias (Ly 1978; Tibbutt 1974), and seven studies were at high risk of other bias (Dotter 1979; Jerjes-Sánchez 1995; Kline 2014; Kucher 2014; Meyer 2014; Taherkhani 2014; Tibbutt 1974). Only Meyer 2014 provided sufficient detail for assessment of all domains as having low or high risk of bias, and Marini 1988 and Sharifi 2013 did not provide enough information on any domain to allow a clear determination of risk. Furthermore, for four studies, all domains had either unclear or high risk of bias (Dotter 1979; Kucher 2014; Ly 1978; Tibbutt 1974).

All in all, we identified for inclusion in this review four studies with high risk of overall bias, that is, two or more assessment domains carried high risk of bias (Jerjes-Sánchez 1995; Ly 1978; Taherkhani 2014; Tibbutt 1974). We therefore conducted a sensitivity analysis that excluded these studies. See Figure 2 and Figure 3 for a summary of the general risk of bias of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

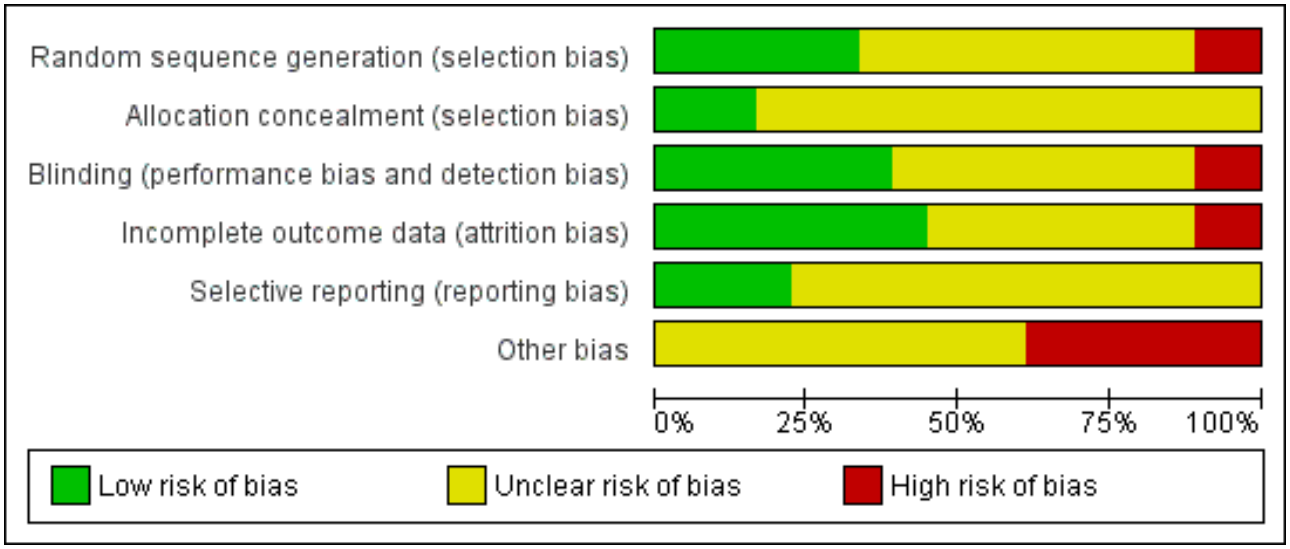
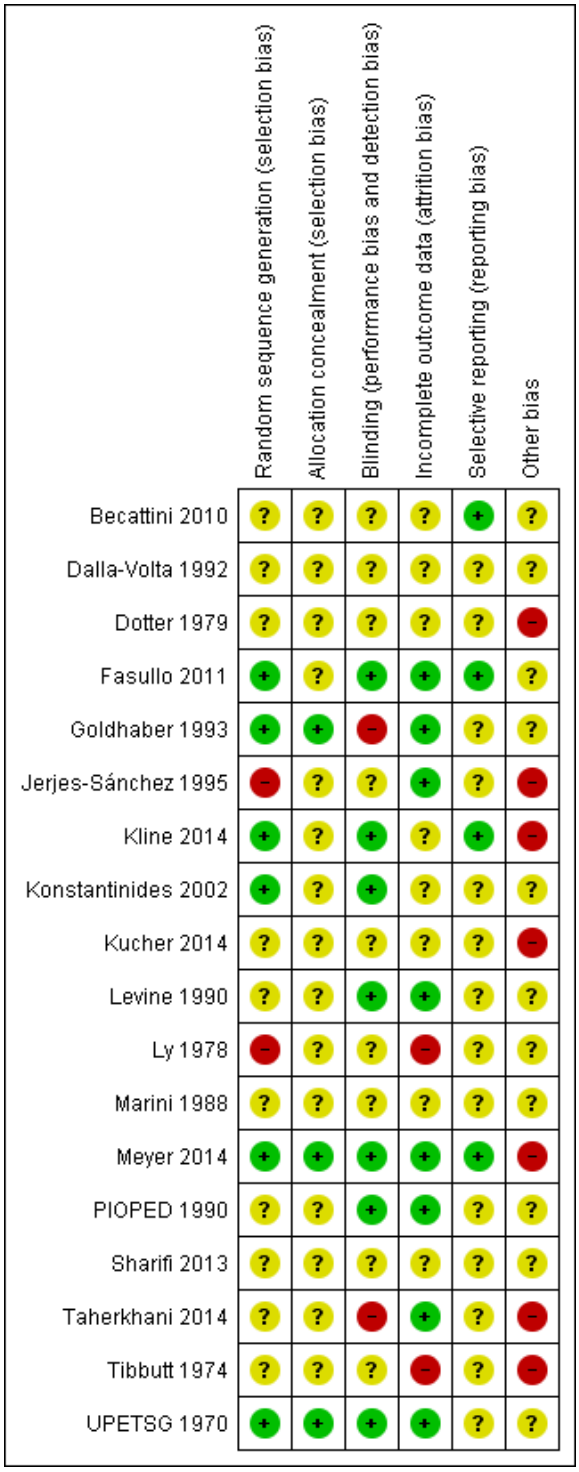


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Six trials clearly described appropriate random sequence generation (Fasullo 2011; Goldhaber 1993; Kline 2014; Konstantinides 2002; Meyer 2014; UPETSG 1970), and nine trials did not (Becattini 2010; Dalla-Volta 1992; Dotter 1979; Kucher 2014; Levine 1990; PIOPED 1990; Sharifi 2013; Taherkhani 2014; Tibbutt 1974). Although two studies used the appropriate method to generate the sequence, Ly 1978 did not randomise five included participants (four in the streptokinase group, one in the heparin group), and numbers were unbalanced between the intervention group and the control group at the onset of PE in Jerjes-Sánchez 1995. Therefore, we judged these two studies as having high risk for selection bias.

Only three of the 18 trials described adequate allocation concealment (Goldhaber 1993; Meyer 2014; UPETSG 1970). Twelve trials poorly reported methods, mainly by omitting any mention of allocation concealment (Becattini 2010; Dalla-Volta 1992; Dotter 1979; Fasullo 2011; Jerjes-Sánchez 1995; Konstantinides 2002; Kucher 2014; Levine 1990; Marini 1988; PIOPED 1990; Taherkhani 2014; Tibbutt 1974). Three trials reported using sealed envelopes during concealment, but their descriptions were not detailed enough (sequential numbering and opaqueness) to allow a definitive judgement (Kline 2014; Ly 1978; Sharifi 2013). We contacted trial authors for further clarification but received no response.

Blinding

Seven trials reported single blinding (Becattini 2010; Dalla-Volta 1992; Kucher 2014; Ly 1978; Sharifi 2013; Taherkhani 2014; Tibbutt 1974), and seven trials used double-blinding (Fasullo 2011; Kline 2014; Konstantinides 2002; Levine 1990; Meyer 2014; PIOPED 1990; UPETSG 1970). Three trials did not document blinding (Dotter 1979; Jerjes-Sánchez 1995; Marini 1988), and one trial was non-blinded (Goldhaber 1993). Taherkhani 2014 reported that blinding was broken, so we assigned it high risk of bias.

Incomplete outcome data

Apart from Dalla-Volta 1992 and Dotter 1979, all trials either described the withdrawal rate or provided sufficient information for this to be calculated. Withdrawal rates varied from 0% in Fasullo 2011, Jerjes-Sánchez 1995, Levine 1990, PIOPED 1990, Taherkhani 2014, and UPETSG 1970, to 45% in Ly 1978 (among participants with an angiographic response to 72 hours of treatment in the heparin group) and 63% in Tibbutt 1974 (for long-term follow-up at six months; data unstable between different follow-up periods). The remaining two studies described post-randomisation exclusions well (Goldhaber 1993; Meyer 2014).

Selective reporting

Four studies had low reporting bias according to their study protocols (Becattini 2010; Fasullo 2011; Kline 2014; Meyer 2014). We were unable to access the protocols of the remaining included studies, so we could not assess their risk of selective reporting bias.

Other potential sources of bias

We judged seven trials to be at high risk of other bias, and the rest carried unclear risk. Reasons included small sample size, potential conflicts of interest, inconsistent randomisation, and non-ITT methods of analysing outcome data. First, all included studies had relatively small sample sizes. The largest sample size in the included studies was 1006 participants (Meyer 2014), and the smallest was only eight (Jerjes-Sánchez 1995). The limited number of participants could introduce a potential sources of bias. Likewise, pharmaceutical companies funded some studies, which may constitute a conflict of interest, even though some study authors state there was no influence from these companies during the whole study period (Dotter 1979; Kline 2014; Kucher 2014; Meyer 2014). Taherkhani 2014 included a small sample size, and although 59 participants had submassive pulmonary thromboembolism, only 50 participants were randomised. In the same way, Tibbutt 1974 included a small sample size, and two participants were transferred from the control group to the treatment group; moreover, investigators did not analyse outcome data on an ITT basis. Therefore, we assessed these studies as having high risk of other potential bias.

Effects of interventions

See: **Summary of findings for the main comparison** Thrombolytic therapy versus heparin: primary outcome measures for pulmonary embolism

Of the 18 trials that matched the inclusion criteria of this review, we were not able to include one trial in the meta-analysis because it provided no data that we could extract (Marini 1988). Therefore, our meta-analysis included 17 trials with a total of 2167 participants. We analysed primary outcome measures on an ITT basis. We analysed all participants who dropped out of the study according to their original group, regardless of whether or not they completed or received that treatment.

Primary outcome measures

Death from all causes

The 17 trials included in the meta-analysis reported a total of 83 deaths: 30 in the thrombolytics group and 53 in the heparin group. Pooled analyses show that across all studies, giving thrombolytics reduced the incidence of death (OR 0.57, 95% CI 0.37 to 0.87, 2167 participants, P = 0.01, low-quality evidence; Analysis 1.1). The analysis showed that statistical heterogeneity between studies was at a low level (Chi^2 = 12.08, P = 0.74, I^2 = 0%). However, after we excluded the studies at high risk of bias as part of the sensitivity analysis (Jerjes-Sánchez 1995; Ly 1978; Taherkhani 2014; Tibbutt 1974), we found no clear evidence to support a difference between the two groups for mortality (OR 0.66, 95% CI 0.42 to 1.06, 2054 participants, P = 0.08; Analysis 2.1). The analysis still shows that statistical heterogeneity between studies was at a low level (Chi^2 = 6.76, P = 0.87, I^2 = 0%). Because some studies carried high risk of bias, we downgraded the quality of evidence for this outcome from high to low (Summary of findings for the main comparison). We also performed a subgroup analysis according to different types of PE (massive/submassive/unknown types of PE) and found no clear subgroup effects between subgroups (P = 0.31). Only the massive PE subgroup showed that thrombolytic therapy may have an effect on death (Analysis 3.1). We found no clear evidence to support a difference between thrombolytic therapy and heparin for death in the other subgroups.

An additional report of Meyer 2014 included for this 2018 update described long-term mortality rates for patients with intermediate-risk PE. Researchers in this study followed about 70% of participants over two years (median 37.8 months) and reported that tenecteplase treatment did not affect long-term mortality rates compared to placebo and heparin. We were unable to include the data in our meta-analysis as the other included studies reported short-term mortality (follow-up period less than three months for most studies). Further analyses may be possible for future updates.

Recurrence of pulmonary emboli

Ten studies reported on the recurrence of pulmonary emboli (Becattini 2010; Dalla-Volta 1992; Dotter 1979; Fasullo 2011; Goldhaber 1993; Konstantinides 2002; Levine 1990; Meyer 2014; Sharifi 2013; UPETSG 1970). Pooled data comparing thrombolytics versus heparin show that the thrombolytics group experienced less recurrence than the heparin group (OR 0.51, 95% CI 0.29 to 0.89, 1898 participants, P = 0.02, low-quality evidence; Analysis

1.2). Analyses show that statistical heterogeneity between studies was at a low level (Chi^2 = 5.27, P = 0.73, I^2 = 0%). We did not perform a sensitivity analysis, as the studies identified as having high risk of bias did not report this outcome. However, for most included studies, we downgraded the quality of evidence for this outcome from high to low for high risk of selection, performance, and detection bias (Summary of findings for the main comparison). We also performed a subgroup analysis according to different types of PE (submassive/unknown types of PE) and found no conclusive evidence showing a difference between subgroups (P = 0.33). The 'unknown types of PE' subgroup provided no clear evidence to support a difference between thrombolytic therapy and heparin (Analysis 3.2).

Major and minor haemorrhagic events

Major haemorrhagic events

Twelve studies reported on major haemorrhagic events (Becattini 2010; Dalla-Volta 1992; Fasullo 2011; Goldhaber 1993; Kline 2014; Konstantinides 2002; Levine 1990; Ly 1978; Meyer 2014; PIOPED 1990; Tibbutt 1974; UPETSG 1970). The total number of these events was 134: 98 in the thrombolytics group and 36 in the heparin group. Pooled analyses show that across 12 studies comparing thrombolytics versus heparin, more major bleeding events occurred after treatment with thrombolytics (OR 2.90, 95% CI 1.95 to 4.31, 1897 participants, P < 0.0001, low-quality evidence; Analysis 1.3). The result was not changed even after Ly 1978 and Tibbutt 1974 were excluded for high risk of bias (OR 3.00, 95% CI 1.99 to 4.53, 1842 participants, P < 0.0001; Analysis 2.2). Analysis shows low levels of statistical heterogeneity between studies both before (Chi^2 = 10.70, P = 0.38, I^2 = 7%) and after (Chi^2 = 10.16, P = 0.25, I^2 = 21%) the sensitivity analysis. We downgraded the quality of evidence for this outcome from high to low for possible bias (Summary of findings for the main comparison). We also performed a subgroup analysis according to different types of PE (submassive/unknown types of PE) and found no subgroup effects between subgroups (P = 0.27; Analysis 3.3).

Minor haemorrhagic events

Ten studies reported on minor haemorrhagic events (Becattini 2010; Dalla-Volta 1992; Fasullo 2011; Kucher 2014; Levine 1990; Ly 1978; Meyer 2014; Taherkhani 2014; Tibbutt 1974; UPETSG 1970). Pooled analyses comparing thrombolytics versus heparin show more minor haemorrhagic events in the thrombolytics group (OR 3.03, 95% CI 1.60 to 5.73, 1553 participants, P < 0.001, very low-quality evidence; Analysis 1.4). Analyses show that statistical heterogeneity between the included studies was at a substantial level (Chi^2 = 20.71, P = 0.01, I^2 = 57%), so we used a random-effects model for the pooled analysis. After excluding the three studies at high risk of bias (Ly 1978; Taherkhani 2014; Tibbutt 1974), we still observed this difference between the two groups (OR 4.05, 95% CI 2.17 to 7.54, 1448 participants, P < 0.01; Analysis 2.3). We downgraded the quality of evidence for this outcome from high to very low for possible bias and large heterogeneity (Summary of findings for the main comparison). We also performed a subgroup analysis according to different types of PE (submassive/unknown types of PE) and found a subgroup effect between subgroups (P = 0.007); we found a difference between the two groups in the 'submassive PE' subgroup but not in the 'unknown types of PE' subgroup (Analysis 3.4).

Secondary outcome measures

Haemodynamic improvement and thrombolysis

Pulmonary arterial systolic pressure improvement

One study compared urokinase versus heparin in 147 participants at 24 hours after treatment (UPETSG 1970), and one study compared streptokinase versus heparin in 21 participants at 72 hours after treatment (Tibbutt 1974); both show that thrombolytic treatment had a small effect on pulmonary arterial systolic pressure improvement (mean difference (MD) -4.41 mmHg, 95% CI -4.62 to -4.20; MD -11.60 mmHg, 95% CI -20.81 to -2.39, respectively; Analysis 4.1). Although not pooled, these results indicate that thrombolytics may decrease pulmonary arterial systolic pressure to a greater extent than heparin, and that the effect is similar for various thrombolytics. However, the high risk of bias attached to Tibbutt 1974 warrants caution when results are interpreted.

Mean pulmonary arterial pressure improvement

Three studies comparing thrombolytics versus heparin show contradictory results in the improvement in mean pulmonary arterial pressure (PIOPED 1990; Tibbutt 1974; UPETSG 1970). Although rt-PA versus heparin at 1.5 hours shows no clear effect for thrombolytic treatment according to PIOPED 1990 (MD -3.00 mmHg, 95% CI -16.91 to 10.91; Analysis 4.2), the remaining two studies reported a small effect on mean pulmonary arterial pressure improvement at 24 and 72 hours in favour of thrombolytic treatment (MD -4.41 mmHg, 95% CI -4.62 to -4.20; MD -7.50 mmHg, 95% CI -12.80 to -2.20, respectively; Analysis 4.2).

Right ventricular end-diastolic pressure improvement

Two studies show contradictory results with regards to right ventricular end-diastolic pressure improvement. UPETSG 1970 compared urokinase versus heparin in 142 participants, and after 24 hours, noted a small difference in right ventricular end-diastolic pressure improvement in favour of thrombolytic treatment (MD -2.21 mmHg, 95% CI -2.35 to -2.07; Analysis 4.3). On the other hand, Tibbutt 1974 compared streptokinase versus heparin in 19 participants, observing no clear difference after 72 hours (MD 1.20 mmHg, 95% CI -2.59 to 4.99; Analysis 4.3). However, we judged Tibbutt 1974 to be at high risk of bias in this review, so results must be interpreted with caution.

Total pulmonary resistance improvement

UPETSG 1970 compared urokinase versus heparin in 113 participants, finding a small difference in favour of urokinase at 24 hours after treatment (MD -0.33 dyn·s·cm^{-5}, 95% CI -0.35 to -0.31; Analysis 4.4). Tibbutt 1974 compared streptokinase versus heparin in 12 participants at 72 hours after treatment, finding no clear difference between treatment and control (MD 0.30 dyn·s·cm^{-5}, 95% CI -0.83 to 1.43; Analysis 4.4). PIOPED 1990 compared rt-PA versus heparin in 13 participants at 1.5 hours after treatment, and although these results favour rt-PA, no clear difference between the two groups is evident (MD -180.00 dyn·s·cm^{-5}, 95% CI -883.55 to 523.55; Analysis 4.4). Again, high risk of bias for Tibbutt 1974 warrants caution when results are interpreted.

Cardiac index improvement (L/min/m^2)

Two studies show contradictory results for cardiac index improvement (Tibbutt 1974; UPETSG 1970). Tibbutt 1974 compared streptokinase versus heparin in 13 participants, observing a small

difference in cardiac index improvement in favour of heparin (MD -0.60, 95% CI -1.05 to -0.15; Analysis 4.5). UPETSG 1970, which compared urokinase versus heparin in 115 participants, reported a small difference in cardiac index improvement in favour of urokinase (MD 0.20, 95% CI 0.15 to 0.25; Analysis 4.5). Results for Tibbutt 1974 must be interpreted with caution due to high risk of bias.

Other haemodynamic outcomes

UPETSG 1970, with 160 participants, compared urokinase versus heparin at 24 hours after treatment, showing small differences in favour of urokinase in right ventricular systolic pressure (MD -6.90 mmHg, 95% CI -7.25 to -6.55; Analysis 4.6), right arterial mean pressure (MD -1.94 mmHg, 95% CI -2.05 to -1.83; Analysis 4.7), arterial-venous oxygen difference (MD -0.31 vol %, 95% CI -0.37 to -0.25; Analysis 4.8), and arterial PO_2 (MD 8.45 mmHg, 95% CI 7.84 to 9.06; Analysis 4.9).

Perfusion lung scanning

UPETSG 1970 compared urokinase versus heparin, expressing perfusion defects as a percentage of total normal perfusion of both lungs. At days 1 and 2, results show a difference in favour of urokinase (day 1: MD 3.50%, 95% CI 1.32 to 5.68; Analysis 5.1; day 2: MD 3.10%, 95% CI 0.15 to 6.05; Analysis 5.2). Subsequent results include the following: at day 5: MD 2.00% (95% CI -1.60 to 5.60; Analysis 5.3); at day 14: MD 0.20% (95% CI -4.26 to 4.66; Analysis 5.5); and at one year MD -1.10% (95% CI -7.57 to 5.37; Analysis 5.7). These results show that on days 1 and 2 after treatment, either the total normal perfusion of both lungs or the proportion of lung not perfused in those treated with thrombolytics was greater than in those treated with heparin, and on days 5 and 14 and at one year follow-up, there was no clear effect for urokinase. A second study comparing rt-PA versus heparin (Goldhaber 1993), in which perfusion defects were expressed as the proportion of lung not perfused, also shows a small effect in favour of rt-PA at day 1 (MD 0.13%, 95% CI 0.05 to 0.21; Analysis 5.1).

Dalla-Volta 1992 compared alteplase plus heparin versus heparin alone, showing no clear effect on total lung score between the two groups at day 7 (MD 1.70, 95% CI -1.04 to 4.44; Analysis 5.4); however, results show a small difference in favour of alteplase at day 30 after treatment (MD 2.80, 95% CI 0.35 to 5.25; Analysis 5.6). Comparison of scores in terms of change from baseline in both groups provides no clear evidence to support a difference between the two groups at day 7 or at day 30 (day 7: MD 1.80, 95% CI -0.51 to 4.11; Analysis 5.4; day 30: MD 0.70, 95% CI -1.37 to 2.77; Analysis 5.6). These results show that alteplase plus heparin and heparin alone can improve total lung scores with similar effect, but at day 30, the score in the alteplase plus heparin group was higher than the score in the heparin alone group.

Levine 1990 compared rt-PA plus heparin versus placebo plus heparin, showing no difference in the number of participants with greater than 50% improvement on lung scan at 24 hours after treatment (OR 3.84, 95% CI 0.94 to 15.73; Analysis 6.1). We could not estimate this in the PIOPED 1990 study.

Pulmonary angiogram assessment

Researchers evaluated pulmonary angiograms using the Miller index (Miller 1971). The overall total score for pulmonary angiograms in the Dalla-Volta 1992 study shows a small reduction in the alteplase plus heparin group (MD -3.4, 95% CI -4.72 to -2.08; Analysis 7.1).

Ly 1978 and Tibbutt 1974 compared streptokinase versus heparin, and, when pooled, results show a small difference in angiographic score changes from baseline to 72 hours in favour of streptokinase (MD -9.3, 95% CI -12.81 to -5.78; Analysis 7.2). This indicates that changes in angiographic score from baseline to 72 hours after treatment were greater in participants treated with streptokinase than in those treated with heparin. These results must be interpreted with caution, because both studies carried high risk of bias according to our review criteria.

Echocardiograms

Five studies performed echocardiograms (Becattini 2010; Fasullo 2011; Goldhaber 1993; Kucher 2014; Taherkhani 2014). Goldhaber 1993 compared rt-PA plus heparin versus heparin alone; panellists decided by consensus whether right ventricular wall motion was normal or mildly (1+), moderately (2+), or severely (3+) hypokinetic. Tricuspid regurgitation was visually assessed according to the size of the largest colour doppler jet as absent, mild (1+), moderate (2+), or severe (3+). This study shows that the rt-PA group had increased numbers of participants with improved right ventricular wall movement (OR 2.90, 95% CI 0.98 to 8.60 at 3 hours; OR 3.20, 95% CI 1.20 to 8.57 at 24 hours; Analysis 8.1) and tricuspid regurgitation (OR 6.35, 95% CI 1.90 to 21.17 at 3 hours; OR 3.20, 95% CI 1.20 to 8.57 at 24 hours; Analysis 8.2).

Fasullo 2011 compared alteplase plus heparin versus heparin alone, assessing inferior vein cava, doppler acceleration time, paradoxical systolic septal motion, tricuspid annular plane systolic excursion, and B-type natriuretic peptide (BNP) values (at baseline; at 24, 48, and 72 hours; at six days; at discharge; and at three months and six months). Investigators found earlier improvement in the thrombolytics group in comparison with the placebo group, with evident differences after 24 hours that lasted throughout hospitalisation and during the follow-up period. Another study compared USAT (rt-PA) plus heparin versus heparin alone (Kucher 2014), reporting the right-to-left ventricular dimension (RV/LV) ratio at 24 hours and at three months as a primary outcome. Results show a difference between the two groups at 24 hours, but at three months, they show no clear effect for the rt-PA group (P = 0.36). This study also shows that USAT (rt-PA) had better outcomes at 24 hours than at three months in terms of tricuspid annular systolic excursion, right ventricular-to-left ventricular pressure gradient, and minimum inferior vena cava diameter. Taherkhani 2014 compared alteplase or streptokinase plus enoxaparin versus enoxaparin alone. This study reported no clear effect differences between the two groups in normalisation of the RV.

In this review, we found that after treatment, most echocardiogram parameters were better in the thrombolytics group than in the control group. For example, Fasullo 2011 reported the paradoxical systolic septal motion (OR 0.24, 95% CI 0.07 to 0.82 at 24 hours; OR 0.35, 95% CI 0.13 to 0.92 at 48 hours; OR 0.29, 95% CI 0.10 to 0.88 at 72 hours; OR 0.12, 95% CI 0.01 to 2.49 at six days; Analysis 8.3); Fasullo 2011 and Kucher 2014 reported right-to-left ventricular ratio at 24 hours after treatment (MD -0.13, 95% CI -0.16 to -0.11); and Fasullo 2011 reported additional time points: 48 hours (MD -0.19, 95% CI -0.20 to -0.18), 72 hours (MD -0.14, 95% CI -0.15 to -0.13), six days (MD -0.22, 95% CI -0.23 to -0.21), discharge (MD -0.33, 95% CI -0.34 to -0.32), three months (MD -0.14, 95% CI -0.34 to 0.05; pooled

Fasullo 2011 and Kucher 2014), and six months (MD -0.21, 95% CI -0.22 to -0.20) (see Analysis 8.4). Researchers reported similar time points for tricuspid annular plane systolic excursion: 24 hours (MD 0.45, 95% CI -1.18 to 2.07; pooled Fasullo 2011 and Kucher 2014), 48 hours (MD 1.00, 95% CI -0.13 to 2.13), 72 hours (MD 1.80, 95% CI 0.67 to 2.93), six days (MD 2.50, 95% CI 1.57 to 3.43), discharge (MD 2.00, 95% CI 0.75 to 3.25), three months (MD 0.33, 95% CI -3.18 to 3.85; pooled Fasullo 2011 and Kucher 2014), and six months (MD 1.30, 95% CI 0.28 to 2.32) (see Analysis 8.5). Kucher 2014 reported the right ventricular-to-right atrial pressure gradient (MD -6.30, 95% CI -13.06 to 0.46 at 24 hours; MD 3.20, 95% CI -4.77 to 11.17 at three months; Analysis 8.6) and the minimum inferior vena cava diameter (MD -6.60, 95% CI -9.36 to -3.84 at 24 hours; MD -0.50, 95% CI -2.79 to 1.79 at three months; Analysis 8.7).

BNP values show faster reduction in the thrombolytics group than in the placebo group during hospitalisation at six days after admission. Becattini 2010 also reported reduction in echocardiography parameters and found small differences in decreases in both right ventricle end-diastolic dimension and the right-to-left end-diastolic dimension ratio at 24 hours in favour of tenecteplase, but the difference was not maintained during the seven-day follow-up period (data were unavailable). These figures indicate that treatment with thrombolytics plus heparin results in more participants with improved right ventricular wall movement and tricuspid regurgitation than treatment with heparin alone.

Chronic thromboembolic pulmonary hypertension

Only three studies compared thrombolytic therapy plus heparin versus heparin alone in terms of pulmonary hypertension (Fasullo 2011; Sharifi 2013; Taherkhani 2014). Fasullo 2011 reported that participants in the thrombolytics group had lower pulmonary hypertension than participants in the heparin group at 24 hours (MD -8.00, 95% CI -14.76 to -1.24). Fasullo 2011 and Sharifi 2013 reported the outcome at 48 hours (MD -7.37, 95% CI -9.20 to -5.53), and Fasullo 2011 reported the outcome at 72 hours (MD -8.00, 95% CI -11.74 to -4.26). Fasullo 2011 and Taherkhani 2014 reported at six days (MD -5.69, 95% CI -9.37 to -2.02); Fasullo 2011 at discharge (MD -8.00, 95% CI -9.78 to -6.22) and at three months (MD -7.00, 95% CI -17.18 to 3.18); Fasullo 2011 and Sharifi 2013 at six months (MD -11.95, 95% CI -23.71 to -0.19); and Sharifi 2013 at 28 months (MD -15.00, 95% CI -17.32 to -12.68) (see Analysis 8.8).

Differences in coagulation parameters over time

Fibrinogen

Two studies comparing thrombolytic versus heparin treatment at less than three hours after treatment show a small difference in fibrinogen levels in favour of thrombolytics (total MD -2.68 g/L, 95% CI -4.36 to -1.00; Analysis 9.1; Dalla-Volta 1992; PIOPED 1990). However, we found no clear evidence to support a difference between the two groups at 24 hours (MD -1.61 g/L, 95% CI -3.99 to 0.76) nor at 48 hours (MD -0.60 g/L, 95% CI -1.40 to 0.20) after treatment (see Analysis 9.1). This indicates that thrombolytic treatment results in a lower level of fibrinogen than heparin treatment. Levine 1990 also reported this comparison; however, we could not extract the data from this study, as it reported changes in mean fibrinogen levels in a figure, showing that the thrombolytics group had a lower level of fibrinogen than the placebo group.

D-dimer

As a molecular marker of haemostatic activation, D-dimer indicates fibrin turnover both from intravascular fibrin formation and from subsequent lysis of a fibrin clot. Results show a difference between participants treated with thrombolytics plus heparin and those treated with heparin alone in two studies at two hours after treatment (MD 21.04 µg/mL, 95% CI -4.60 to 46.69; Analysis 9.2; Dalla-Volta 1992; PIOPED 1990), and in one study at 24 hours after treatment (MD 5.30 µg/mL, 95% CI 2.12 to 8.48; Analysis 9.2; Dalla-Volta 1992). These results show that D-dimer concentrations were higher in the thrombolytics plus heparin group than in the heparin alone group.

Plasminogen

Dalla-Volta 1992 reported a difference in concentrations of plasminogen at two hours (MD -60.30%, 95% CI -71.92 to -48.68) and at 24 hours (MD -36.00%, 95% CI -48.06 to -23.94) after treatment in favour of alteplase (see Analysis 9.3). This shows that treatment with alteplase plus heparin results in a lower plasminogen concentration than treatment with heparin alone.

Post-thrombotic syndrome

No data were available for this outcome. If data become available, we will include them in future updates.

Escalation of treatment

Two studies reported the number of participants who needed escalation of treatment after receiving thrombolytics versus heparin (Konstantinides 2002; Taherkhani 2014). Konstantinides 2002 compared alteplase plus heparin versus heparin alone, finding that fewer participants in the alteplase plus heparin group needed escalation of treatment for in-hospital events compared with the heparin alone group. Pooling these data with data from alteplase or streptokinase plus enoxaparin versus enoxaparin alone (Taherkhani 2014), we found that results still show a small difference in favour of alteplase (OR 0.32, 95% CI 0.16 to 0.64, P = 0.001; Analysis 10.1).This indicates that fewer participants required rescue thrombolysis in the thrombolytic plus heparin group than in the heparin alone group.

Hospital stay

Three studies that compared thrombolytics versus heparin reported length of hospital stay (Kucher 2014; Sharifi 2013; Taherkhani 2014). Analyses show that statistical heterogeneity between included studies was at a considerable level (Chi^2 = 45.89, P < 0.001, I^2 = 96%), and given the heterogeneity of the interventions, we used a random-effects model for the pooled analysis. Regarding the delivery technique for the thrombolytic drug, one study used the USAT system (Kucher 2014), whereas a second study delivered a 'safe dose' of rt-PA through intravenous injection (Sharifi 2013), and the last study used alteplase or streptokinase (Taherkhani 2014). Pooled analysis of the three studies yielded no clear evidence to support a difference between the two groups in length of hospital stay (MD -0.89, 95% CI -3.13 to 1.34; Analysis 10.2).

Survival time

Duration of follow-up varied, and researchers reported deaths up to 72 hours (Tibbutt 1974), 10 days (Levine 1990), 14 days (Goldhaber 1993; Ly 1978; UPETSG 1970), 19 days (PIOPED 1990),

30 days (Dalla-Volta 1992; Konstantinides 2002), and 180 days after randomisation (Fasullo 2011). Fasullo 2011 and Konstantinides 2002 show a beneficial effect of thrombolytics over control in clinical event-free survival time. The other studies did not report this outcome. However, we could not extract available data from the two studies to conduct a pooled analysis because they provided only a figure for survival time. Thus we cannot draw a specific conclusion on survival time nor on thrombolytic effects on death.

Composite clinical outcome

Two studies reported the important composite clinical outcome (Kline 2014; Meyer 2014). Meyer 2014 reported all-cause death or haemodynamic decompensation, and Kline 2014 reported recurrent venous thromboembolism (VTE), poor functional capacity, and low perception of wellness as measured by the 36-item Short Form Health Survey (SF-36). Analysis shows more death and haemodynamic decompensation events in the placebo group than in the thrombolytics group (OR 0.44, 95% CI 0.23 to 0.87; Analysis 10.3). However, we found no clear evidence to support a difference between the two groups in terms of other outcomes. As Kline 2014 and Meyer 2014 reported different composite clinical outcomes, it is not appropriate to pool these composite results.

Quality of life

One study reported participants' quality of life (QoL) in the follow-up period (Kline 2014). Kline 2014 reported the number of participants who remained in the intensive care unit on day 2 and the QoL as measured by the VEINES QoL score and SF-36. This study shows that QoL was similar between the two treatment groups.

Healthcare cost comparison

None of the included trials reported on cost comparison. If data become available, we will report this information in future updates.

DISCUSSION

Summary of main results

We have described the main results in Summary of findings for the main comparison.

Outcomes analysed

Overall, results for included outcomes were unsatisfactory and susceptible to bias due to the fact that most outcomes in the subgroups were extracted from only one or two studies. Most studies included small sample sizes, and some had low methodological quality. Upon assessing all of the included studies in this update, we found only three studies with four or more bias domains assessed as having low risk of bias (Fasullo 2011; Meyer 2014; UPETSG 1970). However, Meyer 2014 received funds from several companies, which may have caused conflicts of interest. In addition, some trials did not assess the most important outcomes defined in this review or did not evaluate the potential complications of thrombolytic therapy.

Clinical interpretation of the data

Thrombolytic agents showed benefit in terms of death compared with heparin (OR 0.57, 95% CI 0.37 to 0.87, P = 0.01) and reduced the odds ratio for recurrence of PE (OR 0.51, 95% CI 0.29 to 0.89, P = 0.02). However, upon excluding four studies at high risk of bias, we found no clear evidence to support a difference between the two groups in risk of death (OR 0.66, 95% CI 0.42 to 1.06, P = 0.08). Results show more major and minor haemorrhagic events in the thrombolytics group than in the control group (OR 2.90, 95% CI 1.95 to 4.31, P < 0.001; OR 3.03, 95% CI 1.60 to 5.73, P < 0.001, for major and minor haemorrhagic events, respectively) even after exclusion of trials at high risk of bias for these outcomes. One study reported on stroke, which occurred more often in the thrombolytics group than in the control group (OR 12.10, 95% CI 1.57 to 93.39). The total number of deaths was 83, and the total number of major haemorrhagic events was 56 among 2116 participants over all studies. From the confidence intervals, we can see a relatively precise estimate of treatment effect for recurrence of PE and for major and minor haemorrhagic events. However, the treatment effect for mortality was influenced by exclusion of studies at high risk of bias from the sensitivity analysis, even though only slight alterations in the confidence intervals were evident. Thus, additional studies are needed before firm conclusions can be drawn.

Many of the results for the secondary outcome measures of this review are based on only one or two studies. In addition, studies used different follow-up periods and interventions, entailing some unavoidable heterogeneity. The very limited results indicate that thrombolytic therapy was better than heparin in terms of improving haemodynamic outcomes, perfusion lung scanning, pulmonary angiogram assessment, and echocardiograms. Given the risk of bias in the included studies and the inconsistent results, we cannot draw a strong conclusion about the benefit of thrombolytic agents versus heparin in this review.

Overall completeness and applicability of evidence

We assessed the effectiveness and safety of thrombolytic therapy for people with acute pulmonary embolism. We found that thrombolytic therapy was better than comparison treatments in reducing the odds ratio of death and recurrence of PE, and it improved some composite clinical outcomes and haemodynamic parameters (perfusion lung scanning, pulmonary angiogram assessment, and echocardiograms). All participants in the included studies were adults aged 18 or over, with a mean age of about 60. However, the included trials did not include strict subgroups of elderly participants. Only Meyer 2014 included a subgroup for participants over 75, and results of this study provide no clear evidence to support a difference between the two groups in death or haemodynamic decompensation (OR 0.63, 95% CI 0.24 to 1.66). On the other hand, tenecteplase increased the odds ratio of major extracranial bleeding (OR 20.38, 95% CI 2.69 to 154.53). Any differences between adults and elderly people therefore need further investigation.

Based on data from Konstantinides 2002, Perlroth 2007 pointed out that the heparin group required treatment escalation approximately three times more often than the thrombolytics group, but researchers observed no difference in the risk of death from PE. Investigators also found that treatment with heparin alone was more effective and less costly than treatment with alteplase plus heparin among participants with submassive PE and right ventricular dysfunction. However, we were not able to show any differences between thrombolytic therapy and the comparison treatment in terms of healthcare costs and post-thrombotic syndrome, as no included studies reported on these outcomes. In clinical practice, haemodynamic parameters and

the age of patients with PE must be considered, especially for haemodynamically unstable patients and patients over 75.

The included studies involved different types of thrombolytics, including alteplase, urokinase, streptokinase, rt-PA, ultrasound-assisted catheter-directed thrombolysis system, and tenecteplase, usually followed by heparin. The control intervention was heparin alone or placebo plus heparin. No studies compared thrombolytics versus surgical intervention.

In this update, we included one additional report of a previously included study (Meyer 2014). The researcher in this study followed about 70% of participants over two years (median 37.8 months) and found that tenecteplase treatment did not affect long-term mortality among patients with intermediate-risk PE. This report also provided echocardiography data for only about 30% of participants (144/506 (28.5%) in the tenecteplase group and 146/499 (28.9%) in the control group) with long-term follow-up (at least 24 months), showing that tenecteplase treatment did not reveal clear differences in residual pulmonary hypertension nor in RV dysfunction. We could not use these data in our meta-analysis because the other included studies reported only short-term (follow-up period less than three months for most studies) mortality. Using data from this report in the meta-analysis would have increased heterogeneity too much. Thus, future studies should further investigate the effect of thrombolytic treatment with long-term follow-up on mortality.

Thrombolytics for massive PE (haemodynamically unstable patients)

It is clinically very important to differentiate haemodynamically stable and unstable patients (massive PE). However, we have identified only one study to date that compared thrombolytic therapy versus heparin in patients with massive PE (Jerjes-Sánchez 1995). Four studies included both massive and unknown PE types (Dotter 1979; Ly 1978; Tibbutt 1974; UPETSG 1970). The proportion of massive PE varied, standing at 8% in Ly 1978, 9% in UPETSG 1970, 23% in Tibbutt 1974, and 71% in Dotter 1979. As we did not know the types of PE for all participants included in these studies, we decided to include these four studies in the 'type of PE unknown' group. In PIOPED 1990, all included participations had an unclear PE type. Therefore, we included this study in the same group.

Jerjes-Sánchez 1995 shows unbalanced allocation in the two groups at onset of PE, so we judged this study as having high risk of bias due to the high risk of selective reporting and the very small sample size. In this RCT, eight participants received 1,500,000 IU of streptokinase in one hour through a peripheral vein followed by heparin or heparin alone. The four participants who were randomised to streptokinase (mean time of onset of symptoms of the first event of PE: 2.5 hours) improved in the first hour after treatment, survived, and over two years of follow-up did not present with pulmonary arterial hypertension. All four participants treated with heparin alone (mean time of onset of symptoms for the first event of PE: 34.75 hours) died within one to three hours after arrival to the emergency department. We excluded this study along with another three studies at high risk of bias from the sensitivity analysis (Ly 1978; Taherkhani 2014; Tibbutt 1974), and this appreciably influenced the results for all-cause death between the two groups. Thus, the data from Jerjes-Sánchez 1995 had a big influence on the pooled analysis. Even though we performed a subgroup analysis according to different types of PE (massive/submassive/unknown types of PE) for the primary outcomes, these results cannot be extrapolated to massive PE due to the limitations of Jerjes-Sánchez 1995.

Quality of the evidence

We have described the main results in Summary of findings for the main comparison.

Randomisation and blinding

Only three studies reported both appropriate random sequence generation and allocation concealment (Goldhaber 1993; Meyer 2014; UPETSG 1970), and seven reported satisfactory blinding (Fasullo 2011; Kline 2014; Konstantinides 2002; Levine 1990; Meyer 2014; PIOPED 1990; UPETSG 1970). Goldhaber 1993 reported no blinding, and Taherkhani 2014 indicated that blinding was broken. Although two studies used the appropriate method to generate the random sequence, Ly 1978 included five participants who were not randomised, and Jerjes-Sánchez 1995 reported unbalanced numbers between intervention and control groups at the onset of PE. The remaining trials did not provide clear details about random sequence generation, allocation concealment, or blinding. Two studies were unclear in all items for risk of bias assessment (Marini 1988; Sharifi 2013), and in four studies, all risk of bias domains were at unclear or high risk (Dotter 1979; Kucher 2014; Ly 1978; Tibbutt 1974). This could have biased study results in favour of treatment.

Sample size

Only one or two studies reported any of the outcome measures, so some effect sizes have a confidence interval over 95% (such as for incidence of stroke). For some outcomes, we may not have been able to detect any real effects of thrombolytics because of small sample size.

Conflicts of interest

Four included studies were funded by related pharmaceutical companies (Dotter 1979; Kline 2014; Kucher 2014; Meyer 2014), and some study authors worked for these companies (Meyer 2014). This could potentially result in conflicts of interest in drafting and reporting results of the study, even though study authors stated there was no influence over the whole study period.

Heterogeneity

Within each subgroup, we used Chi^2 analyses to test for statistical evidence of heterogeneity among studies, and we used I^2 to measure the degree of inconsistency across studies. When Chi^2 analysis was significant and I^2 values were in excess of 50%, we analysed differences in participant selection, baseline values, risk of bias, design, and methods that could possibly explain the heterogeneity.

Heterogeneity in responses did not appear to result from differences in methods used for most of the primary outcomes (including overall mortality, recurrence of pulmonary emboli, and major haemorrhagic events) nor for some of the secondary outcomes (mean pulmonary arterial pressure improvement, pulmonary angiogram assessment (72 hours after treatment), and echocardiograms). We obtained dynamic measurements from studies comparing thrombolytics versus heparin, showing a similar effect on those outcomes listed above. We found no dose-related or time-related relationships in these dynamic analyses.

We noted moderate heterogeneity in dynamic analysis of minor bleeding in studies comparing thrombolytics versus heparin (Becattini 2010; Dalla-Volta 1992; Fasullo 2011; Kucher 2014; Levine 1990; Ly 1978; Meyer 2014; Taherkhani 2014; Tibbutt 1974; UPETSG 1970), and we found a difference between the two therapies. Therefore, when we use this result in clinical practice, we must consider heterogeneity in the meta-analysis. A great degree of heterogeneity was present in the dynamic analysis for D-dimer concentration at two hours after treatment (Dalla-Volta 1992; PIOPED 1990), pulmonary artery systolic pressure (Fasullo 2011; Sharifi 2013; Taherkhani 2014), and right ventricle-to-left ventricle ratio (Fasullo 2011; Kucher 2014), showing differences between the two treatment groups. This may be a consequence of the different types of thrombolytics and heparin used in the two studies (see Characteristics of included studies table).

Due to the above issues, the overall quality of evidence presented in this review is low.

Potential biases in the review process

We analysed outcomes on an ITT basis, using a random-effects model for pooled analysis of heterogeneous data (I^2 = 40% to 100%). We did this to reduce the bias of estimated intervention effects.

We classified studies as having high risk of overall bias if two or more risk of bias domains carried high risk of bias. We conducted a sensitivity analysis by excluding these studies to assess the effects of this exclusion on the estimated intervention effect.

Agreements and disagreements with other studies or reviews

Almost all studies show that thrombolytic therapy can reduce the primary outcomes defined by the study, especially echocardiographic parameters. Our meta-analysis of all included studies shows beneficial results for thrombolysis in terms of death from all causes. However, the sensitivity analysis, from which we which removed studies labelled as having high risk of bias, provides no clear evidence to support a difference between the two groups in terms of death. Results from Jerjes-Sánchez 1995 show apparent benefit for the thrombolytics group, and removing this study from the sensitivity analysis may explain the changes in results.

In a meta-analysis in Chatterjee 2014, study authors reported that theirs was the first analysis of thrombolysis in PE with sufficient statistical power to detect associations with a meaningful mortality reduction. However, these investigators included the data from Jerjes-Sánchez 1995, which we labelled as carrying high risk of bias, Furthermore, Chatterjee 2014 did not perform a sensitivity analysis according to the quality of included studies and did not assess conflicts of interest in the included trials, which also may introduce bias to the review process. According to the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Peto OR works well when individual odds ratios are close to one (i.e. intervention effects are small), and when events are not particularly common (the ideal event rate is below 1%). In Chatterjee 2014, the range of the OR was 0.03 to 5.80 and the maximum event rate was 100% (4/4) in the control group. Thus, the Peto OR method used by Chatterjee 2014 to pool data may not be the most appropriate way to analyse the data.

Our review included different subgroup analyses compared with Chatterjee 2014 and published guidelines (NICE 2012). In our review, we placed studies that included participants with unclear types of PE into the 'type of PE unknown' group, which was more precise than subgroups used by Chatterjee 2014 and NICE 2012 (namely, unstable/massive and stable/submassive). The National Institute for Health and Care Excellence (NICE) guideline did not reveal obvious reductions in overall mortality in the unstable/massive and stable/submassive PE subgroups (OR 0.52, 95% CI 0.24 to 1.15; OR 0.67, 95% CI 0.30 to 1.51, respectively). Four other reviews did not report obvious reductions in overall mortality, especially for patients with submassive PE or haemodynamically stable patients (Cao 2014; Liu 2014; Marti 2014; Nakamura 2014). Therefore, larger clinical trials focussing on this association are needed.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests that thrombolytics reduce death following acute pulmonary embolism compared with heparin. The thrombolytic therapies included in this review are heterogeneous. Thrombolytic therapy may be helpful in reducing the recurrence of PE but may cause more major and minor haemorrhagic events and stroke, including intracranial haemorrhage. Trial results show a three-fold increase in major bleeding, and these results appear robust and not sensitive to the exclusion of lower-quality studies. We also note that most of the studies included in this review considered patients with submassive PE. Only one study focussed on patients with massive PE, finding an apparent benefit for thrombolysis. More high-quality double-blind RCTs are needed to assess the safety and cost-effectiveness of thrombolytic therapy for patients with acute PE.

Implications for research

Investigators planning future randomised trials should:

- use a study design that incorporates double-blinding and adequate concealment of treatment allocation;
- focus their assessment on common outcomes (e.g. mortality, haemorrhagic events (especially for intracranial haemorrhage), escalation of treatment);
- plan and evaluate measures of cost-effectiveness and quality of life;
- define the different types of PE to differentiate clinical subgroups; and
- assess differences between different age groups.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Becattini 2010

Methods	**Study design**: multi-centre, double-blind, randomised, placebo-controlled study **Method of randomisation**: not described **Blinding**: blind for assessment of efficacy of tenecteplase **Duration**: July 2006 to December 2006 **Exclusions post randomisation**: not clearly stated **Losses to follow-up**: 7 participants
Participants	**Country**: Italy **Setting**: 15 Italian centres **No. of participants**: 58: 28 in tenecteplase + heparin group, 30 in placebo + heparin group **Age (mean ± SD)**: 72.1 ± 1.2 tenecteplase + heparin group, 64.5 ± 2.5 placebo + heparin group.

Becattini 2010 *(Continued)*

	Sex: 13 males, 15 females in tenecteplase + heparin group; 10 males, 20 females in placebo + heparin group **Inclusion criteria**: aged between 18 and 85 years with objective diagnosis of PE and onset of symptoms no more than 10 days before randomisation, normal blood pressure (SBP ≥ 100 mmHg), and RVD at echocardiography performed within 24 hours from the diagnosis of PE. The diagnosis of PE was to be done by multi-detector CT scan, pulmonary angiography, or lung scan **Exclusion criteria**: chronic pulmonary hypertension, severe COPD, hypertension (SBP > 180 mmHg, DBP > 110 mmHg, or both), clinically relevant bleeding within the last 6 months, a haemorrhagic diathesis, active peptic ulcer, arterial aneurysm, arterial/venous malformation, cancer at increased risk for bleeding, history of stroke, intracranial or spinal surgery. Major surgery, biopsy, or trauma in the 2 months preceding admission were additional criteria for exclusion. Patients were excluded if they had received therapeutic doses of heparin (unfractionated or low-molecular-weight heparin) for longer than 72 hours before randomisation, thrombolytic treatment within the previous 4 days, or glycoprotein IIb/IIIa antagonists within the preceding 7 days; if they were on oral anticoagulation or had prolonged cardiopulmonary resuscitation (> 10 minutes) in the last 2 weeks. Severe hepatic or renal failure and subacute bacterial endocarditis were additional criteria for exclusion. Women were excluded in case of pregnancy, lactation, or delivery in the 30 days before randomisation
Interventions	All participants received UFH and VKA **Treatment group**: Tenecteplase was given as an IV weight-adjusted bolus at a dose ranging from 30 to 50 mg, with a 5-mg step every 10 kg from < 60 to ≥ 90 kg. Maximum bolus dose allowed was of 5000 IU (4000 IU for participants with bodyweight < 67 kg) **Control group**: placebo instead of tenecteplase **Length of follow-up**: follow-up at 24 hours, 7 days after inclusion; at or before hospital discharge for the outcome echocardiography assessment; at 7 days or before discharge for the outcome clinical deterioration; at 30 days from randomisation for the outcome recurrence of PE and death; at 7 days from randomisation or before discharge for the outcome adverse events
Outcomes	• Reduction in RVD • Clinical deterioration, requiring 1 or more of the following: catecholamine infusion for sustained hypotension or shock, endotracheal intubation, thrombolytic treatment, cardiopulmonary resuscitation, emergency surgical embolectomy, or catheter fragmentation • Recurrence of PE • Death • Complications (bleeding events)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding for assessment of efficacy of tenecteplase; no other information provided
Incomplete outcome data (attrition bias)	Unclear risk	About 12% of participants lost to follow-up

Becattini 2010 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Reported all outcomes
Other bias	Unclear risk	Small sample size may be a source of other bias

Dalla-Volta 1992

Methods	**Study design**: multi-centre, open, randomised, controlled, parallel study **Method of randomisation**: not described **Blinding**: single-blind for evaluation of angiography and lung scan **Duration**: October 1988 to November 1990 **Exclusions post randomisation**: not clearly stated **Losses to follow-up**: not stated
Participants	**Country**: Italy **Setting**: hospital **No. of participants**: 36: 20 in alteplase + heparin group, 16 in heparin alone group **Age (mean ± SD)**: 65.7 ± 10.9 in alteplase + heparin group, 63.4 ± 14.5 in heparin alone group **Sex**: 7 males, 13 females in alteplase group; 5 males, 11 females in heparin alone group **Inclusion criteria**: aged 18 to 80 years, clinical signs and symptoms indicating PE, within 10 days of onset; pulmonary angiogram showing vascular obstruction > 30% corresponding to Miller index score > 11 **Exclusion criteria**: cardiogenic shock defined by SBP < 90 mmHg and urinary output < 20 mL/h; surgical procedure or organ biopsy in previous 7 days; gastrointestinal or genitourinary bleeding during previous 3 months; stroke or transient ischaemic attack in previous 3 months; puncture of non-compressible vessels; uncontrolled hypertension; haematological disorders and contraindication to use of heparin; severe hepatic or renal insufficiency; pregnancy or lactation
Interventions	**Treatment group**: alteplase 100 mg (10 mg bolus + 50 mg IV for 1 hour + 40 mg in 2 hours), then heparin IV (continuous) **Control group**: heparin 1750 IU/h IV for 7 to 10 days **Length of follow-up**: at 2 hours and 24 hours after end of infusion (blood coagulation tests), at 7 to 30 days (lung scan)
Outcomes	• Lung scan • Complications (bleeding) • Blood coagulation test (APTT, PTT, platelet, D-dimer, plasminogen, fibrinogen)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Dalla-Volta 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind for evaluation of angiography and lung scan
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Dotter 1979

Methods	**Study design**: randomised parallel study **Method of randomisation**: not described **Blinding**: not described **Duration**: not described **Exclusions post randomisation**: not clearly stated **Losses to follow-up**: not stated
Participants	**Country**: USA **Setting**: hospital (University of Oregon Medical School Clinical Research Center or intensive care unit) **No. of participants**: 31: 15 in streptokinase group, 16 in heparin alone group **Age (range)**: 18 to 85 years old **Gender**: 12 males, 19 females **Inclusion criteria**: positive pulmonary angiogram (following initial diagnosis on the basis of chest x-ray, ECG, lung scan, and laboratory test) **Exclusion criteria**: haemorrhagic diathesis, severe systemic hypertension (grade Ⅲ or Ⅳ), streptococcal infection, active tuberculosis, serious liver disease with bleeding, cerebrovascular accident in previous 6 months, suspected carotid artery thrombosis, atrial fibrillation, major surgery in previous 10 days, pregnancy at any stage or the postpartum period, hepatic or renal biopsy in previous 10 days, translumbar aortography in previous 2 weeks
Interventions	**Treatment group**: streptokinase administered by constant peripheral vein infusion as a loading dose of 250,000 IU over a 20- to 30-minute period, followed by maintenance dosage of not less than 100,000 IU/h for 18 to 72 hours. The rate of infusion of the maintenance dose was adjusted on the basis of the TT at periodic intervals during treatment, followed by heparin and oral anticoagulants (1200 ± 300 units/h by infusion) **Control group**:

Dotter 1979 *(Continued)*

	Loading dose of 1500 units of heparin per kilogram of body weight followed by a similar constant rate infusion, monitored by Lee-White clotting times or activated clotting times at 4-hour intervals during the first 24 hours, and subsequently at 12-hour intervals **Length of follow-up**: not clearly stated; may be 2 hours, 4 hours, 8 hours, 12 hours, 16 hours, 20 hours, 24 hours, 72 hours, and 7 days
Outcomes	• Blood coagulation test (TT, fibrinogen, plasminogen, fibrinogen/fibrin degradation products) • Angiographic results • Pulmonary artery pressure changes • Morbidity/complications (bleeding, pyrexia, allergic reaction, etc) • Mortality
Notes	This study provides just a comparison, with no report of the method of randomisation used, how treatment allocation was concealed, analysis methods used, or numbers of post-randomisation dropouts or withdrawals. Study was supported in part by Hoechst-Roussel Pharmaceuticals, Inc. This study had previously been excluded and was reassessed and included in this update according to strict criteria for included studies in the *Cochrane Handbook for Systematic Reviews of Interventions*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Small sample size may be a source of other bias. This study was supported in part by Hoechst-Roussel Pharmaceuticals, Inc.

Fasullo 2011

Methods	**Study design**: double-blind, randomised, placebo-controlled study **Method of randomisation**: preliminary computer algorithm **Blinding**: blinded for assessment of outcomes and assignment of all participants **Duration**: January 2005 to June 2009 **Exclusions post randomisation**: not clearly stated **Losses to follow-up**: none

Fasullo 2011 *(Continued)*

Participants	**Country**: Italy **Setting**: hospital **No. of participants**: 72: 37 in alteplase + heparin group, 35 in placebo + heparin alone group **Age (mean ± SD)**: 55 ± 16.7 in alteplase + heparin group, 57 ± 15.5 in placebo ± heparin alone group **Sex**: 21 males, 16 females in alteplase + heparin group; 20 males, 15 females in placebo + heparin alone group **Inclusion criteria**: symptom onset within previous 6 hours for first episode of acute SPE; normal blood pressure SBP > 100 mmHg; RVD at echocardiogram; positive lung spiral computed tomography and dyspnoea; chest pain; tachypnoea; hypoxaemia $PO_2 \leq 75$ mmHg; $PCO_2 < 40$ mmHg; oxygen saturation < 90% in room air; D-dimer elevation; electrocardiography with S1-Q3-T3 pattern; inversion of T waves in V1 to V4; right bundle branch block or right axis deviation **Exclusion criteria**: active internal bleeding, recent intracranial bleeding, intracranial tumour or seizure history, ischaemic stroke in previous 2 months, neurosurgery during last month, surgery in previous 10 days, puncture of incompressible vessel in previous 10 days, trauma in previous 15 days, uncontrolled hypertension (SBP > 180 mmHg and DBP > 110 mmHg), haemorrhagic disorder of thrombocytopaenia (< 100,000), severe impaired hepatic or renal function, gastrointestinal bleeding in previous 10 days, pregnancy, > 75 years of age. Also excluded were those with arterial aneurysm or arterial/venous malformation and cancer at increased risk for bleeding and patients with chronic pulmonary hypertension or severe COPD; those who had received therapeutic doses of heparin (UFH or LMWH) for longer than 72 hours before randomisation, thrombolytic treatment within the previous 4 days, or glycoprotein IIb/IIIa antagonists within the preceding 7 days; and those taking oral anticoagulation
Interventions	**Before randomisation**: IV bolus of 5000 IU of UFH **Treatment group**: alteplase 100 mg (Actilyse as a 10-mg bolus, followed by a 90-mg intravenous infusion over a period of 2 hours), then heparin and warfarin (continuous) **Control group**: matching placebo, heparin, and warfarin **Length of follow-up**: every week for the first month, every 2 weeks for the subsequent 3 months, and every month successively for the next 6 months (recurrence of PE). At every follow-up, clinical, ECG, echocardiographic, and laboratory assessments were performed. In addition, spiral CT and lower abdominal CT and Doppler echography of the inferior limbs were repeated 3 and 6 months after thrombolytic treatment
Outcomes	• Feasibility and safety: bleeding • Effects on echocardiographic parameters: reduction in RVD • Clinical outcome: recurrence of PE or death and clinical deterioration during hospitalisation and at 180 days from randomisation
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Preliminary computer algorithm
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Blinding for assessment of outcomes and assignment of all participants

Fasullo 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Reported all outcomes
Other bias	Unclear risk	Small sample size may be a source of other bias

Goldhaber 1993

Methods	**Study design**: single-centre, randomised controlled trial **Method of randomisation**: consecutively numbered sealed envelopes generated by permuted block random number sequences **Blinding**: non-blinded **Duration**: November 1988 to July 1991 **Exclusions post randomisation**: 1 **Losses to follow-up**: 1
Participants	**Country**: USA **Setting**: hospital **No. of participants**: 101: 46 in rt-PA group, 55 in heparin group **Age (mean)**: 58 in alteplase group, 59 in heparin only group **Sex**: 16 males, 30 females in rt-PA group; 28 males, 27 females in heparin group **Inclusion criteria**: aged 18 years or over; symptoms and signs of PE within 14 days; PE confirmed by high-probability ventilation-perfusion lung scans, pulmonary angiograms, or both within 24 hours of randomisation; abnormal but not high-probability scans were considered eligible if angiograms demonstrated pulmonary arterial thrombus **Exclusion criteria**: major internal bleeding in previous 6 months; intracranial or intraspinal disease; operation or biopsy in previous 10 days (or open heart surgery within previous 14 days); occult blood in stool; platelet count < 100,000/μL; SBP > 200 mmHg or DBP > 110 mmHg; severe impairment in hepatic function; pregnancy; active infective endocarditis; haemorrhagic retinopathy; or any concurrent condition considered to limit survival to within 1 month
Interventions	**Treatment group**: rt-PA 100 mg by infusion over 2 hours (50 mg/h), then administered 1000 IU/h heparin, when PTT or TT was < 2 times control. Subsequent heparin dose achieved PTT = 1.5 to 2.5 times the upper limit of normal **Control group**: heparin, initial dose 5000 IU bolus followed by 1000 IU/h continuous IV, 4 hours after the dose of heparin according to PTT. Target PTT = 1.5 to 2.5 times upper limit of normal Participants received heparin for at least 5 days and were given oral anticoagulants **Length of follow-up**: echocardiography at 3 hours and 24 hours; perfusion lung scan at 24 hours after treatment started. Adverse events followed up for 14 days or longer
Outcomes	• Mortality and recurrent PE

Goldhaber 1993 *(Continued)*

- Complications
- Perfusion lung assessment
- Echocardiogram (right ventricular end-diastolic area, right ventricular hypokinesis)

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated by permuted block random number sequences
Allocation concealment (selection bias)	Low risk	Consecutively numbered sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat; 1 loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Jerjes-Sánchez 1995

Methods	**Study design**: single-centre, prospective, randomised controlled trial **Method of randomisation**: "withdrawal of a sealed envelope from a closed box that initially contained 40 envelopes numbered consecutively from 1 to 40; even numbers were assigned to SK + heparin and odd numbers to heparin"; no information provided for concealment of the sequence **Blinding**: not described **Duration**: not described **Exclusions post randomisation**: none **Losses to follow-up**: none
Participants	**Country**: not described **Setting**: not described **No. of participants**: 8: 4 in streptokinase group, 4 in heparin alone group **Age (mean ± SD)**: 51 ± 22.89 in streptokinase group, 46.5 ± 10.28 in heparin alone group **Sex**: 3 males, 1 female in streptokinase group; 2 males, 2 females in heparin alone group **Inclusion criteria**: patient age ≥ 15 years; previously healthy patients; PE diagnosis sustained by high clinical suspicion; PE proven by high-probability V/Q lung scan, suggestive echocardiogram, or radionuclide venogram; massive PE, defined as > 9 obstructed segments on V/Q lung scan with or without car-

Jerjes-Sánchez 1995 *(Continued)*

	diogenic shock, < 9 obstructed segments on V/Q lung scan but with RVD, extensive DVT, or both; symptoms or signs of PE within 14 days after onset of symptoms **Exclusion criteria**: previous PE; < 3 segmental defects on V/Q lung scan, with normal echocardiogram and without DVT; absolute contraindication for thrombolytic therapy
Interventions	**Treatment group**: streptokinase group received 1,500,000 IU of SK over 1 hour by the peripheral vein, followed by a bolus of 10,000 IU of heparin, then a constant infusion of 1000 IU/h of heparin titrated to a partial thromboplastin time of 2.0 to 2.5 times control **Control group**: heparin group followed the same regimen, but without streptokinase **Length of follow-up**: no information provided
Outcomes	Mortality
Notes	This study had previously been excluded and was reassessed and included in this update according to strict criteria for included studies provided in the *Cochrane Handbook for Systematic Reviews of Interventions*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"The patients were randomised to streptokinase followed by heparin or to heparin alone by withdrawal of a sealed envelope from a closed box that initially contained 40 envelopes numbered consecutively from 1 to 40; even numbers were assigned to SK plus heparin and odd numbers to heparin"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Small sample size; baseline imbalanced (especially for onset of PE - 2.5 hours in thrombolytics group vs 34.75 hours in heparin group)

Kline 2014

Methods	**Study design**: multi-centre, randomised, placebo-controlled trial **Method of randomisation**: study statistician prepared the sequence of randomisation and linked it to a unique study ID number; sequence was concealed with a sealed envelope **Blinding**: double-blind; investigator and outcomes assessors were blinded **Duration**: June 2008 to October 2012 **Exclusions post randomisation**: none

Kline 2014 *(Continued)*

	Losses to follow-up: 7 participants at 3 months
Participants	**Country**: USA **Setting**: 8 academic medical centres **No. of participants**: 83: 40 in single bolus tenecteplase group, 43 in placebo group **Age (mean ± SD)**: 57 ± 14 tenecteplase group, 54 ± 14 placebo group **Sex**: 20 males, 20 females in tenecteplase group; 29 males, 14 females in placebo group **Inclusion criteria**: age > 17 years; PE diagnosed on computed tomographic pulmonary angiography performed within 24 hours; normal arterial SBP with evidence of right ventricular strain **Exclusion criteria**: systolic hypotension (< 90 mmHg), inability to walk, contraindications to fibrinolysis, end-stage conditions
Interventions	All participants were treated with full-dose LMWH. Research pharmacist prepared placebo or tenecteplase in 0.9% saline in an opaque syringe. A site investigator injected the syringe contents as soon as practical. Decisions about long-term anticoagulant therapy were made at the discretion of the clinical care team **Treatment group**: tiered-dose tenecteplase (Genentech Inc., San Francisco, CA, USA) + LMWH **Control group**: placebo + LMWH **Length of follow-up**: 5 days and 3 months
Outcomes	**Primary outcomes**: • 5 days: PE-related or treatment-related adverse outcomes: death, circulatory shock, need for intubation, haemorrhage • 90 days: VTE recurrence, poor functional capacity, poor physical health-related quality of life. **Secondary outcomes**: • 5 days: dependence upon intensive care services, rate of unbinding, rate of hospital discharge, haemoglobin and fibrinogen concentrations, total number of days of minor bleeding, frequency of all-cause Good Clinical Practice-defined adverse events • 90 days: proportion with a New York Heart Association functional class ≥ 3, mean 6-minute walking distance, change in pulse oximetry with walking, mental health component score, subjective self-assessment of overall health status
Notes	The trial was terminated early because the principal investigator relocated to a new hospital, which led to insoluble problems in transferring contracts. This study was funded by an investigator-initiated grant from Genentech, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sequence of randomisation was prepared by the study statistician and was linked to a unique study ID number
Allocation concealment (selection bias)	Unclear risk	Study author just stated: "concealment was conducted using sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded: investigator and outcomes assessors were blinded

Kline 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	About 8.4% of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	The study was funded by an investigator-initiated grant from Genentech, Inc.

Konstantinides 2002

Methods	**Study design**: multi-centre, randomised, controlled trial **Method of randomisation**: adequate according to a standard randomisation programme **Blinding**: double-blind **Duration**: September 1997 to August 2001 **Exclusions post randomisation**: not stated **Losses to follow-up**: not described
Participants	**Country**: Germany **Setting**: 49 medical centres **No. of participants**: 256: 118 in heparin + alteplase group, 138 in heparin + placebo group **Age (mean ± SD)**: 61.2 ± 10.1 males and 64.4 ± 9.5 females in alteplase group, 60.5 ± 9.7 males and 62.2 ± 12.4 females in placebo group **Sex**: 54 males, 64 females in alteplase group; 68 males, 70 females in placebo group **Inclusion criteria**: acute PE and pulmonary hypertension or RVD detected by ECG, precapillary pulmonary hypertension based on catheterisation of right side of heart followed by confirmation of PE, electrocardiographic signs of right ventricular strain followed by confirmation of PE **Exclusion criteria**: aged over 80 years, haemodynamic instability defined as persistent arterial hypotension (SBP below 90 mmHg) with or without signs of cardiogenic shock, onset of symptoms more than 96 hours before diagnosis, thrombolytic treatment, major surgery or biopsy within previous 7 days, major trauma within previous 10 days, stroke, transient ischaemic attack, craniocerebral trauma, neurological surgery within previous 6 months, gastrointestinal bleeding within previous 3 months, uncontrolled hypertension, known bleeding disorder, intolerance to alteplase, diabetic retinopathy, current oral anticoagulant therapy, pregnancy or lactation, life expectancy less than 6 months, planned use of thrombolytic agents for DVT
Interventions	**Treatment group**: 100 mg alteplase given as 10-mg bolus followed by 90-mg IV infusion over 2 hours **Control group**: matching placebo Both groups also received IV heparin at 1000 IU/h, and rate was adjusted to maintain APTT of 2.0 to 2.5 times the upper limit of normal Oral anticoagulation was started on day 3 after randomisation for all participants **Duration of treatment**: mean duration in hospital 16.7 ± 8.4 days (range 2 to 70) **Length of follow-up**: up to 30 days

Konstantinides 2002 *(Continued)*

Outcomes	• In-hospital death or clinical deterioration that required escalation of treatment after infusion of alteplase or placebo was terminated • Recurrent PE, major bleeding, and ischaemic stroke
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to a standard randomisation programme
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Kucher 2014

Methods	**Study design**: randomised, parallel study **Method of randomisation**: not described for concealment; randomisation performed in blocks of 3 without stratification **Blinding**: open-label and outcomes assessors were blinded **Duration**: November 2010 to January 2013 **Exclusions post randomisation**: not clearly stated **Losses to follow-up**: 4 participants
Participants	**Countries**: Germany and Switzerland **Setting**: 8 tertiary care hospitals **No. of participants**: 59: 30 in ultrasound-assisted catheter-directed thrombolysis (USAT) group, 29 in heparin alone group **Age (mean ± SD)**: 63 ± 14 years **Sex**: 53% were women **Inclusion criteria**: acute symptomatic PE confirmed by contrast-enhanced CT with embolus located in at least 1 main or proximal lower lobe pulmonary artery; RV/LV ratio ≥ 1 obtained from the echocardiographic apical 4-chamber view

Kucher 2014 *(Continued)*

	Exclusion criteria: age < 18 or > 80 years; index PE symptom duration > 14 days; insufficient echocardiographic image quality in the apical 4-chamber view that prohibited measurement of the RV/LV ratio; known significant bleeding risk; administration of thrombolytic agents within previous 4 days; active bleeding; known bleeding diathesis; known coagulation disorder; platelet count < 100,000/μL; previous use of VKA with INR > 2.5 on admission; history of any intracranial or intraspinal surgery or trauma or intracranial/intraspinal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; gastrointestinal bleeding < 3 months; internal eye surgery or haemorrhagic retinopathy < 3 months; major surgery, cataract surgery, trauma, obstetrical delivery, cardiopulmonary resuscitation, or other invasive procedure < 10 days; allergy, hypersensitivity, or thrombocytopaenia from heparin, rt-PA; severe contrast allergy to iodinated contrast; known right-to-left cardiac shunt; large (> 10 mm) right atrial or right ventricular thrombus; haemodynamic decompensation defined as the need for cardiopulmonary resuscitation, or systolic blood pressure < 90 mmHg for at least 15 minutes, or drop in systolic blood pressure by at least 40 mmHg for at least 15 minutes with signs of end-organ hypoperfusion, or need for catecholamine administration to maintain adequate organ perfusion and systolic blood pressure > 90 mmHg; severe hypertension on repeated readings; pregnancy, lactation, or parturition < 30 days; participation in any other investigational drug or device study; life expectancy < 90 days; inability to comply with study assessments
Interventions	**Treatment group**: all participants were treated via USAT called EkoSonic MACH4e Endovascular Systems (EKOS Corporation, Bothell, WA, USA). A continuous infusion of rt-PA at 1 mg/h and saline coolant at 35 mL/h per catheter and intravascular ultrasound delivery were then initiated. After 5 hours of treatment, the infusion rate of rt-PA was reduced to 0.5 mg/h per catheter for 10 hours. Maximum rt-PA dose was 20 ± 1 mg for participant with bilateral device placement and 10 ± 0.5 mg for participant with unilateral device placement. At 15 ± 1 hour, rt-PA infusion and ultrasound delivery were discontinued **Control group**: UFH was administered immediately after randomisation as an intravenous bolus of 80 IU/kg, followed by an infusion of 18 IU/kg/h (with a maximum initial infusion rate of 1800 IU/h). The intervention for participants already receiving UFH, LMWH, or fondaparinux was adjusted according to different conditions and APTT. The minimum suggested duration of anticoagulation therapy was 3 months **Length of follow-up**: 90 days
Outcomes	• Difference in RV/LV ratio from baseline to 24 hours • Death • Haemodynamic decompensation • Major and minor bleeding • Recurrent VTE • Serious adverse events up to 90 days post randomisation
Notes	The outcome was analysed based on per-protocol population. This study was funded by EKOS Corporation (Bothell, WA, USA). Dr. Kucher reports being a consultant for EKOS Corp and having received honoraria from Sanofi-Aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Bayer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label, but outcome assessors were blinded

Kucher 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6.7% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Small sample size may be a source of other bias; possible conflicts of interest

Levine 1990

Methods	**Study design**: multi-centre, randomised controlled trial **Method of randomisation**: unclear **Blinding**: double-blind **Duration**: not described **Exclusions post randomisation**: none **Losses to follow-up**: none
Participants	**Country**: Canada **Setting**: hospital **No. of participants**: 58: 33 in rt-PA group, 25 in placebo group **Age (mean ± SD)**: 61.5 ± 2.7 years in rt-PA group, 59.6 ± 3.6 years (range 56 to 63) in placebo group **Sex**: 18 males, 15 females in rt-PA group; 11 males, 14 females in placebo group **Inclusion criteria**: acute symptomatic PE documented by pulmonary angiography or ventilation perfusion lung scan, plus DVT confirmed by venography or B-mode ultrasonography **Exclusion criteria**: active bleeding process, active peptic ulcer disease, bleeding diathesis, platelet count < 100,000 µL, recent cerebrovascular accident (within previous 2 months), major surgery within previous 10 days, obstetrical delivery or organ biopsy, severe hypertension (SBP > 200 mmHg), pregnancy, clinical symptoms suggestive of PE or longer than 2 weeks in duration, received parenteral heparin for longer than 72 hours, massive PE with hypotension and haemodynamic instability
Interventions	**Treatment group**: rt-PA 0.6 mg/kg of ideal body weight reconstituted in 50 mL sterile water as bolus injection over 2 minutes **Control group**: placebo (saline solution) following the same procedure as for treatment group Both groups received initial heparin bolus of 5000 IU, then 30,000 IU for first 24 hours continuous infusion, interrupted only for the duration of the study drug infusion **Duration of study period**: 10 days **Length of follow-up**: 24 hours and 7 days post treatment
Outcomes	• Mortality and recurrent PE during 10-day study period • Side effects • Perfusion lung scan assessment • Fibrinogen level • Alpha$_2$-antiplasmin level

Levine 1990 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind for primary outcome measure
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Ly 1978

Methods	**Study design**: single-centre, randomised, controlled trial **Method of randomisation**: sealed envelopes on the basis of random numbers **Blinding**: single-blind for interpretation of pulmonary angiographs **Duration**: not described **Exclusions post randomisation**: 1 (heparin group) **Losses to follow-up**: not described
Participants	**Country**: Norway **Setting**: Ulleval Hospital **No. of participants**: 25: 14 in streptokinase group, 11 in heparin group **Mean age (range)**: 56 (23 to 70) in heparin group, 51 (37 to 68) in streptokinase group **Sex**: 3 males, 8 females in streptokinase group; 8 males, 6 females in heparin group **Inclusion criteria**: symptoms (< 5 days) of acute major PE, confirmed by angiography **Exclusion criteria**: minor embolism affecting less than 1 lobar artery, known bleeding tendency or recent gastrointestinal or urogenital bleeding, major surgery within last 10 days, recent cerebrovascular episodes, severe hypertension, severe renal or hepatic insufficiency, pregnancy, recent delivery or known malignant disease, aged > 70 years
Interventions	**Treatment group**: streptokinase (Streptase) 250,000 IU loading dose + 0.9% saline 20 mL IV in 20 minutes, then 100,000 IU/h maintenance dose continuous IV for 72 hours, then oral warfarin. If TT < 2 times normal control value, heparin 10,000 to 30,000 IU/d

Ly 1978 *(Continued)*

	Control group: heparin (Apotekernes Laboratorium, Oslo, Norway) 15,000 IU initial dose IV followed by 30,000 IU/day continuous IV. Dose of heparin was adjusted by TT. Daily dose varied from 30,000 to 60,000 IU **Length of follow-up**: not stated
Outcomes	• Death and treatment failure • Clinical response (improvement or deterioration) • Complications • Angiographic score before and after 72 hours of treatment Angiographic scores were analysed with and without the 5 non-randomised participants (see Notes)
Notes	5 included participants were NOT randomised (4 in streptokinase group, 1 in heparin group). The decision to include these participants was made before the start of treatment Of streptokinase-treated participants, 1 with massive PE was transferred from another hospital for fibrinolytic treatment; 1 was considered to be a candidate for pulmonary embolectomy but the physician decided to treat him with streptokinase instead; 1 had a history of 10 days (angiographic score 24) and 1 probably had the first of 2 embolic episodes 3 weeks earlier (angiographic score 16) Participant allocated to heparin had ulcerative colitis (angiographic score 20)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random numbers. 5 included participants were not randomised (4 in streptokinase group, 1 in heparin group). The decision to include these participants was made before the start of treatment
Allocation concealment (selection bias)	Unclear risk	Used sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind for interpretation of pulmonary angiographs
Incomplete outcome data (attrition bias) All outcomes	High risk	45% of participants in the heparin group were withdrawn with an angiographic response to 72 hours of treatment
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Marini 1988

Methods	**Study design**: single-centre, prospective, randomised, controlled trial **Method of randomisation**: not described **Blinding**: not described **Duration**: not described **Exclusions post randomisation**: none

Marini 1988 *(Continued)*

	Losses to follow-up: none
Participants	**Country**: not described **Setting**: not described **No. of participants**: 30: 10 in urokinase 800,000 IU/12 h for 3 days group; 10 in heparin 30,000 IU/12 h for 7 days group; 10 in urokinase single dose of 3,300,000 IU in 12 hours group **Mean age**: 52 in urokinase 800,000 IU/12 h for 3 days group; 47 years in heparin 30,000 IU/12 h for 7 days group; 60 years in urokinase single dose of 3,300,000 IU in 12 hours group **Sex**: 5 males in urokinase 800,000 IU/12 h for 3 days group; 7 males in heparin 30,000 IU/12 h for 7 days group; 6 males in urokinase single dose of 3,300,000 IU in 12 hours group **Inclusion criteria**: younger than 72 years; > 9 unperfused lung segments; clinically identified embolic episode within previous 7 days; fibrinogen plasma concentration, Lee-White clotting time, platelet count, PTT within normal plasma level **Exclusion criteria**: contraindication for thrombolytic therapy, angiographic procedure, or both
Interventions	**Treatment group**: Urokinase 800,000 IU/12 h a day for 3 days or single dose of 3,300,000 IU in 12 hours **Control group**: Heparin 30,000 IU in a day for 7 days group **Length of follow-up**: 24 hours; 3, 7, and 30 days; 6 and 12 months
Outcomes	• Number of unperfused lung segments • Mean pulmonary artery pressure • Fibrinogen and plasminogen concentrations
Notes	No data could be extracted. Therefore, this study was not included in the meta-analysis. This study had previously been excluded and was reassessed and included in this update according to strict criteria for included studies in the *Cochrane Handbook for Systematic Reviews of Interventions*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	No information provided

Marini 1988 *(Continued)*

Other bias	Unclear risk	Small sample size may be a source of other bias

Meyer 2014

Methods	**Study design**: multi-centre, randomised, placebo-controlled trial **Method of randomisation**: computer-generated randomisation scheme; concealment of the sequence was sufficient (via the Internet), and treatment allocation was concealed from all investigators **Blinding**: double-blind; participants and all investigators were blinded **Duration**: November 2007 to July 2012 **Exclusions post randomisation**: 4 in tenecteplase group, 2 in placebo group **Losses to follow-up**: none
Participants	**Country**: 12 countries: Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, Poland, Portugal, Slovenia, Spain **Setting**: hospital **No. of participants**: 1006: 506 in tenecteplase group, 500 in placebo group **Age (mean ± SD)**: 66.5 ± 14.7 in tenecteplase group, 65.8 ± 15.9 in placebo group **Sex**: 47.8% males in tenecteplase group, 46.3% males in placebo group **Inclusion criteria**: aged ≥ 18, objectively confirmed acute PE with onset of symptoms 15 days or less before randomisation, RVD confirmed by echocardiography or spiral CT of the chest, myocardial injury confirmed by a positive test for troponin I or troponin T **Exclusion criteria**: haemodynamic collapse at presentation; known significant bleeding risk; administration of thrombolytic agents within previous 4 days; vena cava filter insertion or pulmonary thrombectomy within previous 4 days; uncontrolled hypertension; treatment with an investigational drug under another study protocol in the previous 7 days (or more, according to local requirements); previous enrolment in this study; known hypersensitivity to tenecteplase, alteplase, unfractionated heparin, or any of the excipients; pregnancy, lactation, or parturition within previous 30 days; known coagulation disorder; any other condition that the investigator feels would place the patient at increased risk if investigational therapy is initiated
Interventions	All participants received UFH, except participants who had already received LMWH or fondaparinux **Treatment group**: a single weight-based intravenous bolus (given over a period of 5 to 10 seconds) of the fibrinolytic agent tenecteplase. Doses ranged from 30 to 50 mg, depending on body weight. **Control group**: placebo; a single intravenous bolus of the same volume and appearance as the bolus of tenecteplase **Length of follow-up**: 7, 30, and 180 days
Outcomes	**Primary outcomes**: Clinical composite of death from any cause or haemodynamic decompensation (or collapse) within 7 days after randomisation **Secondary outcomes**: • Death within 7 days and 30 days after randomisation • Haemodynamic decompensation within 7 days • Major adverse events within 30 days

Meyer 2014 *(Continued)*

- Ischaemic or haemorrhagic stroke within 7 days
- Extracranial major bleeding
- Serious adverse events within 30 days

Notes	Some study authors were employed by or received funds or personal fees from related companies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Via the Internet; treatment allocation concealed from all investigators
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and all investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 6 participants were excluded in the period post randomisation
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Although study authors state: "None of the trial funders had any role in the design or conduct of the trial, the analysis of the data, or the preparation of the manuscript", some study authors were employed by or received funds or personal fees from related companies

PIOPED 1990

Methods	**Study design**: multi-centre, randomised, controlled trial **Method of randomisation**: not described **Blinding**: double-blind **Duration**: November 1986 to June 1987 **Exclusions post randomisation**: none **Losses to follow-up**: none
Participants	**Country**: USA **Setting**: 6 participating hospitals **No. of participants**: 13: 9 in rt-PA group, 4 in placebo group **Age (range)**: 20 to 78 years **Sex**: 9 males, 4 females **Inclusion criteria**: acute PE

PIOPED 1990 *(Continued)*

	Exclusion criteria: not reported
Interventions	**Treatment group**: rt-PA 40 to 80 mg administered IV at a rate of approximately 1 mg/min, in combination with heparin **Control group**: matching placebo + heparin **Length of follow-up**: 1.5 hours, 3 hours, 7 days
Outcomes	• Mean angiographic scores • Mismatched perfusion defects • Total pulmonary resistance and mean pulmonary arterial pressure • Fragment D-dimers • Complications (bleeding)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Sharifi 2013

Methods	**Study design**: single-centre, open, prospective, randomised, controlled trial **Method of randomisation**: generation of randomised sequence not described; sequence concealed by sealed envelopes **Blinding**: outcomes assessors **Duration**: May 2008 to March 2010 **Exclusions post randomisation**: none **Losses to follow-up**: 3 in tPA group, 4 in control group
Participants	**Country**: not described **Setting**: not described

Sharifi 2013 *(Continued)*

	No. of participants: 121: 61 in tPA group, 60 in control group **Age (mean ± SD)**: 58 ± 9 in tPA group, 59 ± 10 in control group **Sex**: 46% M in tPA group, 45% M in control group **Inclusion criteria**: adult patients presenting with signs and symptoms suggestive of PE plus imaging documentation on computed tomographic angiography or ventilation/perfusion scanning; patients meeting the criteria of 'moderate' PE with ≥ 2 new signs and symptoms **Exclusion criteria**: onset of symptoms > 10 days; > 8 hours since the start of parenteral anticoagulation; systemic arterial SBP < 95 or ≥ 200/100 mmHg; eligibility for full-dose thrombolysis; contraindication to UFH or LMWH; severe thrombocytopaenia; major bleeding within < 2 months requiring transfusion; surgery or major trauma within < 2 weeks; brain mass; neurological surgery, intracerebral haemorrhage, or subdural haematoma within < 1 year; end-stage illness and conditions; inability to perform echocardiography
Interventions	All participants received either UFH or subcutaneous enoxaparin **Treatment group**: tPA + anticoagulation The dose of tPA was 50% of the standard dose (100 mg) commonly used for treatment of PE, termed 'safe dose' thrombolysis **Control group**: anticoagulation alone **Length of follow-up**: 28 ± 5 days
Outcomes	**Primary outcomes**: • Pulmonary hypertension • Composite endpoint of pulmonary hypertension and recurrent PE at intermediate-term follow-up **Secondary outcomes**: • Total mortality • Duration of hospital stay • Bleeding at index • Recurrent PE • Composite endpoints of mortality and recurrent PE
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Study author just stated: "concealment was conducted using sealed envelope"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Only outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5.5% losses in follow-up

Sharifi 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Taherkhani 2014

Methods	**Study design**: single-centre, randomised, controlled trial **Method of randomisation**: via a computerised system; randomisation performed in blocks **Blinding**: single-blind **Duration**: April 2011 to November 2013 **Exclusions post randomisation**: not stated **Losses to follow-up**: not described
Participants	**Country**: Iran **Setting**: Loghman Hakim Hospital **No. of participants**: 50: 25 in enoxaparin + alteplase or streptokinase group, 25 in enoxaparin alone group **Age (mean ± SD)**: 54.8 ± 14.1 in enoxaparin + alteplase or streptokinase group, 56.6 ± 10.5 in enoxaparin alone group **Sex**: 10 males, 15 females in enoxaparin + alteplase or streptokinase group; 10 males, 15 females in enoxaparin alone group **Inclusion criteria**: patients with submassive pulmonary thromboembolism whose diagnosis was confirmed by multi-slice computed tomography angiography; patients fulfilling at least 1 of the following criteria: echocardiographically detected RV dysfunction or RV enlargement without left ventricular or mitral valve disease and echocardiographically detected pulmonary artery hypertension, defined as a tricuspid regurgitant jet velocity greater than 2.8 m/s **Exclusion criteria**: age > 80 or < 18 years; haemodynamic instability, defined as persistent arterial hypotension (i.e. systolic pressure below 90 mmHg), with or without signs of cardiogenic shock; major surgery or biopsy within preceding 7 days; major trauma within preceding 10 days; stroke, transient ischaemic attack, craniocerebral trauma, or neurological surgery within preceding 6 months; gastrointestinal bleeding within preceding 3 months; uncontrolled hypertension; known bleeding disorder; current therapy with an oral anticoagulant; current pregnancy or lactation; life expectancy less than 6 months because of underlying disease; planned use of thrombolytic agents for extensive DVT
Interventions	**Treatment group** (enoxaparin + alteplase or streptokinase group): enoxaparin (1 mg/kg subcutaneous twice a day) + alteplase (100 mg/90 min) or streptokinase (1,500,000 IU/2 h) **Control group** (enoxaparin alone group): enoxaparin (1 mg/kg subcutaneous twice a day) Both groups also received oral anticoagulant therapy, starting on day 3 after randomisation, and the warfarin dosage was adjusted to maintain an international normalised ratio of 2.5 to 3.5 **Length of follow-up**: 1 month
Outcomes	• In-hospital death or clinical deterioration necessitating escalation of treatment • Major bleeding or ischaemic stroke during hospitalisation • Pulmonary hypertension • RV dilatation at the end of the first week

Taherkhani 2014 *(Continued)*

- Exertional dyspnoea at the end of the first month

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	According to a computerised system; randomisation performed in blocks (no details of the blocks)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blind; blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Small sample size. In this study, 59 participants had submassive pulmonary thromboembolism; however, the researcher selected only 50 participants for randomisation

Tibbutt 1974

Methods	**Study design**: 2-centre, randomised, controlled trial **Method of randomisation**: not described **Blinding**: single-blind analysis of angiographs; not possible to use double-blinding due to recognisable physical characteristics of streptokinase in solution **Duration**: not described **Exclusions post randomisation**: 5 in treatment group, 2 in control group **Losses to follow-up**: 10 in streptokinase group, 9 in heparin group
Participants	**Country**: UK **Setting**: Brompton Hospital (n = 21) and Radcliffe Infirmary (n = 9) **No. of participants**: 30: 17 in treatment group, 13 in control group **Age (range)**: mean 51 (29 to 71) in streptokinase group, 47 (25 to 63) in heparin group **Sex**: 4 males, 9 females in streptokinase group; 11 males, 6 females in heparin group **Inclusion criteria**: acute or progressive life-threatening PE verified by angiography **Exclusion criteria**: recent surgery, gastrointestinal disease, malignant hypertension, recent cerebrovascular episode, pregnancy, recent delivery

Tibbutt 1974 *(Continued)*

Interventions	**Treatment group**: loading dose of streptokinase (600,000 IU in 100 mL normal saline or 5% glucose solution) + 100 mg hydrocortisone infused over 30 minutes through pulmonary artery catheter. Followed by 100,000 IU/h streptokinase IV for 72 hours **Control group**: 5000 IU heparin (in 100 mL normal saline or 5% glucose solution) + 100 mg hydrocortisone infused over 30 minutes through pulmonary artery catheter. Followed by 2500 IU for 72 hours At 60 hours from start of infusion, warfarin given at 25 mg and continued with laboratory control for next 6 months Dose adjusted according to coagulation test (protamine heparin titration, fibrinogen titre, PTT) **Length of follow-up**: 72 hours and 6 months
Outcomes	• Pulmonary angiographic score • Haemodynamic measurements • Side effects
Notes	2 participants transferred from control group to treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind analysis for angiographs. Not possible to use double-blinding due to recognisable physical characteristics of streptokinase in solution
Incomplete outcome data (attrition bias) All outcomes	High risk	63% losses in long-term follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Two participants transferred from control group to treatment group and data were not analysed as ITT; small sample size may be a source of other bias

UPETSG 1970

Methods	**Study design**: multi-centre, randomised controlled trial **Method of randomisation**: telephone to Drug Assignment Center **Blinding**: double-blind **Duration**: October 1968 to August 1970 **Exclusions post randomisation**: 1 **Losses to follow-up**: 1

UPETSG 1970 *(Continued)*

Participants	**Country**: USA **Setting**: 14 centres **No. of participants**: 160: 82 in urokinase group, 78 in heparin group **Age (years)**: not clearly stated **Sex**: 47 males, 35 females in urokinase group; 45 males, 33 females in heparin group **Inclusion criteria**: well-documented clinical episode suggesting PE had occurred within 5 days of institution of therapy **Exclusion criteria**: recent operation, contraindication to use of anticoagulant or thrombolytic therapy
Interventions	**Treatment group**: 2 brands of urokinase - Urokinase (Abbott) and Winkinase (Sterling-Winthrop) - were given randomly by 12-hour infusion. Loading dose of 2000 CTA IU/lb in 10 minutes, then 2000 CTA IU/lb for 12 hours via infusion pump **Control group**: heparin; loading dose of 75 IU/lb, then 10 IU/lb/h for 12-hour infusion Both groups then received heparin for a minimum of 5 days, followed by heparin or warfarin therapy for a total of 14 days. Dosage not clear **Follow-up**: 6 to 18 hours after completion of test drug infusion, then at 2 weeks and 3, 6, and 12 months
Outcomes	• Morbidity during 2-week study period • Complications • Pulmonary angiography (24 hours) • Lung scanning • Haemodynamic measurements
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drug Assignment Center
Allocation concealment (selection bias)	Low risk	Telephone to Drug Assignment Center
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

APTT: activated partial thromboplastin time.

BP: blood pressure.
COPD: chronic obstructive pulmonary disease.
CT: computed tomography.
CTA: Committee on Thrombolytic Agents.
DBP: diastolic blood pressure.
DVT: deep vein thrombosis.
ECG: electrocardiogram.
INR: international normalised ratio.
ITT: intention-to-treat.
IU: international units.
IV: intravenous.
LMWH: low-molecular-weight heparin.
LV: left ventricle.
PE: pulmonary embolism.
PTT: prothrombin time.
rt-PA: recombinant tissue plasminogen activator.
RVD: right ventricle dysfunction.
RV/LV: right-to-left ventricular dimension ratio.
SBP: systolic blood pressure.
SD: standard deviation.
SK: streptokinase.
SPE: submassive pulmonary embolism.
TT: thrombin time.
UFH: unfractionated heparin.
USAT: ultrasound-assisted catheter-directed thrombolysis system.
VKA: vitamin K antagonists.
V/Q: ventilation/perfusion (lung scan).
VTE: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdelsamad 2011	Compared different doses of streptokinase
Agnelli 1997	Compared 2 kinds of rt-PA
Alexandru Ion 2017	Not a true RCT
Barrios 2017	Not a true RCT
Bell 1974	Compared 2 thrombolytics
Bell 1976	Compared streptokinase to urokinase
Bell 1977	Compared 3 doses of thrombolytic
Bhardwaj 2010	Not a true RCT
Carroll 2018	Not a true RCT
Charbonnier 1984	Compared defibrase to heparin
Chen 2009	Compared different doses of rt-PA
Comerota 2009	Study focusses on acute DVT
De Takats 1973	Not randomised

Study	Reason for exclusion
Erkan 2002	Thrombolytic drugs were given to all groups. Thrombolytics were compared
Francois 1986	Compared 2 thrombolytics
Goldhaber 1989	Compared rt-PA to streptokinase
Goldhaber 1992	Compared rt-PA to urokinase
Goldhaber 1994	Compared different doses of the same thrombolytic drug
IRCT201104245625N2	Compared different use types of thrombolytic regimens
Jin 2012	Compared different thrombolytic regimens
Jing 2018	Not a true RCT
Konstantinides 1998	Not a true RCT
Lehnert 2017	Not a true RCT
Liu 2012	Not a true RCT
Marder 1978	Compared biochemical effects of 2 types of urokinase (tissue culture urokinase with urinary source urokinase); no comparison with heparin or placebo
Meneveau 1997	Compared rt-PA to streptokinase
Meneveau 1998	Compared streptokinase to alteplase
Meyer 1992	Compared streptokinase to alteplase
Miller 1971	No mention of method of randomisation; only the last 8 participants were randomly allocated to either streptokinase or heparin
Muhl 2007	Compared 2 thrombolytics
NCT00680628	This trial was terminated, as the principal investigator changed institutions, and it was not possible to solve issues with contracts
NCT00968929	Compared different types of thrombolytic regimens
NCT01956955	Compared LMWH and UFH in combination with thrombolytic treatment
Ohayon 1986	Compared different doses of urokinase and compared urokinase vs streptokinase
Palla 1997	Not a true RCT
Pang 2007	Not a true RCT
Prandoni 1985	Not a true RCT
Research Group on Urokinase and PE 1984	Compared different doses of urokinase
Saponjski 2002	Not randomised

Study	Reason for exclusion
Sasahara 1975	Compared 2 thrombolytics
Sharma 2000	Not a true RCT
Sors 1994	Compared bolus vs infusion of alteplase
Tebbe 1999	Compared reteplase vs alteplase
Tebbe 2009	Compared 2 thrombolytics
UKEP Study Group 1987	Compared 2 doses of thrombolytic
UPET Study Group 1974	Compared 3 doses of thrombolytic
Verstraete 1988	Compared intrapulmonary vs intravenous administration of rt-PA
Wang 2006	Compared 2 thrombolytics
Wang 2009	Compared different thrombolytic regimens
Wang 2010	Compared different times of urokinase and different doses of rt-PA
Wu 2010	Compared different doses of rt-PA
Xu 2016	Not a true RCT
Yang 2007	Comparison of local and systemic thrombolytics
Yang 2011	Compared 2 thrombolytics
Yilmazel 2018	Compared 2 thrombolytics
Zhu 2008	Not randomised

DVT: deep vein thrombosis.
LMWH: low-molecular-weight heparin.
RCT: randomised controlled trial.
rt-PA: recombinant tissue plasminogen activator.
UFH: unfractionated heparin.

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2017-005075-91-DK

Trial name or title	Low dose thrombolysis, ultrasound assisted thrombolysis or heparin for intermediate high risk PE
Methods	Randomised controlled trial with open-label and 3 arms
Participants	Participants with acute PE, intermediate high risk (visible impact on right ventricular structure and function, and biochemical markers of myocardial damage according to ESC Guidelines) **Inclusion criteria:** • Age ≥ 18 years • Informed consent for trial participation • Intermediate high-risk PE according to ESC criteria

EUCTR2017-005075-91-DK *(Continued)*

- Thrombus visible in main, lobar, or segmental pulmonary arteries on CT angiography
- 14 days of symptoms or less

Exclusion criteria:

- Altered mental state (Glasgow Coma Scale score < 14)
- No qualifying CT angiography performed (> 24 hours since CT angiography)
- Females of child-bearing potential, unless negative hCG test is present
- Thrombolysis for PE within 14 days of randomisation
- Thrombus passing through patent foramen ovale (risk of paradoxical embolism)
- Ongoing oral anticoagulation therapy (heparins, aspirin, antiplatelet therapy, and novel oral anticoagulant allowed)
- Comorbidity making 6-month survival unlikely
- Absolute contraindications for thrombolysis
  * Haemorrhagic stroke or stroke of unknown origin at any time
  * Ischaemic stroke in preceding 6 months
  * Central nervous system damage or neoplasms
  * Recent major trauma/surgery/head injury in preceding 3 weeks
  * Gastrointestinal bleeding within the last month
  * Known bleeding risk
- Relative contraindications do not preclude randomisation. Relative contraindications include transient ischaemic attack in preceding 6 months, oral anticoagulant therapy, pregnant or within 1 week postpartum, non-compressible puncture site, traumatic resuscitation, refractory hypertension (SBP > 180 mmHg), advanced liver disease, infective endocarditis, active peptic ulcer.

Interventions	**Treatment group**: Alteplase: low-dose thrombolysis Alteplase: ultrasound-assisted thrombolysis **Control group**: UFH IV or LMWH (usual care)
Outcomes	**Primary outcomes are evaluated within 96 hours from randomisation** • Reduction in modified Miller score (score of thrombus involvement and segmental flow) comparing thrombolysis groups (combining groups with and without USAT) to heparin/LMWH group (P < 0.01; n = 140 vs n = 70) • Reduction in modified Miller score (score of thrombus involvement and segmental flow) comparing thrombolysis administered by USAT or IV (P < 0.04; n = 70 vs n = 70) **Secondary outcomes are evaluated within 3 months from randomisation** • Reduction in modified Miller score (score of thrombus involvement and segmental flow) comparing the group treated with thrombolysis without USAT vs thrombolysis with USAT • Reduction in D-dimer from baseline to 48 to 96 hours post randomisation • Incidence of tricuspid regurgitation gradient > 40 mmHg at 3-month follow-up echocardiography • Relative reduction in troponin I/T from baseline to 48 to 96 hours post intervention • Bleeding complications (major and minor bleeding complication according to thrombolysis in myocardial infarction classification) • Dyspnoea index (visual analogue scale) after 48 to 96 hours and after 3 months • Mortality in the 3 groups (log-rank) and hazard ratio in multi-variable analysis using UFH/LMWH as reference • Reduction in N-terminal-pro-BNP at 48 to 96 hours and at 3 months • Six-minute walk distance at 3 months comparing the 3 groups

EUCTR2017-005075-91-DK *(Continued)*

	• Quality of life at 3-month follow-up comparing the 3 groups (36-Item Short Form Health Survey (SF-36) and other scales)
Starting date	2018
Contact information	Telephone number: 4535453545 Fax number: 4535453519 Email: jesper.kjaergaard.05@regionh.dk
Notes	-

EudraCT: 2005-001070-27

Trial name or title	Open, randomised, mono-site pilot trial for comparison of thrombolytic efficacy of tenecteplase and alteplase in patients with acute PE
Methods	Randomised controlled pilot trial with open-label and parallel-group design
Participants	N = 20; patients with acute PE and indication for thrombolytic therapy are included in the study
Interventions	Tenecteplase and alteplase
Outcomes	—
Starting date	7 July 2005
Contact information	—
Notes	No further details on trial methods available

NCT01531829

Trial name or title	Low dose rt-PA for acute normotensive PE with RVD
Methods	Randomised controlled trial with open-label and parallel-group design
Participants	N = 460; both sexes; ≥ 18 and ≤ 75 years of age
Interventions	**Treatment group**: low-dose (50 mg/2 h) rt-PA + LMWH regimen **Control group**: LMWH
Outcomes	**Primary outcome measures:** • Composite endpoint of death from any cause or treatment failure, recurrence of VTE (time frame: 7 days) • Improvement in right ventricular functions on echocardiography and pulmonary artery obstruction on CT angiography (time frame: 7 days) • Serious life-threatening bleeding such as cerebral haemorrhage and other major bleeding episodes (time frame: 7 days) • Clinically relevant non-major bleedings (time frame: 7 days)

NCT01531829 *(Continued)*

	Secondary outcome measures: • Composite endpoint of death from any cause or treatment failure, recurrence of VTE (time frame: 3 months and 6 months) • Improvement in right ventricular function on echocardiography and pulmonary artery obstruction on CT angiography (time frame: 3 months and 6 months) • Serious life-threatening bleeding such as cerebral haemorrhage and other major bleeding episodes (time frame: 3 months and 6 months) • Clinically relevant non-major bleedings (time frame: 3 months and 6 months)
Starting date	July 2009
Contact information	Chen Wang, PhD, MD; cyh-birm@263.net
Notes	No further, recent details available

NCT02604238

Trial name or title	Efficacy and safety of half dose alteplase added to heparin in patients with moderate PE (MONALYSE)
Methods	Prospective, randomised, open-label, controlled trial (parallel assignment)
Participants	130 participants with PE (age: 18 to 65 years old) **Inclusion criteria:** • PE at intermediate risk as defined by Guidelines ESC2014 (documented pulmonary CT angiography) • Pulmonary hypertension (systolic pulmonary pressure ≥ 40 mmHg, documented ECG presence of thrombotic material right-sided) • RVD confirmed by echocardiography or CT chest: dilation of right sections (> 30 mm in parasternal or relationship right ventricle/left ventricle > 1), paradoxical movement of interventricular septum TAPSE-reduced tricuspid regurgitation with gradient VD/AD > 30 mmHg in the absence of right ventricular hypertrophy, McConnell sign (apical segment of the free wall of the right ventricle, normal kinetic or hyperkinetic, vs hypokinesia or akinesia of remaining parts of the right ventricular wall) • Myocardial damage confirmed with troponin I or T-positive value of biomarkers of myocardial damage: BNP or NTproBNP • Informed consent **Exclusion criteria:** • Age < 18 years and > 65 years • HASBLED score ≥ 3 (23) • Intracranial tumours • Ischaemic stroke within 2 months • Surgery neurological within 1 month and surgery within 10 days • Trauma within 15 days • Hypotension to hospitalisation (systemic blood pressure < 90 mmHg) • Uncontrolled hypertension (SBP > 180 mmHg and PAD > 110 mmHg) • Clotting disorders • Thrombocytopaenia (< 100,000) • Platelet counts below 100 × 10^9/L severe thrombocytopenia (platelet count < 50,000 ptl/mm^3) • Liver failure

NCT02604238 *(Continued)*

	• Kidney failure • Gastrointestinal bleeding within 10 days • Pregnancy or childbirth within 30 days • Contraindications to use of thrombolytics • Contraindications to use of low-molecular-weight heparin (enoxaparin) • Anticoagulation therapy started more than 8 hours • COPD • Endocarditis • Severe obesity
Interventions	**Treatment group**: administered a "safe dose" of Alteplase (IV infusion of 40 mg within 2 hours (for patients weighing < 50 kg, a loading dose of bolus of 0.5 mg in 1 minute, followed by IV infusion of 40 mg in 2 hours); infusion will be adjusted to maintain the value of aPTT between 50 and 70 seconds (1.5 to 2.5 times the reference value). All participants are treated with LMWH according to Guidelines ESC2014 heparin; in addition, participants are administered a "safe dose" of Alteplase **Control group**: all participants are treated with LMWH according to Guidelines ESC2014 heparin; no treatment added
Outcomes	**Primary outcome**: pulmonary hypertension reduction documented on ECG **Secondary outcomes**: incidence of recurrent PE fatal or non-fatal; incidence of haemodynamic shock; incidence of hospital death from all causes **Other outcomes:** bleeding extracranial minor and major
Starting date	Not yet recruiting
Contact information	Alberto Conti (aaaconti@hotmail.com) or Lorella Magnani (lorella.magnani@usl1.toscana.it)
Notes	-

NCT03218410

Trial name or title	Surgical pulmonary embolectomy versus catheter-directed thrombolysis in the treatment of PE: a non-inferiority study (Lungembolism)
Methods	Monocentric, randomised, open-label, controlled, clinical, non-inferiority trial
Participants	Acute symptomatic PE (18 years to 80 years) **Inclusion criteria:** • Acute symptomatic PE with thrombus located in the pulmonary main trunk or the left and/or right main pulmonary artery • High-risk PE defined as PE with sustained systemic arterial hypotension (SBP < 90 mmHg), cardiogenic shock, or ongoing need for catecholamine therapy OR intermediate-high risk PE: imaging evidence of RV-dilatation (right-to-left ventricular diameter ratio > 1.0 on ECG or chest CT) and biomarker evidence of RVD (positive troponin T or I test) • Eligibility for both procedures must be established by the specific team • Signed Informed consent (by participant or legal representative) **Exclusion criteria:** • Younger than 18 years or older than 80 years • Symptom duration > 14 days, suggesting acute-on-chronic PE • Known CTEPH

NCT03218410 *(Continued)*

- Suspected CTEPH including RV hypertrophy (RV free wall > 5 mm on echocardiography), severe pulmonary hypertension (systolic pulmonary artery pressure > 80 mmHg on ECG), or CT findings suggestive of CTEPH, including intraluminal webs, bands, strictures, or eccentric filling defects adjacent to the wall of the pulmonary arteries
- Decompensated cardiogenic shock defined as recent (< 48 hours) cardiopulmonary resuscitation therapy or worsening haemodynamic status despite extended fluid and catecholamine support
- Inability to tolerate catheter procedure or surgical embolectomy due to severe comorbidities
- Allergy, hypersensitivity, or thrombocytopenia from heparin, r-tPA, or iodinated contrast, except for mild to moderate contrast allergies for which steroid premedication can be used
- Known significant bleeding risk, or known coagulation disorder (including vitamin K antagonists with INR > 2.0 and platelet count < 100,000/mm^3)
- Severe renal impairment (estimated glomerular filtration rate < 30 mL/min)
- Active bleeding: recent (< 3 months) gastrointestinal bleeding, severe liver dysfunction, bleeding diathesis
- Recent (< 3 months) internal eye surgery or haemorrhagic retinopathy; recent (< 10 days) major surgery, cataract surgery, trauma, CPR, obstetrical delivery, or other invasive procedure
- History of stroke or intracranial/intraspinal bleed, tumour, vascular malformation, aneurysm
- Severe hypertension on repeated readings (systolic > 180 mmHg or diastolic > 105 mmHg)
- Pregnancy, lactation, or parturition within previous 30 days (positive pregnancy test in women of childbearing age)
- Recent (< 1 month) systemic thrombolysis
- Life expectancy < 6 months or chronic non-ambulatory status
- Participating in any other investigational drug or device study or previous enrolment in this study
- Inability to comply with study assessments (e.g. due to cognitive impairment or geographic distance)
- Any other condition that the investigator feels would place the patient at increased risk if the investigational therapy is initiated

Interventions	**Treatment group**: surgical pulmonary embolectomy **Control group**: CDT
Outcomes	**Primary outcome**: Difference in RV/LV ratio by contrast-enhanced chest CT **Secondary outcome**: Difference in pulmonary occlusion score by contrast-enhanced chest CT
Starting date	2017
Contact information	Lars Englberger (+41-31-6322111; lars.englberger@insel.ch)
Notes	-

aPTT: activated partial thromboplastin time.
BNP: B-type natriuretic peptide.
CDT: catheter-directed thrombolysis.
COPD: chronic obstructive pulmonary disorder.
CPR: cardiopulmonary resuscitation.
CT: computed tomography.
CTA: Committee on Thrombolytic Agents.
CTEPH: chronic thromboembolic pulmonary hypertension.
ECG: echocardiogram.
ESC: European Society of Cardiology.
hCG: human chorionic gonadotropin.

INR: international normalised ratio.
IV: intravenous.
LMWH: low-molecular-weight heparin.
LV: left ventricle.
NTproBNP: N-terminal pro-brain natriuretic peptide.
PAD: pulmonary arterial disease.
PE: pulmonary embolism.
ptl: platelets.
rt-PA: recombinant tissue plasminogen activator.
RV: right ventricle.
RVD: right ventricle dysfunction.
SBP: systolic blood pressure.
SF-36: Short Form-36.
TAPSE: tricuspid annular plane systolic excursion.
VTE: venous thromboembolism.
UFH: unfractionated heparin.
USAT: ultrasound-assisted thrombolysis.
VTE: venous thromboembolism.

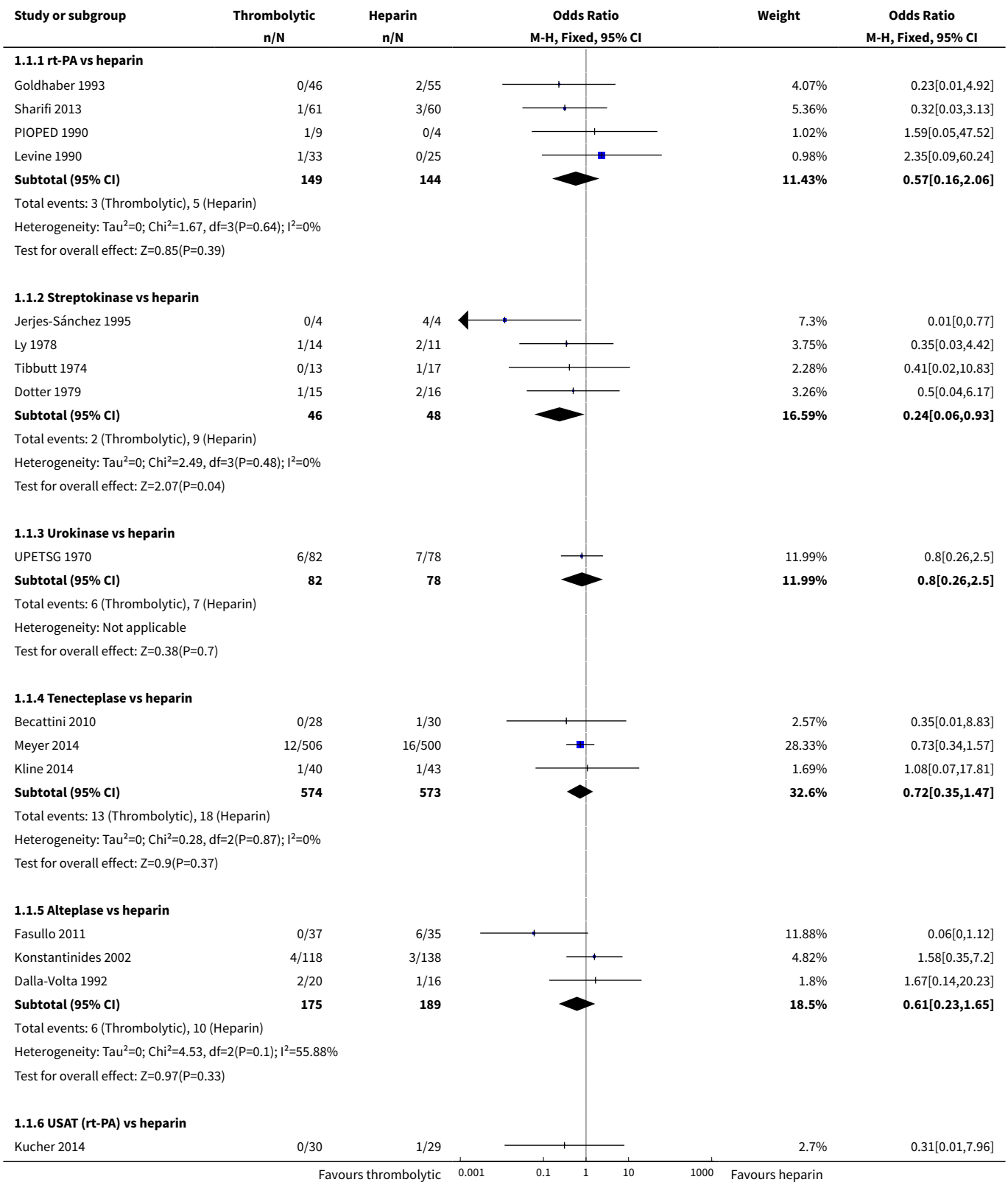
DATA AND ANALYSES

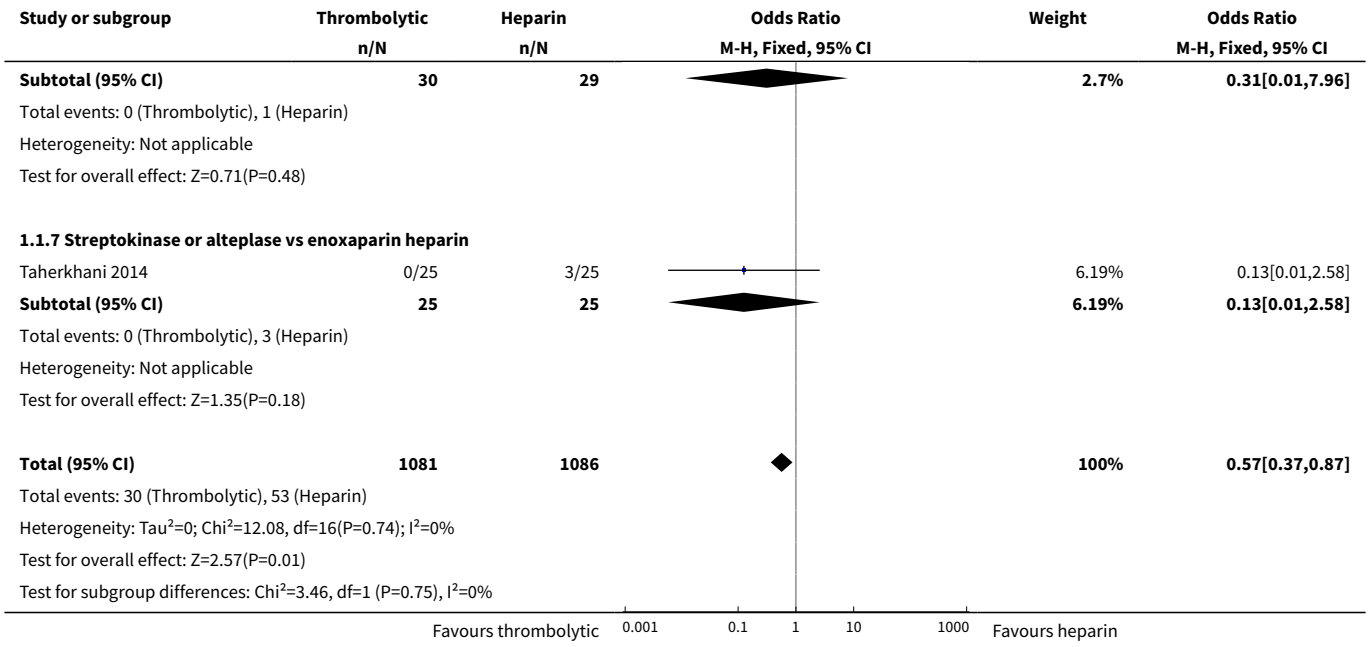
Comparison 1. Thrombolytic therapy versus heparin: primary outcome measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	17	2167	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.37, 0.87]
1.1 rt-PA vs heparin	4	293	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.16, 2.06]
1.2 Streptokinase vs heparin	4	94	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.93]
1.3 Urokinase vs heparin	1	160	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.50]
1.4 Tenecteplase vs heparin	3	1147	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.47]
1.5 Alteplase vs heparin	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.23, 1.65]
1.6 USAT (rt-PA) vs heparin	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.96]
1.7 Streptokinase or alteplase vs enoxaparin heparin	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.58]
2 Recurrence of pulmonary emboli	10	1898	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.89]
2.1 rt-PA vs heparin	3	280	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.91]

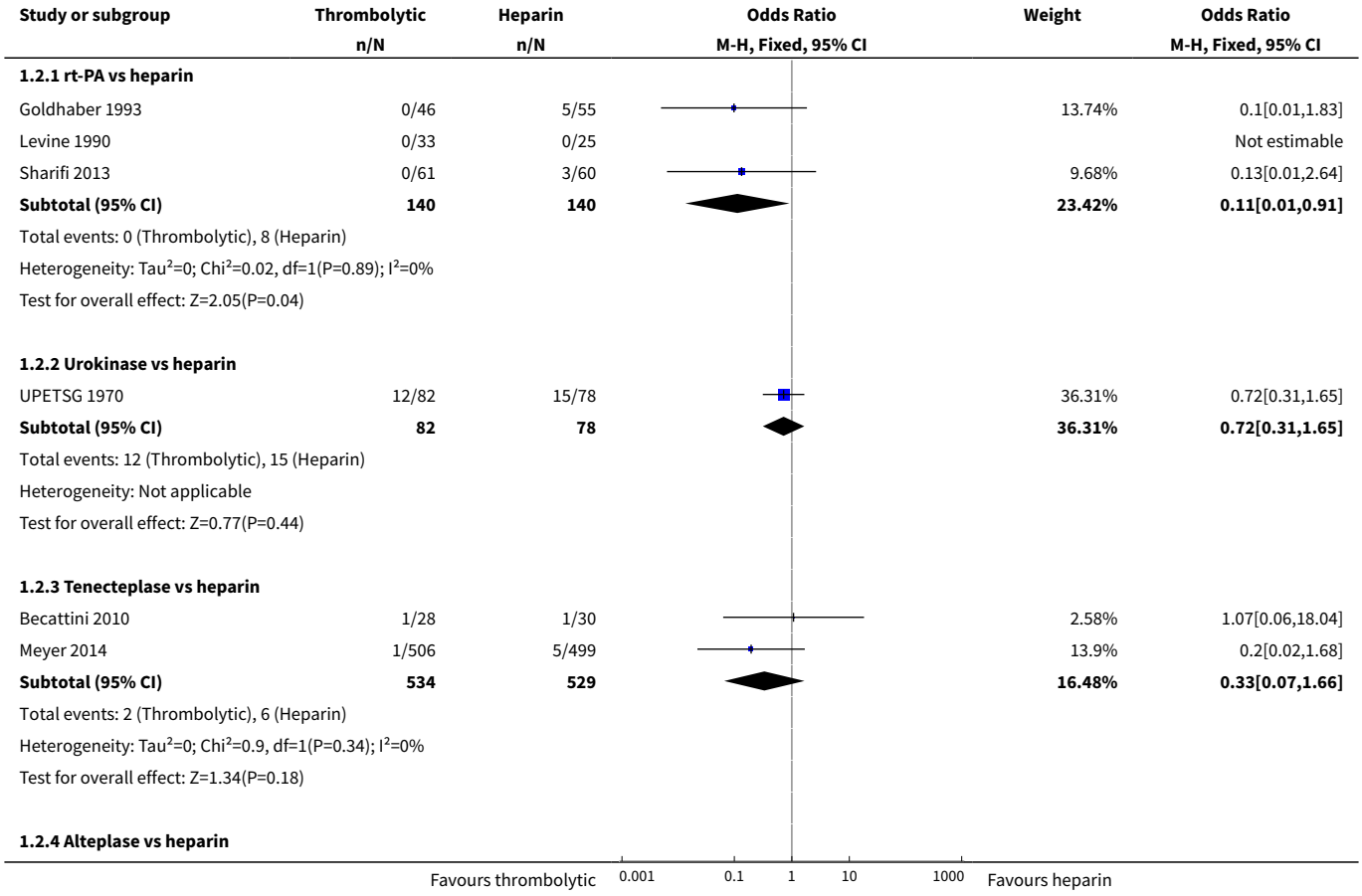
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Urokinase vs heparin	1	160	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.31, 1.65]
2.3 Tenecteplase vs heparin	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.66]
2.4 Alteplase vs heparin	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.25, 2.30]
2.5 Streptokinase vs heparin	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.83]
3 Major haemorrhagic events	12	1897	Odds Ratio (M-H, Fixed, 95% CI)	2.90 [1.95, 4.31]
3.1 rt-PA vs heparin	3	172	Odds Ratio (M-H, Fixed, 95% CI)	2.90 [0.43, 19.30]
3.2 Streptokinase vs heparin	2	55	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.34, 8.07]
3.3 Urokinase vs heparin	1	160	Odds Ratio (M-H, Fixed, 95% CI)	2.23 [1.00, 4.99]
3.4 Tenecteplase vs heparin	3	1146	Odds Ratio (M-H, Fixed, 95% CI)	4.95 [2.71, 9.04]
3.5 Alteplase vs heparin	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.16]
4 Minor haemorrhagic events	10	1553	Odds Ratio (M-H, Random, 95% CI)	3.03 [1.60, 5.73]
4.1 rt-PA vs heparin	1	58	Odds Ratio (M-H, Random, 95% CI)	20.00 [2.41, 165.71]
4.2 Streptokinase vs heparin	2	55	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.17, 2.43]
4.3 Urokinase vs heparin	1	160	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.64, 3.63]
4.4 Tenecteplase vs heparin	2	1063	Odds Ratio (M-H, Random, 95% CI)	7.94 [1.97, 32.02]
4.5 Alteplase vs heparin	2	108	Odds Ratio (M-H, Random, 95% CI)	2.90 [1.26, 6.66]
4.6 USAT (rt-PA) vs heparin	1	59	Odds Ratio (M-H, Random, 95% CI)	3.11 [0.30, 31.79]
4.7 Streptokinase or Alteplase vs enoxa-parin heparin	1	50	Odds Ratio (M-H, Random, 95% CI)	2.09 [0.18, 24.61]

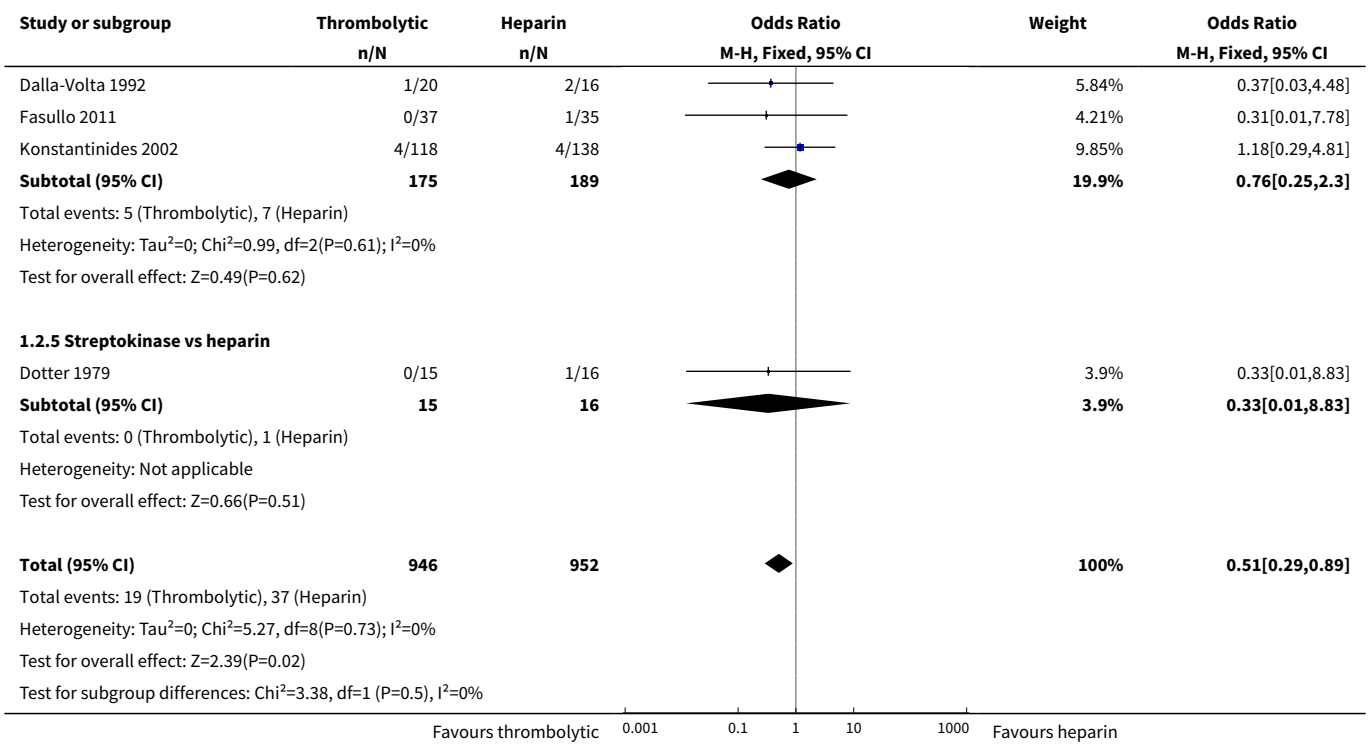
Analysis 1.1. Comparison 1 Thrombolytic therapy versus heparin: primary outcome measures, Outcome 1 Death from all causes.



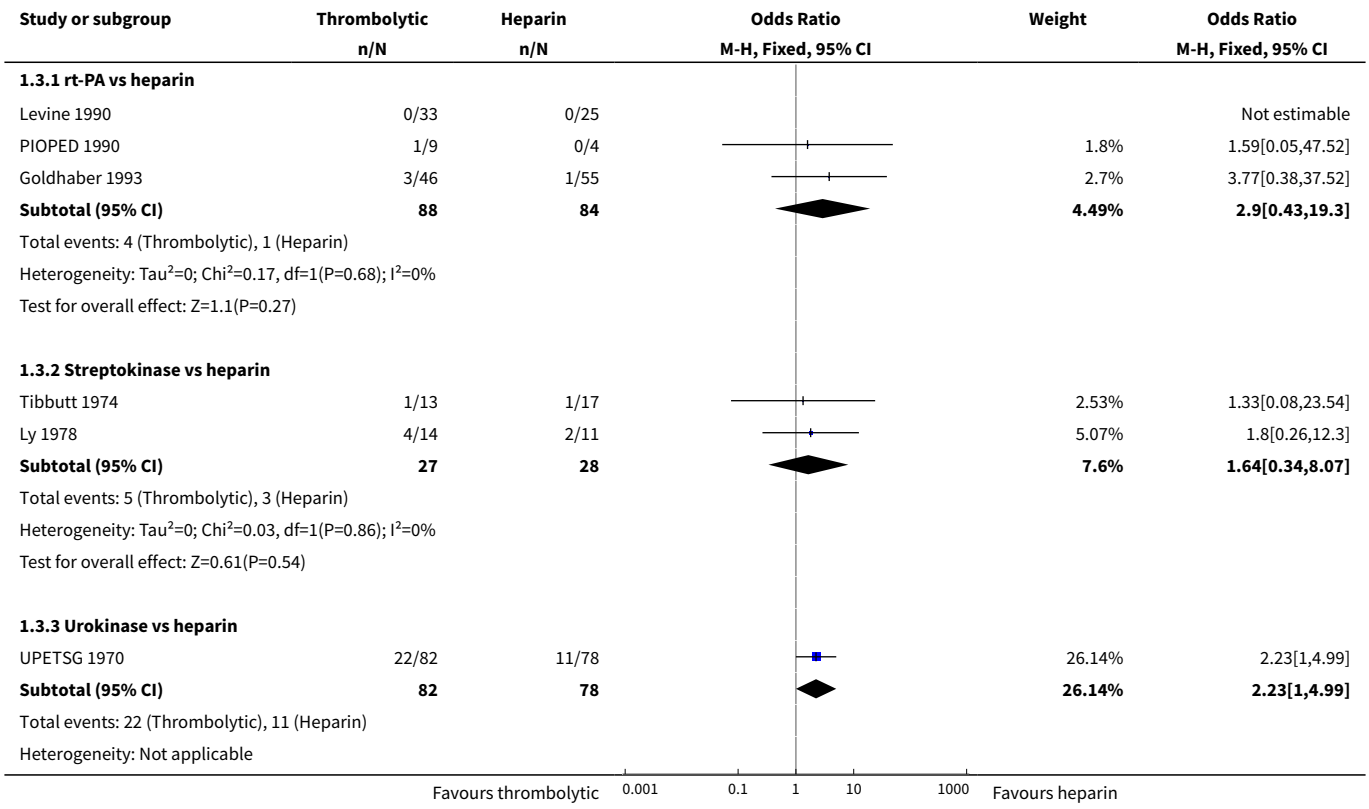


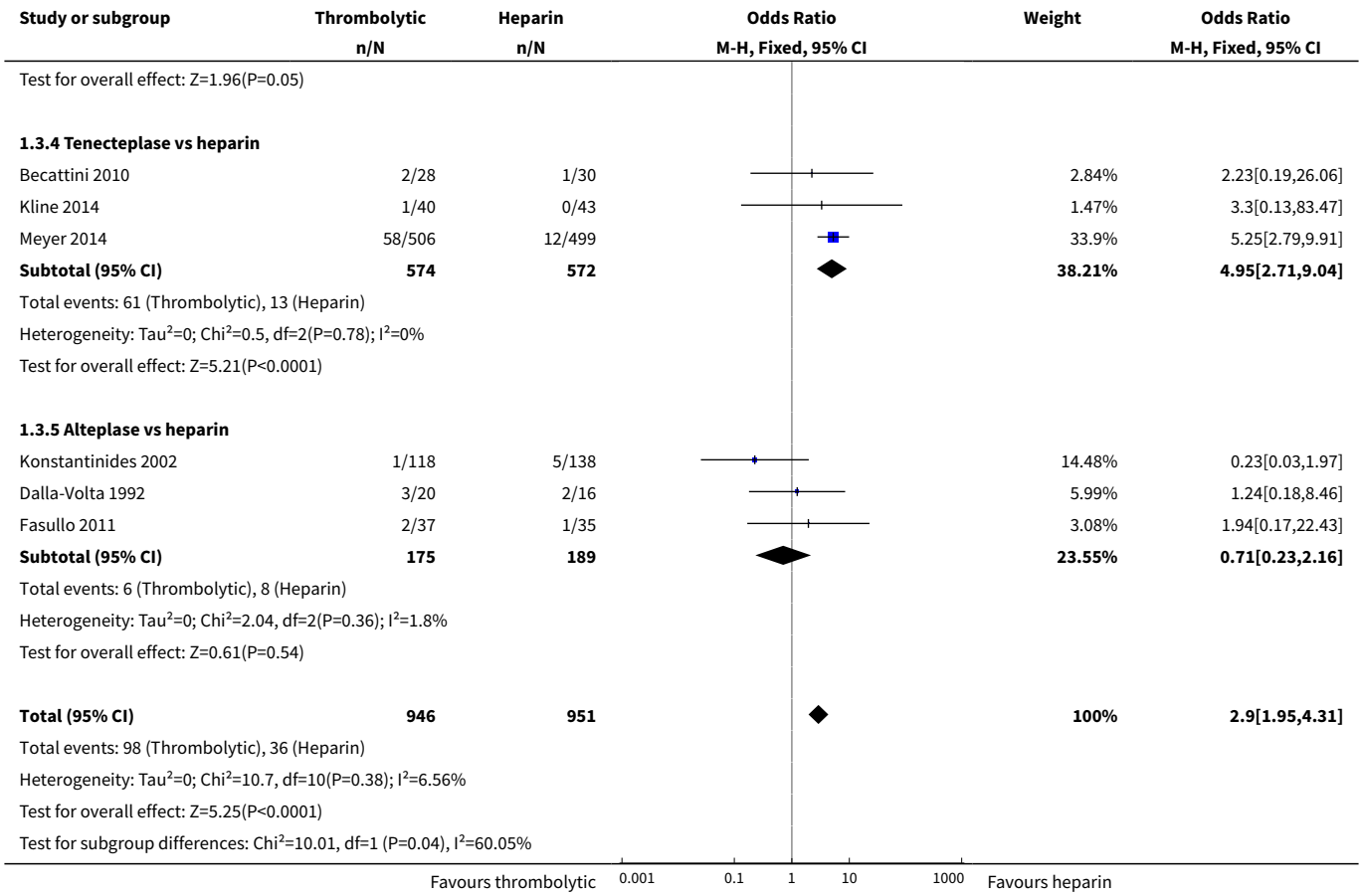
Analysis 1.2. Comparison 1 Thrombolytic therapy versus heparin: primary outcome measures, Outcome 2 Recurrence of pulmonary emboli.



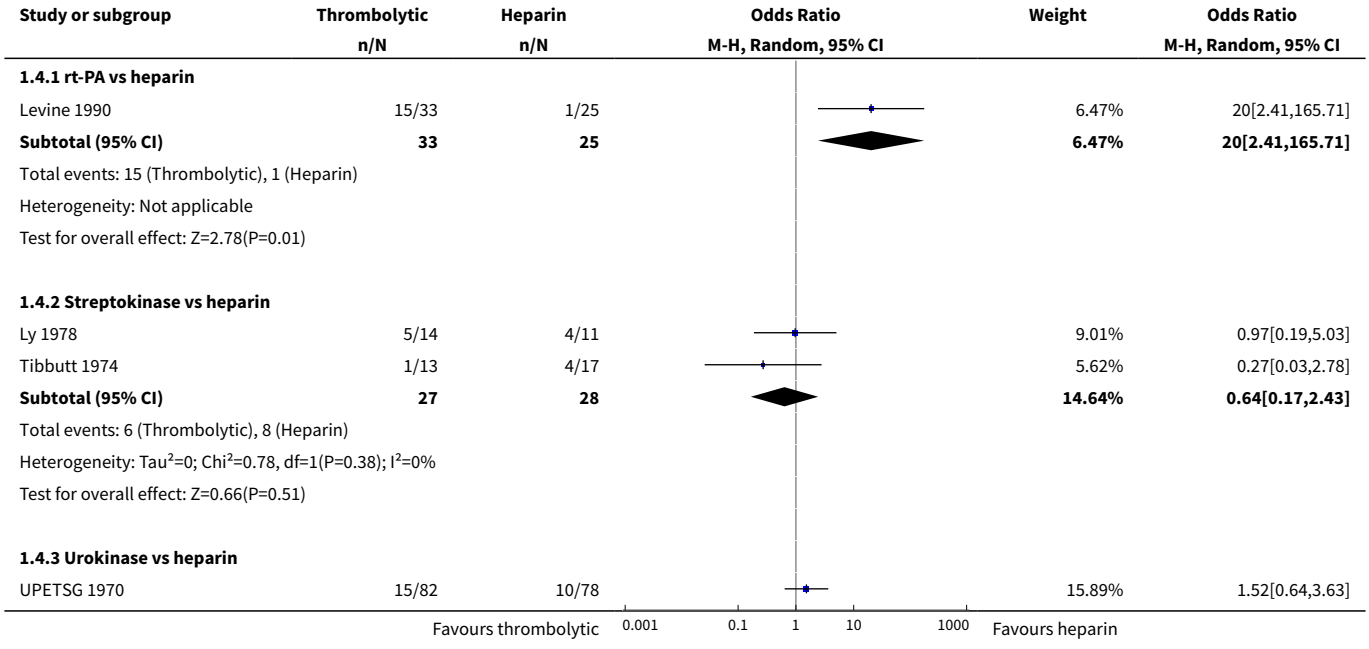


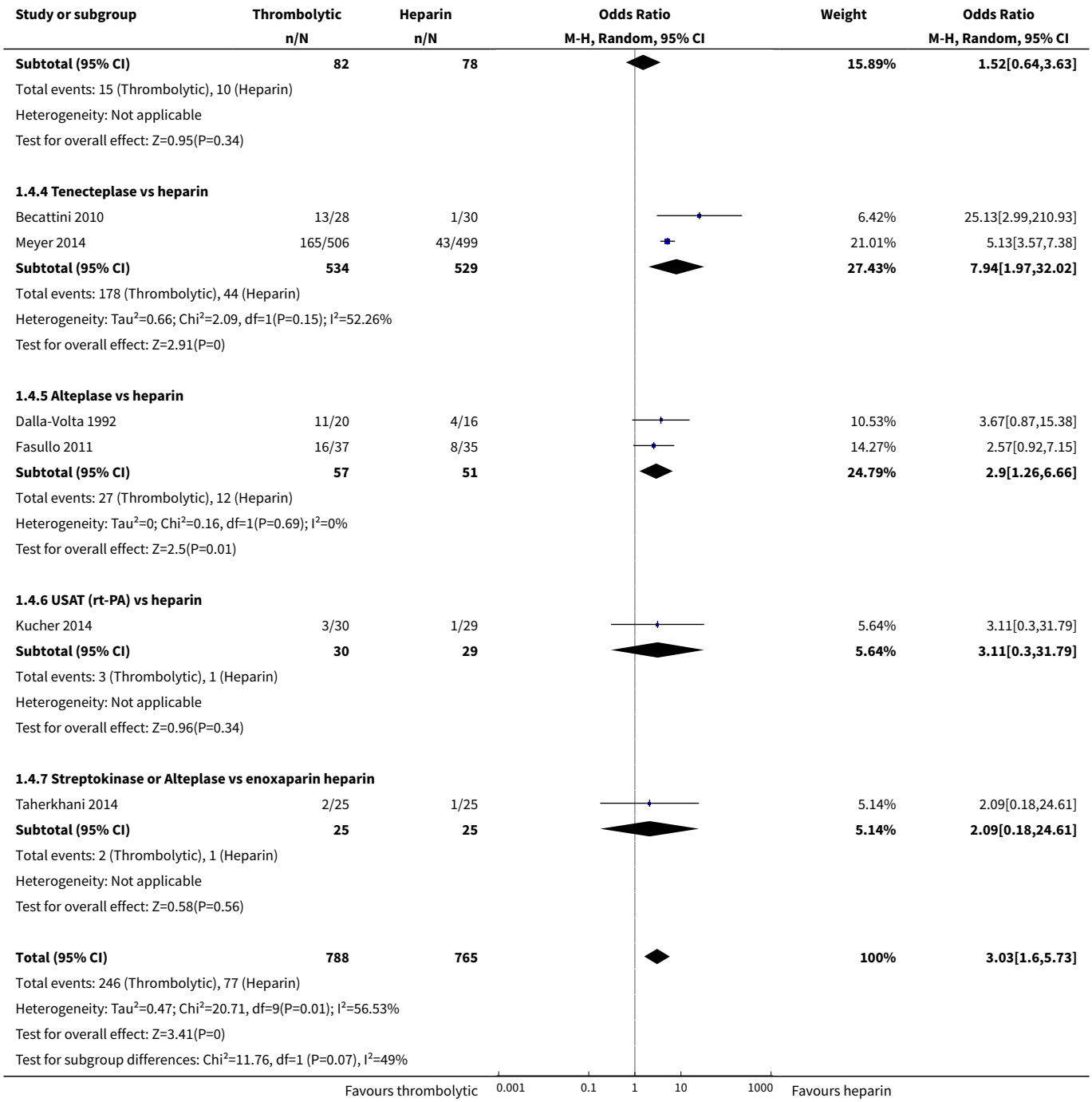
Analysis 1.3. Comparison 1 Thrombolytic therapy versus heparin: primary outcome measures, Outcome 3 Major haemorrhagic events.





Analysis 1.4. Comparison 1 Thrombolytic therapy versus heparin: primary outcome measures, Outcome 4 Minor haemorrhagic events.





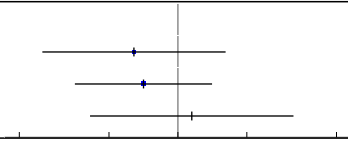
Comparison 2. Thrombolytic therapy versus heparin: primary outcome measures (sensitivity analysis according to study quality)

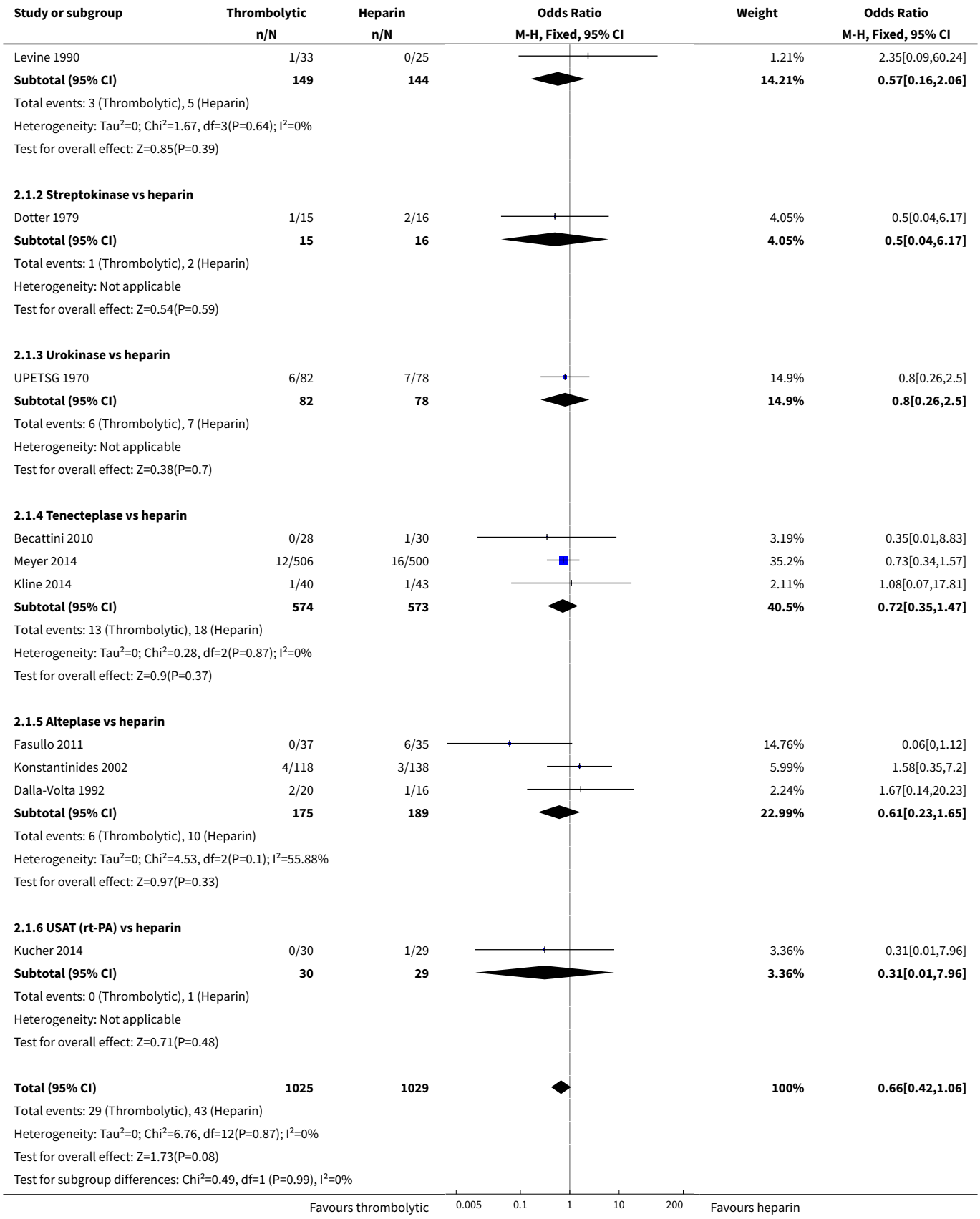
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death from all causes	13	2054	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.42, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 rt-PA vs heparin	4	293	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.16, 2.06]
1.2 Streptokinase vs heparin	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.04, 6.17]
1.3 Urokinase vs heparin	1	160	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.50]
1.4 Tenecteplase vs heparin	3	1147	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.47]
1.5 Alteplase vs heparin	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.23, 1.65]
1.6 USAT (rt-PA) vs heparin	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.96]
2 Major haemorrhagic events	10	1842	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [1.99, 4.53]
2.1 rt-PA vs heparin	3	172	Odds Ratio (M-H, Fixed, 95% CI)	2.90 [0.43, 19.30]
2.2 Urokinase vs heparin	1	160	Odds Ratio (M-H, Fixed, 95% CI)	2.23 [1.00, 4.99]
2.3 Tenecteplase vs heparin	3	1146	Odds Ratio (M-H, Fixed, 95% CI)	4.95 [2.71, 9.04]
2.4 Alteplase vs heparin	3	364	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.16]
3 Minor haemorrhagic events	7	1448	Odds Ratio (M-H, Random, 95% CI)	4.05 [2.17, 7.54]
3.1 rt-PA vs heparin	1	58	Odds Ratio (M-H, Random, 95% CI)	20.00 [2.41, 165.71]
3.2 Urokinase vs heparin	1	160	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.64, 3.63]
3.3 Tenecteplase vs heparin	2	1063	Odds Ratio (M-H, Random, 95% CI)	7.94 [1.97, 32.02]
3.4 Alteplase vs heparin	2	108	Odds Ratio (M-H, Random, 95% CI)	2.90 [1.26, 6.66]
3.5 USAT (rt-PA) vs heparin	1	59	Odds Ratio (M-H, Random, 95% CI)	3.11 [0.30, 31.79]

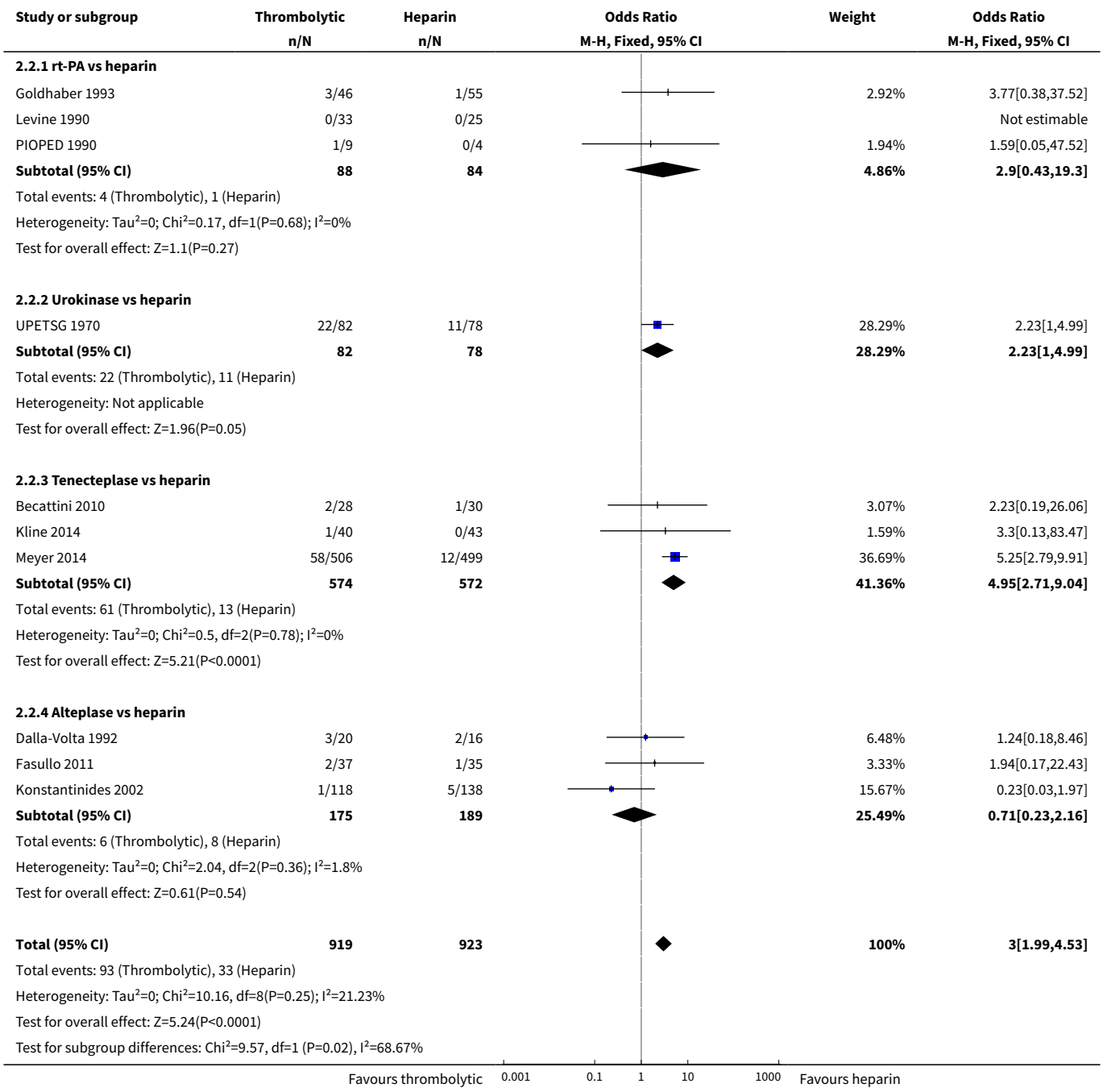
Analysis 2.1. Comparison 2 Thrombolytic therapy versus heparin: primary outcome measures (sensitivity analysis according to study quality), Outcome 1 Death from all causes.

Study or subgroup	Thrombolytic n/N	Heparin n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 rt-PA vs heparin					
Goldhaber 1993	0/46	2/55		5.06%	0.23[0.01,4.92]
Sharifi 2013	1/61	3/60		6.67%	0.32[0.03,3.13]
PIOPED 1990	1/9	0/4		1.27%	1.59[0.05,47.52]



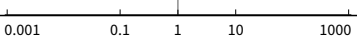


Analysis 2.2. Comparison 2 Thrombolytic therapy versus heparin: primary outcome measures (sensitivity analysis according to study quality), Outcome 2 Major haemorrhagic events.



Analysis 2.3. Comparison 2 Thrombolytic therapy versus heparin: primary outcome measures (sensitivity analysis according to study quality), Outcome 3 Minor haemorrhagic events.

Study or subgroup	Thrombolytic n/N	Heparin n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.3.1 rt-PA vs heparin					
Levine 1990	15/33	1/25		6.89%	20[2.41,165.71]
Subtotal (95% CI)	**33**	**25**		**6.89%**	**20[2.41,165.71]**
Total events: 15 (Thrombolytic), 1 (Heparin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.78(P=0.01)					
2.3.2 Urokinase vs heparin					
UPETSG 1970	15/82	10/78		20.37%	1.52[0.64,3.63]
Subtotal (95% CI)	**82**	**78**		**20.37%**	**1.52[0.64,3.63]**
Total events: 15 (Thrombolytic), 10 (Heparin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
2.3.3 Tenecteplase vs heparin					
Becattini 2010	13/28	1/30		6.82%	25.13[2.99,210.93]
Meyer 2014	165/506	43/499		30.27%	5.13[3.57,7.38]
Subtotal (95% CI)	**534**	**529**		**37.09%**	**7.94[1.97,32.02]**
Total events: 178 (Thrombolytic), 44 (Heparin)					
Heterogeneity: Tau^2=0.66; Chi^2=2.09, df=1(P=0.15); I^2=52.26%					
Test for overall effect: Z=2.91(P=0)					
2.3.4 Alteplase vs heparin					
Dalla-Volta 1992	11/20	4/16		12.08%	3.67[0.87,15.38]
Fasullo 2011	16/37	8/35		17.66%	2.57[0.92,7.15]
Subtotal (95% CI)	**57**	**51**		**29.74%**	**2.9[1.26,6.66]**
Total events: 27 (Thrombolytic), 12 (Heparin)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=2.5(P=0.01)					
2.3.5 USAT (rt-PA) vs heparin					
Kucher 2014	3/30	1/29		5.91%	3.11[0.3,31.79]
Subtotal (95% CI)	**30**	**29**		**5.91%**	**3.11[0.3,31.79]**
Total events: 3 (Thrombolytic), 1 (Heparin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	**736**	**712**		**100%**	**4.05[2.17,7.54]**
Total events: 238 (Thrombolytic), 68 (Heparin)					
Heterogeneity: Tau^2=0.3; Chi^2=12.27, df=6(P=0.06); I^2=51.08%					
Test for overall effect: Z=4.4(P<0.0001)					
Test for subgroup differences: Chi^2=7.32, df=1 (P=0.12), I^2=45.32%					



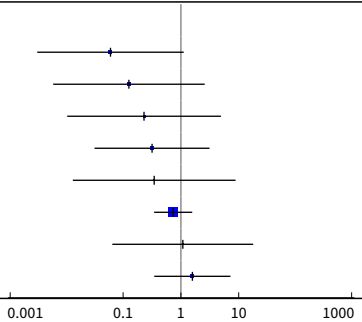
Favours thrombolytic — Favours heparin

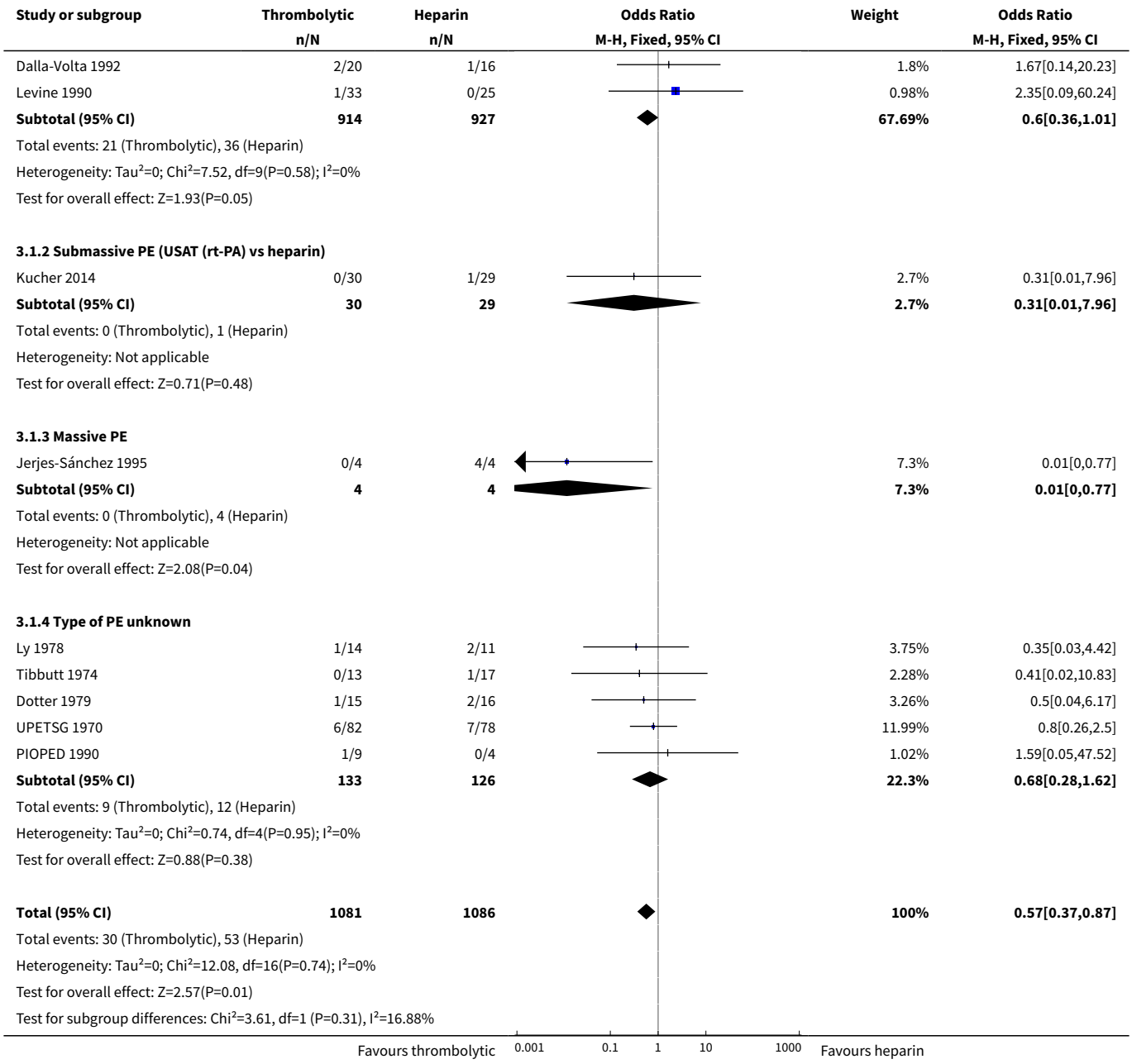
Comparison 3. Thrombolytic therapy versus heparin: primary outcome measures (subgroup analysis according to types of PE)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	17	2167	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.37, 0.87]
1.1 Submassive PE	10	1841	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.36, 1.01]
1.2 Submassive PE (USAT (rt-PA) vs heparin)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.96]
1.3 Massive PE	1	8	Odds Ratio (M-H, Fixed, 95% CI)	0.01 [0.00, 0.77]
1.4 Type of PE unknown	5	259	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.28, 1.62]
2 Recurrence of pulmonary emboli	10	1898	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.89]
2.1 Submassive PE	8	1707	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.86]
2.2 Type of PE unknown	2	191	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.31, 1.52]
3 Major haemorrhagic events	12	1897	Odds Ratio (M-H, Fixed, 95% CI)	2.90 [1.95, 4.31]
3.1 Submassive PE	8	1669	Odds Ratio (M-H, Fixed, 95% CI)	3.35 [2.06, 5.45]
3.2 Type of PE unknown	4	228	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [1.03, 4.18]
4 Minor haemorrhagic events	10	1553	Odds Ratio (M-H, Random, 95% CI)	3.03 [1.60, 5.73]
4.1 Submassive PE	6	1279	Odds Ratio (M-H, Random, 95% CI)	4.91 [2.93, 8.22]
4.2 Submassive PE (USAT (rt-PA) vs heparin)	1	59	Odds Ratio (M-H, Random, 95% CI)	3.11 [0.30, 31.79]
4.3 Type of PE unknown	3	215	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.57, 2.44]

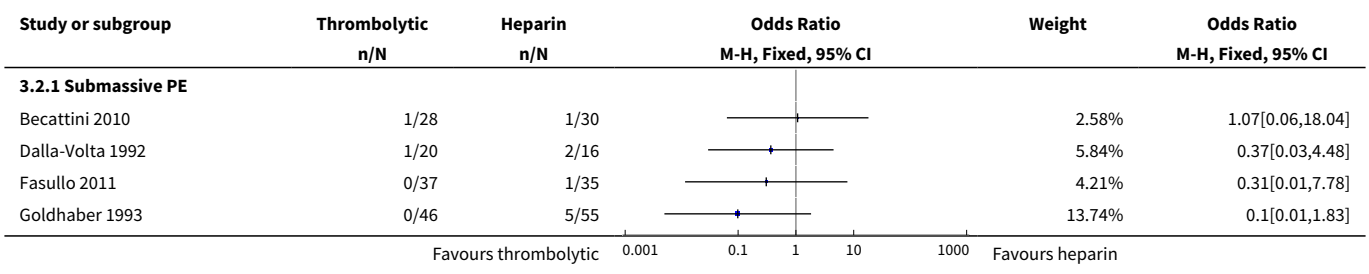
Analysis 3.1. Comparison 3 Thrombolytic therapy versus heparin: primary outcome measures (subgroup analysis according to types of PE), Outcome 1 Death from all causes.

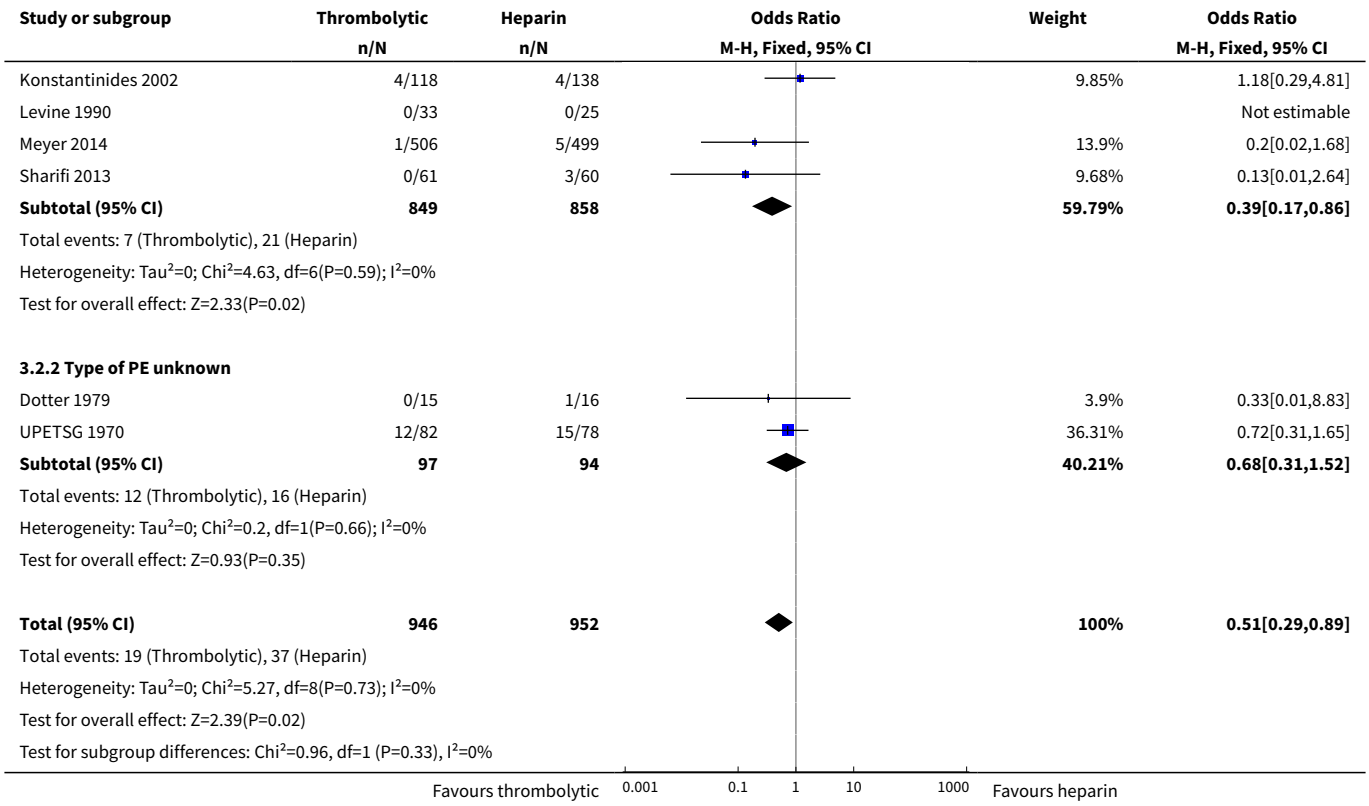
Study or subgroup	Thrombolytic n/N	Heparin n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Submassive PE					
Fasullo 2011	0/37	6/35		11.88%	0.06[0,1.12]
Taherkhani 2014	0/25	3/25		6.19%	0.13[0.01,2.58]
Goldhaber 1993	0/46	2/55		4.07%	0.23[0.01,4.92]
Sharifi 2013	1/61	3/60		5.36%	0.32[0.03,3.13]
Becattini 2010	0/28	1/30		2.57%	0.35[0.01,8.83]
Meyer 2014	12/506	16/500		28.33%	0.73[0.34,1.57]
Kline 2014	1/40	1/43		1.69%	1.08[0.07,17.81]
Konstantinides 2002	4/118	3/138		4.82%	1.58[0.35,7.2]



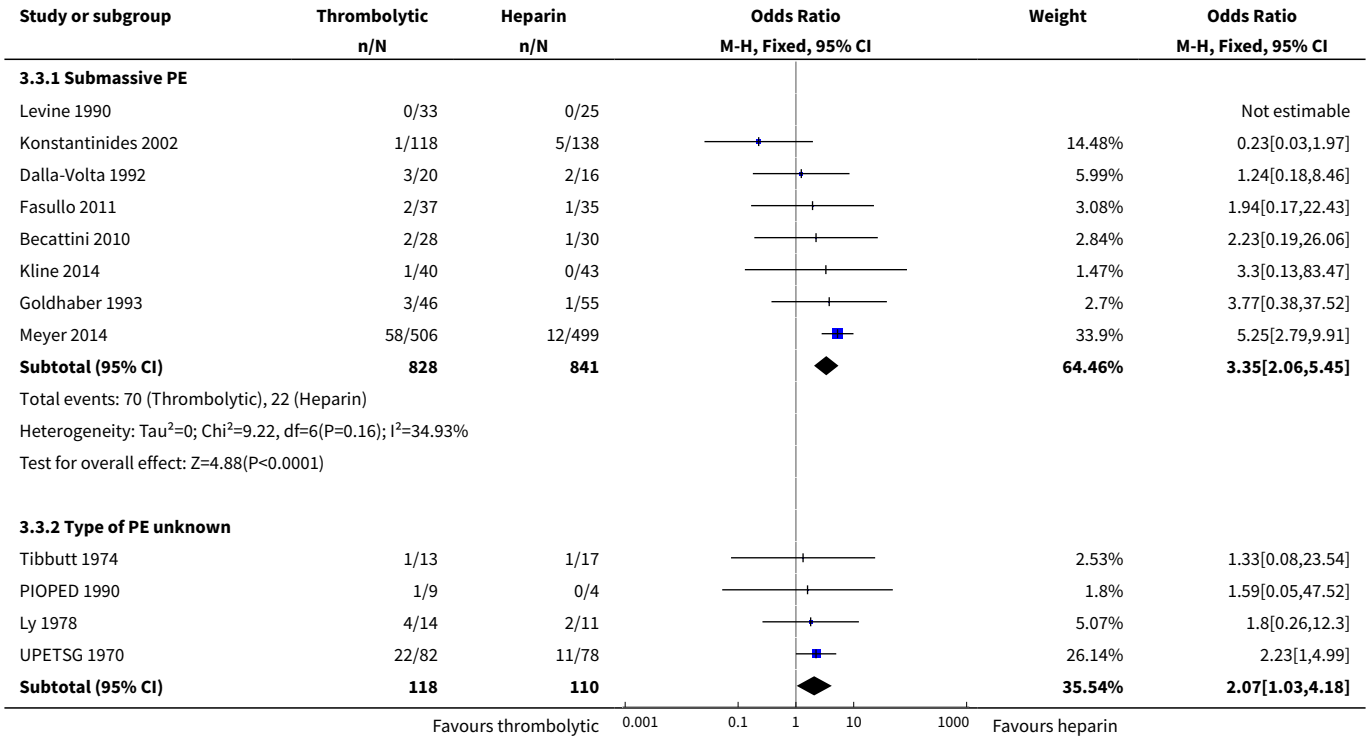


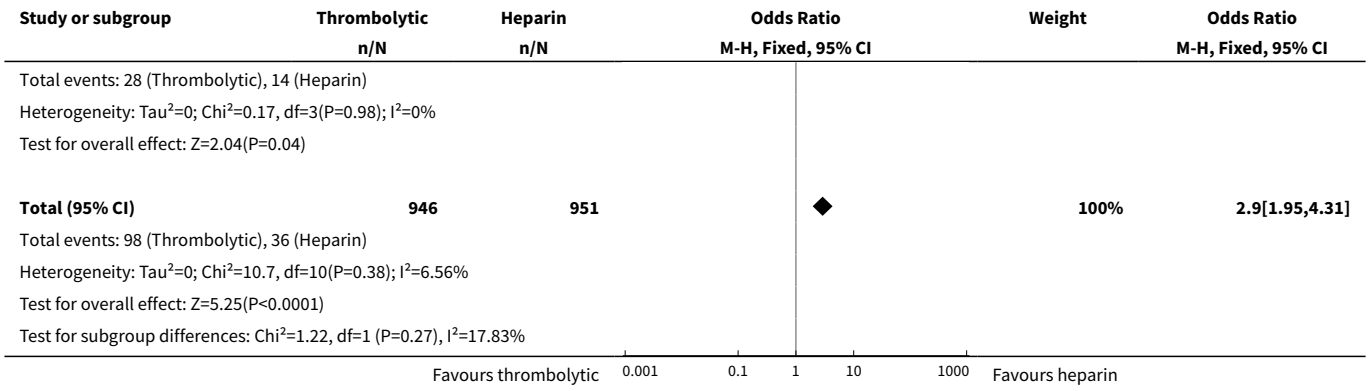
Analysis 3.2. Comparison 3 Thrombolytic therapy versus heparin: primary outcome measures (subgroup analysis according to types of PE), Outcome 2 Recurrence of pulmonary emboli.



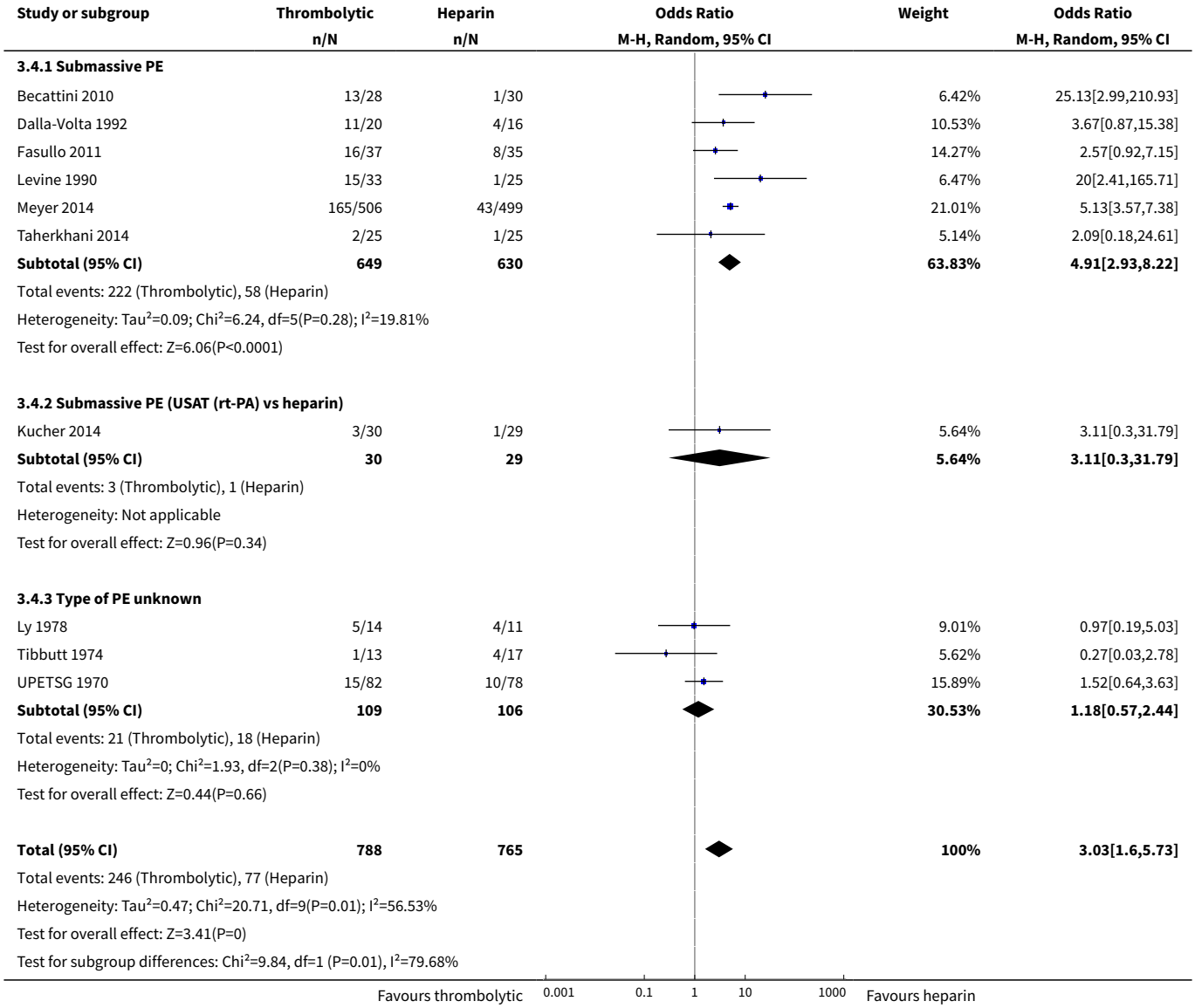


Analysis 3.3. Comparison 3 Thrombolytic therapy versus heparin: primary outcome measures (subgroup analysis according to types of PE), Outcome 3 Major haemorrhagic events.





Analysis 3.4. Comparison 3 Thrombolytic therapy versus heparin: primary outcome measures (subgroup analysis according to types of PE), Outcome 4 Minor haemorrhagic events.



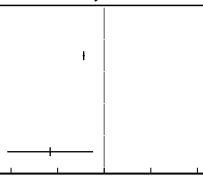
Comparison 4. Thrombolytic therapy versus heparin: haemodynamic outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary arterial systolic pressure improvement (mmHg)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Urokinase vs heparin at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Streptokinase vs heparin at 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean pulmonary arterial pressure improvement (mmHg)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Urokinase vs heparin at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Streptokinase vs heparin at 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 rt-PA vs heparin at 1.5 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Right ventricular end-diastolic pressure improvement (mmHg)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Urokinase vs heparin at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Streptokinase vs heparin at 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Total pulmonary resistance improvement (dyn·s·cm^{-5})	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Urokinase vs heparin at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Streptokinase vs heparin at 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 rt-PA vs heparin at 1.5 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Cardiac index improvement (L/min/m^2)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Streptokinase vs heparin at 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Urokinase vs heparin at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Right ventricular systolic pressure improvement (mmHg) at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Right arterial mean pressure improvement (mmHg) at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Arterial-venous oxygen difference (vol %) at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Arterial PO_2 (mmHg) improvement at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

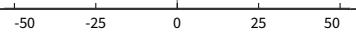
Analysis 4.1. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 1 Pulmonary arterial systolic pressure improvement (mmHg).

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.1.1 Urokinase vs heparin at 24 hours						
UPETSG 1970	76	-5.6 (0.7)	71	-1.2 (0.6)		-4.41[-4.62,-4.2]
4.1.2 Streptokinase vs heparin at 72 hours						
Tibbutt 1974	10	-15.4 (11.7)	11	-3.8 (9.6)		-11.6[-20.81,-2.39]



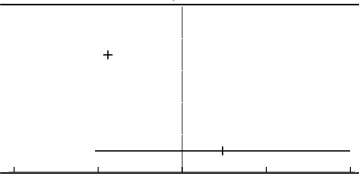
Analysis 4.2. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 2 Mean pulmonary arterial pressure improvement (mmHg).

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.2.1 Urokinase vs heparin at 24 hours						
UPETSG 1970	76	-5.6 (0.7)	71	-1.2 (0.6)		-4.41[-4.62,-4.2]
4.2.2 Streptokinase vs heparin at 72 hours						
Tibbutt 1974	8	-12.3 (5.7)	9	-4.8 (5.4)		-7.5[-12.8,-2.2]
4.2.3 rt-PA vs heparin at 1.5 hours						
PIOPED 1990	9	-3 (8.5)	4	0 (13)		-3[-16.91,10.91]



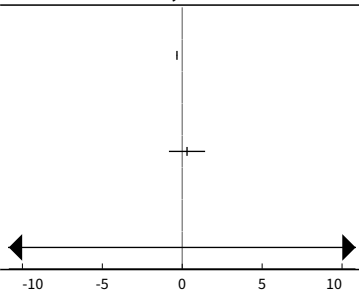
Analysis 4.3. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 3 Right ventricular end-diastolic pressure improvement (mmHg).

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.3.1 Urokinase vs heparin at 24 hours						
UPETSG 1970	75	-2.2 (0.4)	67	-0 (0.4)	+	-2.21[-2.35,-2.07]
4.3.2 Streptokinase vs heparin at 72 hours						
Tibbutt 1974	10	-2.7 (4.8)	9	-3.9 (3.6)		1.2[-2.59,4.99]



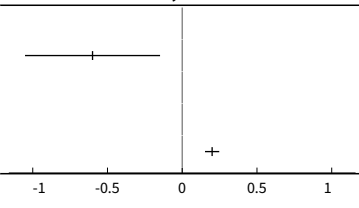
Analysis 4.4. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 4 Total pulmonary resistance improvement (dyn·s·cm^{-5}).

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.4.1 Urokinase vs heparin at 24 hours						
UPETSG 1970	57	-0.3 (0.1)	56	0 (0.1)		-0.33[-0.35,-0.31]
4.4.2 Streptokinase vs heparin at 72 hours						
Tibbutt 1974	6	-8 (1)	6	-8.3 (1)		0.3[-0.83,1.43]
4.4.3 rt-PA vs heparin at 1.5 hours						
PIOPED 1990	9	-190 (203)	4	-10 (705.1)		-180[-883.55,523.55]



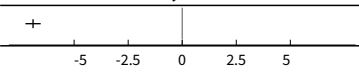
Analysis 4.5. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 5 Cardiac index improvement (L/min/m^2).

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.5.1 Streptokinase vs heparin at 72 hours						
Tibbutt 1974	6	0.1 (0.1)	7	0.7 (0.6)		-0.6[-1.05,-0.15]
4.5.2 Urokinase vs heparin at 24 hours						
UPETSG 1970	57	0.1 (0.1)	58	-0.1 (0.1)	+	0.2[0.15,0.25]



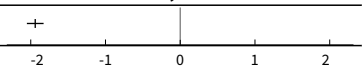
Analysis 4.6. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 6 Right ventricular systolic pressure improvement (mmHg) at 24 hours.

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
UPETSG 1970	75	-10.1 (1.2)	67	-3.2 (1)	+	-6.9[-7.25,-6.55]



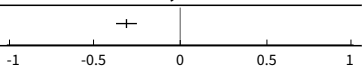
Analysis 4.7. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 7 Right arterial mean pressure improvement (mmHg) at 24 hours.

Study or subgroup	Thrombolytic		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
UPETSG 1970	74	-1.6 (0.3)	72	0.3 (0.4)		-1.94[-2.05,-1.83]



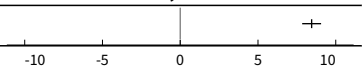
Analysis 4.8. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 8 Arterial-venous oxygen difference (vol %) at 24 hours.

Study or subgroup	Thrombolytic		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
UPETSG 1970	57	-0.2 (0.2)	60	0.1 (0.2)		-0.31[-0.37,-0.25]



Analysis 4.9. Comparison 4 Thrombolytic therapy versus heparin: haemodynamic outcomes, Outcome 9 Arterial PO_2 (mmHg) improvement at 24 hours.

Study or subgroup	Thrombolytic		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
UPETSG 1970	61	8.3 (2)	58	-0.1 (1.3)		8.45[7.84,9.06]



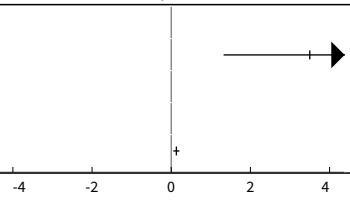
Comparison 5. Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Day 1	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Urokinase vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 rt-PA vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Day 2	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Urokinase vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Day 5	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Urokinase vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Day 7	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Alteplase vs heparin (total lung score)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Day 14	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Urokinase vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Day 30	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Alteplase vs heparin (total lung score)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Absolute resolution (1-year follow-up)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Urokinase vs heparin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

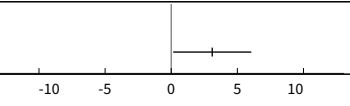
Analysis 5.1. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 1 Day 1.

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.1.1 Urokinase vs heparin						
UPETSG 1970	72	6.2 (7.2)	70	2.7 (6)		3.5[1.32,5.68]
5.1.2 rt-PA vs heparin						
Goldhaber 1993	46	0.2 (0.2)	55	0 (0.2)		0.13[0.05,0.21]



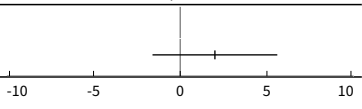
Analysis 5.2. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 2 Day 2.

Study or subgroup	Urokinase N	Urokinase Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.2.1 Urokinase vs heparin						
UPETSG 1970	69	8 (9.8)	64	4.9 (7.5)		3.1[0.15,6.05]



Analysis 5.3. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 3 Day 5.

Study or subgroup	Urokinase		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.3.1 Urokinase vs heparin						
UPETSG 1970	67	11.3 (10.7)	59	9.3 (9.9)		2[-1.6,5.6]

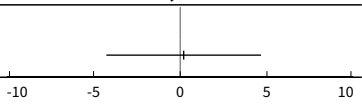


Analysis 5.4. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 4 Day 7.

Study or subgroup	rt-PA+heparin		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.4.1 Alteplase vs heparin (total lung score)						
Dalla-Volta 1992	10	7 (3)	11	5.3 (3.4)		1.7[-1.04,4.44]
5.4.2 Change from baseline						
Dalla-Volta 1992	10	5 (2)	11	3.2 (3.3)		1.8[-0.51,4.11]

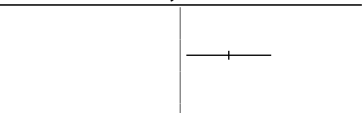
Analysis 5.5. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 5 Day 14.

Study or subgroup	Urokinase		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.5.1 Urokinase vs heparin						
UPETSG 1970	62	14.9 (12.9)	54	14.7 (11.6)		0.2[-4.26,4.66]



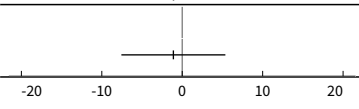
Analysis 5.6. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 6 Day 30.

Study or subgroup	Alteplase + heparin		Heparin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.6.1 Alteplase vs heparin (total lung score)						
Dalla-Volta 1992	11	5.5 (3.3)	11	2.7 (2.5)		2.8[0.35,5.25]
5.6.2 Change from baseline						
Dalla-Volta 1992	11	6.5 (2.1)	11	5.8 (2.8)		0.7[-1.37,2.77]



Analysis 5.7. Comparison 5 Thrombolytic therapy versus heparin: perfusion lung scanning (absolute resolution), Outcome 7 Absolute resolution (1-year follow-up).

Study or subgroup	Urokinase N	Urokinase Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.7.1 Urokinase vs heparin						
UPETSG 1970	30	19.1 (12.9)	27	20.2 (12)		-1.1[-7.57,5.37]

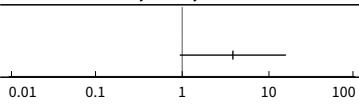


Comparison 6. Thrombolytic therapy versus heparin: number of patients with greater than 50% improvement on lung scan

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 rt-PA vs heparin	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 rt-PA vs heparin	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

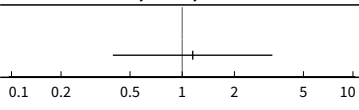
Analysis 6.1. Comparison 6 Thrombolytic therapy versus heparin: number of patients with greater than 50% improvement on lung scan, Outcome 1 Day 1.

Study or subgroup	rt-PA + heparin n/N	Heparin + placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.1.1 rt-PA vs heparin				
Levine 1990	11/32	3/25		3.84[0.94,15.73]



Analysis 6.2. Comparison 6 Thrombolytic therapy versus heparin: number of patients with greater than 50% improvement on lung scan, Outcome 2 Day 7.

Study or subgroup	rt-PA + heparin n/N	Heparin + placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.2.1 rt-PA vs heparin				
Levine 1990	19/32	14/25		1.15[0.4,3.31]

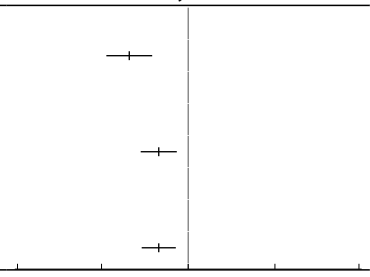


Comparison 7. Thrombolytic therapy versus heparin: pulmonary angiogram assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline at 2 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Alteplase vs heparin (overall total score)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Alteplase vs heparin (left lung)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Alteplase vs heparin (right lung)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change from baseline at 72 hours	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Streptokinase vs heparin	2	47	Mean Difference (IV, Fixed, 95% CI)	-9.30 [-12.81, -5.78]

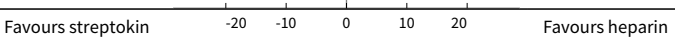
Analysis 7.1. Comparison 7 Thrombolytic therapy versus heparin: pulmonary angiogram assessment, Outcome 1 Change from baseline at 2 hours.

Study or subgroup	rt-PA+heparin N	rt-PA+heparin Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
7.1.1 Alteplase vs heparin (overall total score)						
Dalla-Volta 1992	20	-3.5 (2.7)	16	-0.1 (1.2)		-3.4[-4.72,-2.08]
7.1.2 Alteplase vs heparin (left lung)						
Dalla-Volta 1992	20	-1.9 (2.2)	16	-0.2 (0.8)		-1.7[-2.74,-0.66]
7.1.3 Alteplase vs heparin (right lung)						
Dalla-Volta 1992	20	-1.6 (1.8)	16	0.1 (1.2)		-1.7[-2.68,-0.72]



Analysis 7.2. Comparison 7 Thrombolytic therapy versus heparin: pulmonary angiogram assessment, Outcome 2 Change from baseline at 72 hours.

Study or subgroup	Streptokinase N	Streptokinase Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
7.2.1 Streptokinase vs heparin							
Ly 1978	14	-11.3 (5.7)	10	-3.4 (6.8)		46.33%	-7.9[-13.07,-2.73]
Tibbutt 1974	11	-13.3 (7)	12	-2.8 (4.3)		53.67%	-10.5[-15.3,-5.7]
Subtotal ***	**25**		**22**			**100%**	**-9.3[-12.81,-5.78]**
Heterogeneity: Tau²=0; Chi²=0.52, df=1(P=0.47); I²=0%							
Test for overall effect: Z=5.18(P<0.0001)							



Comparison 8. Thrombolytic therapy versus heparin: echocardiograms

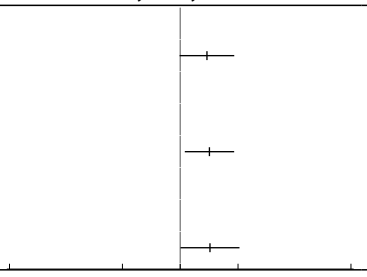
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Right ventricular wall movement improvement	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 3 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 24 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 End of first week	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Tricuspid regurgitation improvement	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 3 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 24 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Paradoxical systolic septal motion	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 24 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 48 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 72 hours after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 6 days after treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Right ventricle-to-left ventricle ratio	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 24 hours after treatment	2	131	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.16, -0.11]
4.2 48 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.20, -0.18]
4.3 72 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.15, -0.13]
4.4 6 days after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.23, -0.21]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.5 Discharge after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.34, -0.32]
4.6 3 months after treatment	2	131	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.34, 0.05]
4.7 6 months after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.22, -0.20]
5 Tricuspid annular plane systolic excursion	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 24 hours after treatment	2	131	Mean Difference (IV, Random, 95% CI)	0.45 [-1.18, 2.07]
5.2 48 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	1.0 [-0.13, 2.13]
5.3 72 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	1.80 [0.67, 2.93]
5.4 6 days after treatment	1	72	Mean Difference (IV, Random, 95% CI)	2.5 [1.57, 3.43]
5.5 Discharge after treatment	1	72	Mean Difference (IV, Random, 95% CI)	2.0 [0.75, 3.25]
5.6 3 months after treatment	2	131	Mean Difference (IV, Random, 95% CI)	0.33 [-3.18, 3.85]
5.7 6 months after treatment	1	72	Mean Difference (IV, Random, 95% CI)	1.30 [0.28, 2.32]
6 Right ventricular-to-right atrial pressure gradient	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 24 hours after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 3 months after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Minimum inferior vena cava diameter	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 24 hours after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 3 months after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Pulmonary hypertension	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 24 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-8.0 [-14.76, -1.24]
8.2 48 hours after treatment	2	193	Mean Difference (IV, Random, 95% CI)	-7.37 [-9.20, -5.53]
8.3 72 hours after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-8.0 [-11.74, -4.26]
8.4 6 days after treatment	2	122	Mean Difference (IV, Random, 95% CI)	-5.69 [-9.37, -2.02]
8.5 Discharge after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-8.0 [-9.78, -6.22]
8.6 3 months after treatment	1	72	Mean Difference (IV, Random, 95% CI)	-7.0 [-17.18, 3.18]
8.7 6 months after treatment	2	193	Mean Difference (IV, Random, 95% CI)	-11.95 [-23.71, -0.19]
8.8 28 months after treatment	1	121	Mean Difference (IV, Random, 95% CI)	-15.0 [-17.32, -12.68]

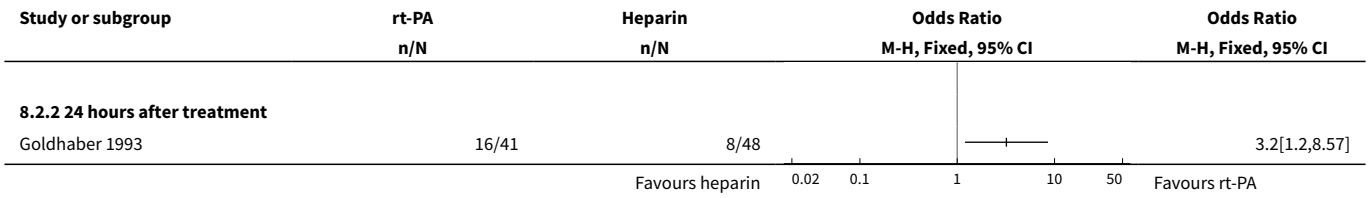
Analysis 8.1. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 1 Right ventricular wall movement improvement.

Study or subgroup	Thrombolytic n/N	Heparin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
8.1.1 3 hours after treatment				
Goldhaber 1993	12/41	6/48		2.9[0.98,8.6]
8.1.2 24 hours after treatment				
Goldhaber 1993	16/41	8/48		3.2[1.2,8.57]
8.1.3 End of first week				
Taherkhani 2014	18/25	11/25		3.27[1.01,10.62]

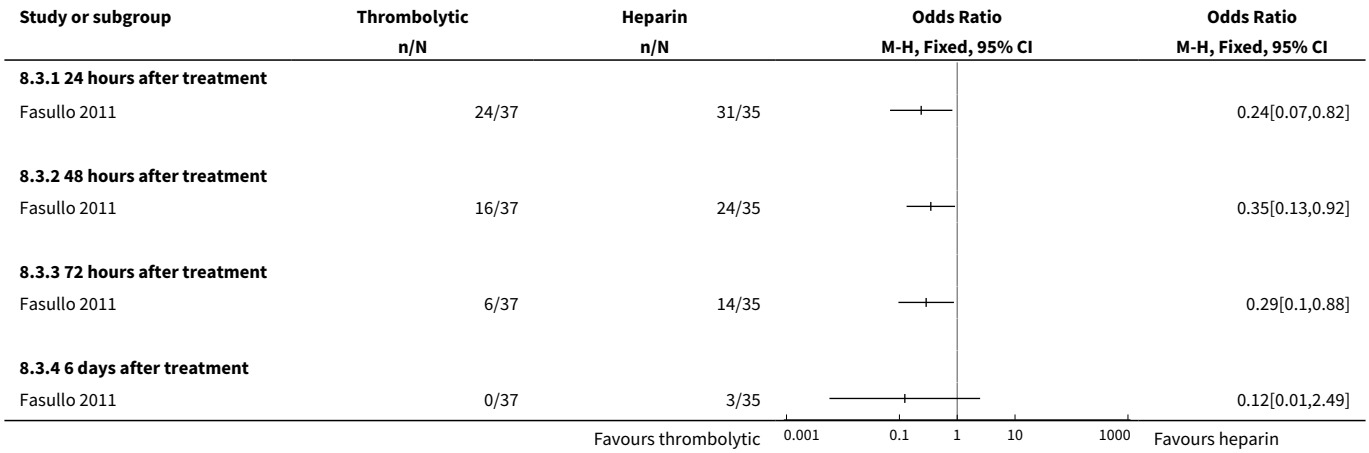


Analysis 8.2. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 2 Tricuspid regurgitation improvement.

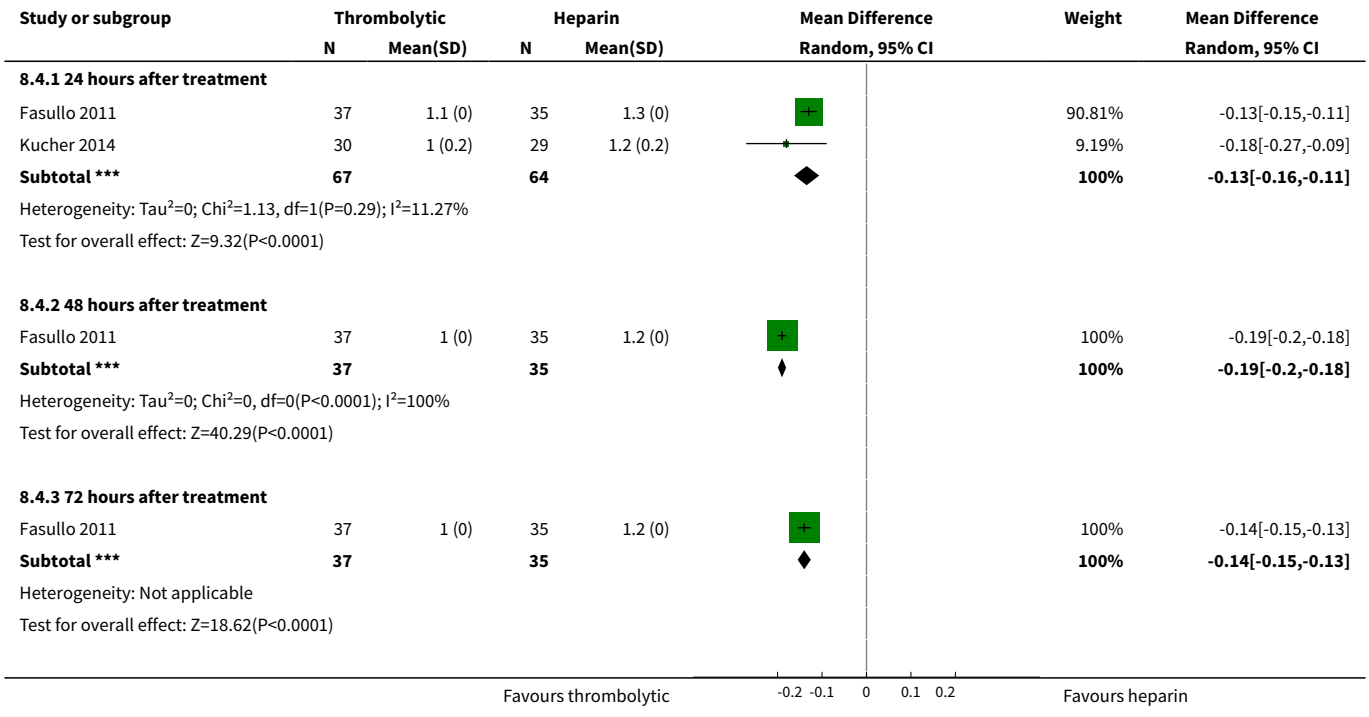
Study or subgroup	rt-PA n/N	Heparin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
8.2.1 3 hours after treatment				
Goldhaber 1993	15/41	4/48		6.35[1.9,21.17]

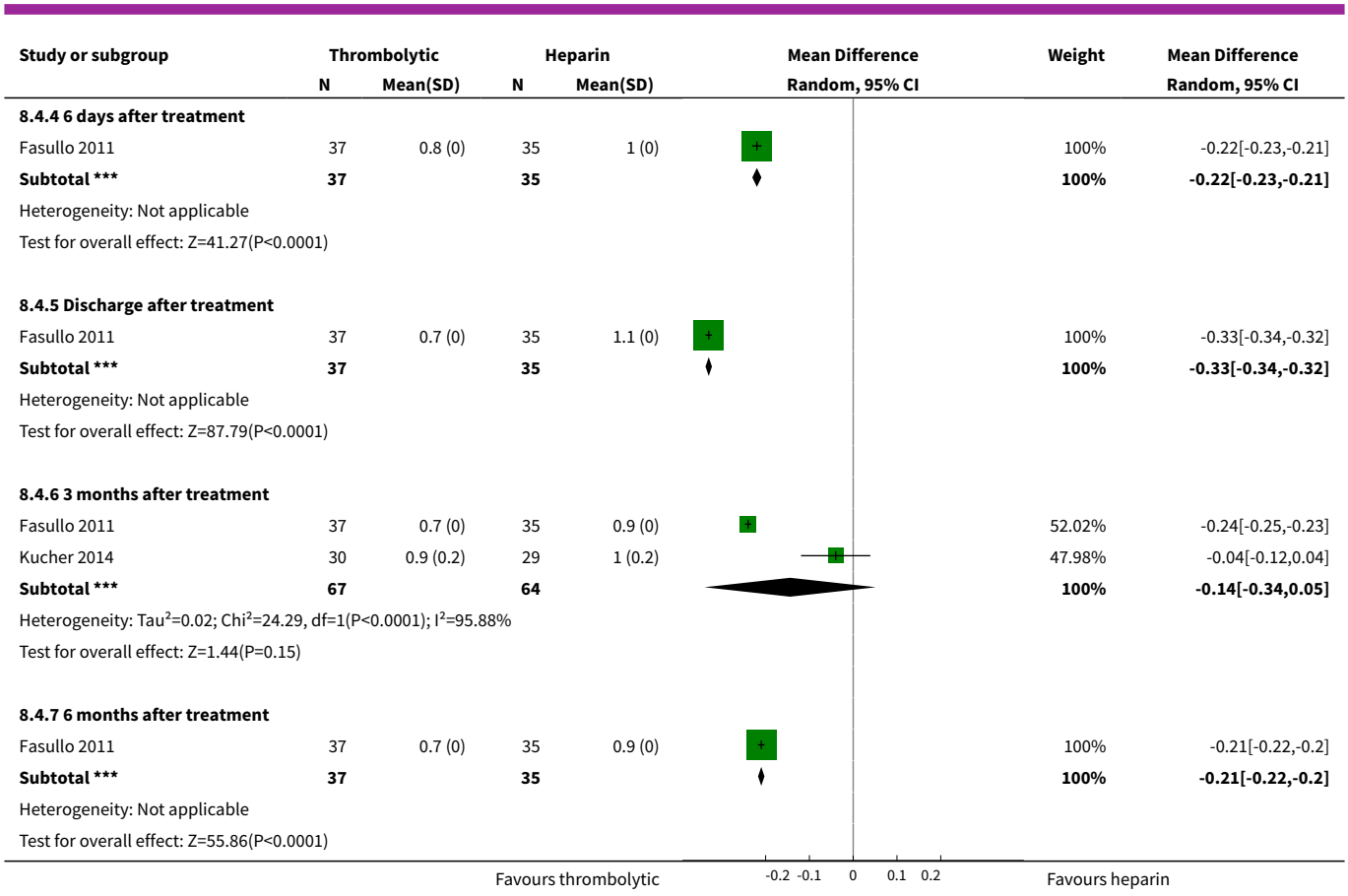


Analysis 8.3. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 3 Paradoxical systolic septal motion.

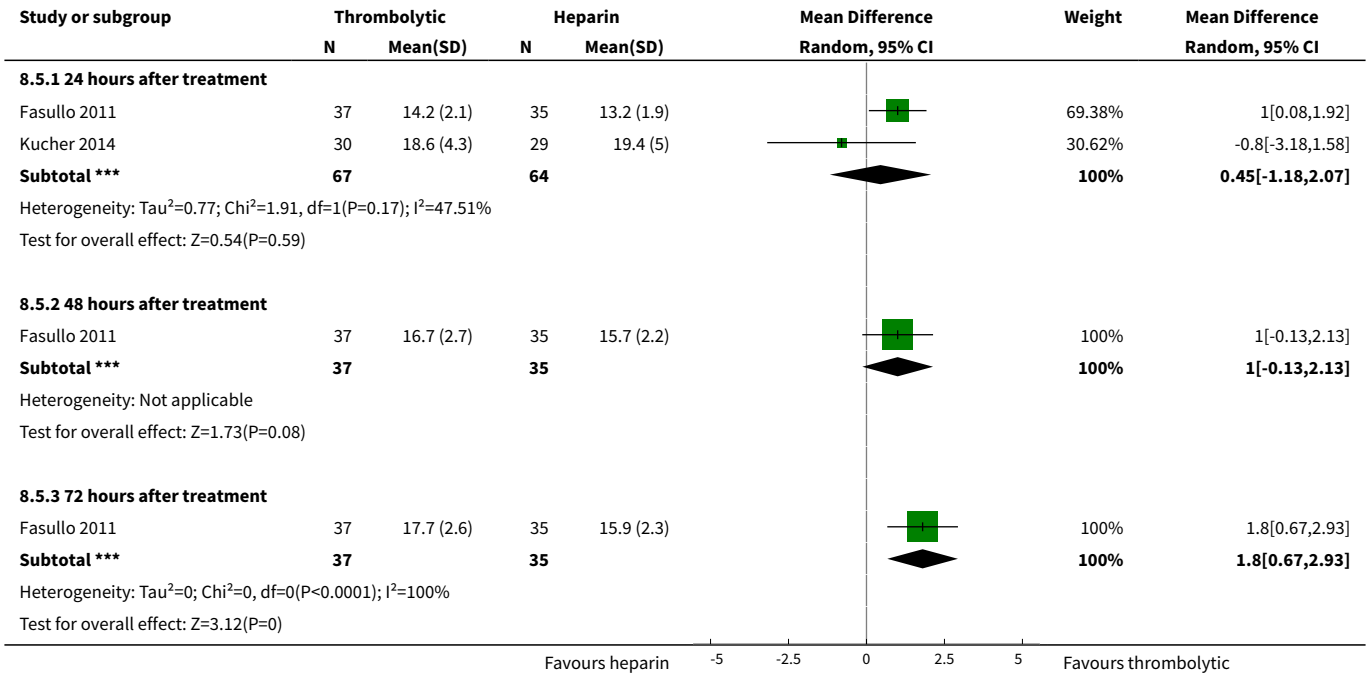


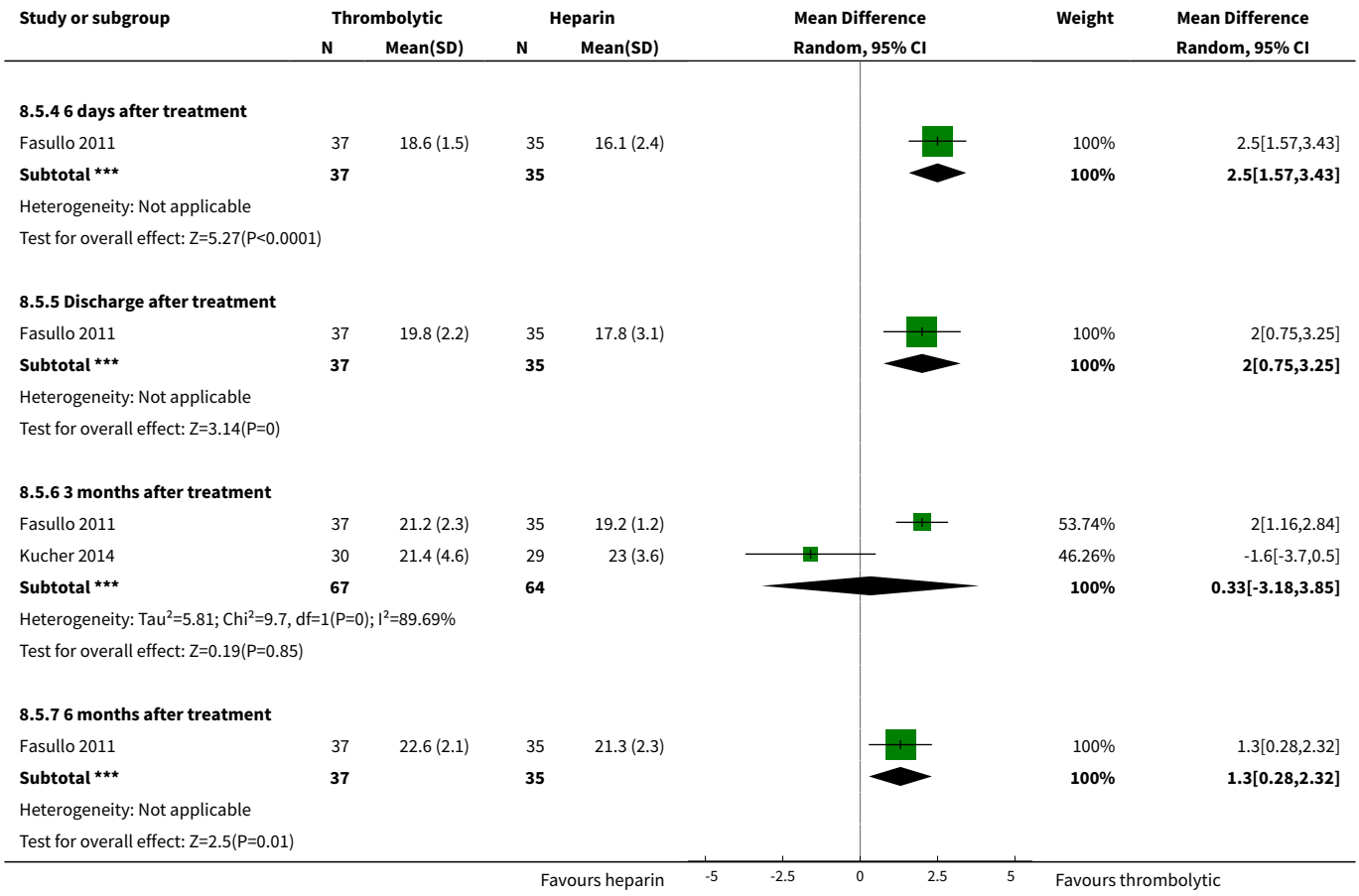
Analysis 8.4. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 4 Right ventricle-to-left ventricle ratio.



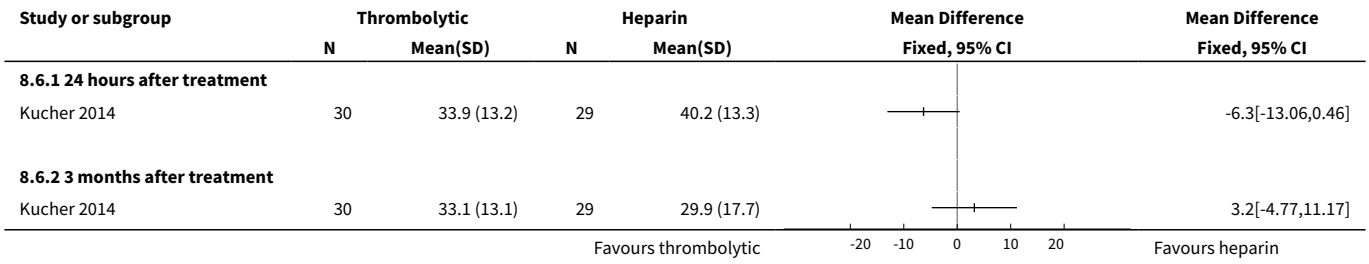


Analysis 8.5. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 5 Tricuspid annular plane systolic excursion.

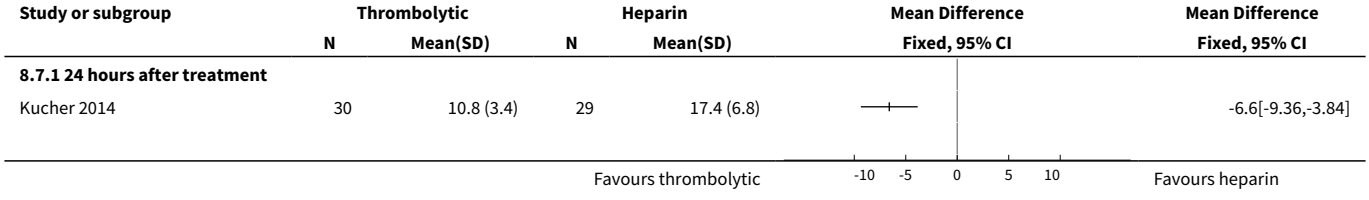




Analysis 8.6. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 6 Right ventricular-to-right atrial pressure gradient.



Analysis 8.7. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 7 Minimum inferior vena cava diameter.



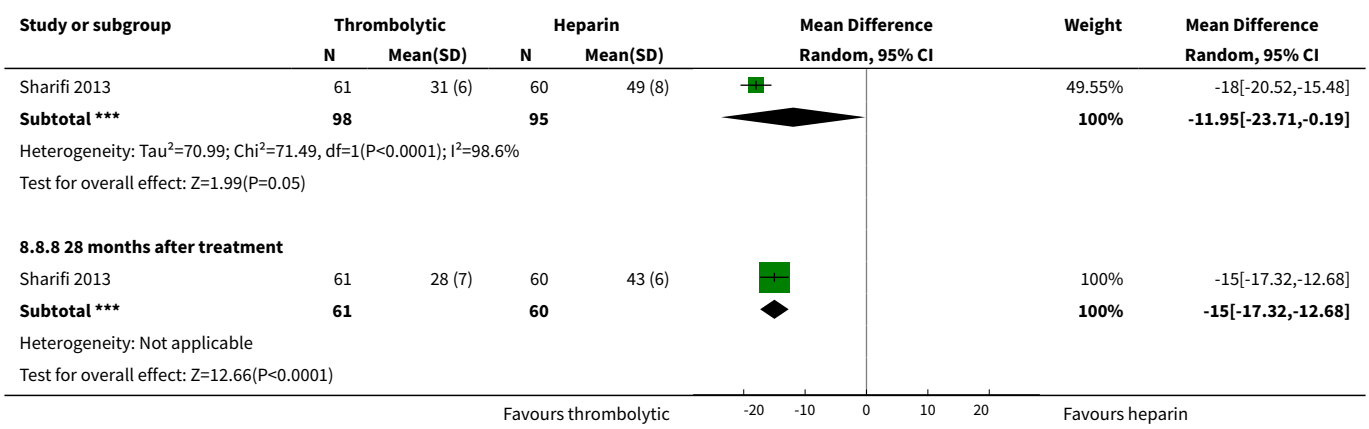
Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.7.2 3 months after treatment						
Kucher 2014	30	9.4 (3.6)	29	9.9 (5.2)		-0.5[-2.79,1.79]

Favours thrombolytic -10 -5 0 5 10 Favours heparin

Analysis 8.8. Comparison 8 Thrombolytic therapy versus heparin: echocardiograms, Outcome 8 Pulmonary hypertension.

Study or subgroup	Thrombolytic N	Thrombolytic Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.8.1 24 hours after treatment							
Fasullo 2011	37	45 (13)	35	53 (16)		100%	-8[-14.76,-1.24]
Subtotal ***	**37**		**35**			**100%**	**-8[-14.76,-1.24]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.32(P=0.02)							
8.8.2 48 hours after treatment							
Fasullo 2011	37	38 (7)	35	47 (11)		18.29%	-9[-13.29,-4.71]
Sharifi 2013	61	34 (7)	60	41 (4)		81.71%	-7[-9.03,-4.97]
Subtotal ***	**98**		**95**			**100%**	**-7.37[-9.2,-5.53]**
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=7.88(P<0.0001)							
8.8.3 72 hours after treatment							
Fasullo 2011	37	35 (7)	35	43 (9)		100%	-8[-11.74,-4.26]
Subtotal ***	**37**		**35**			**100%**	**-8[-11.74,-4.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.19(P<0.0001)							
8.8.4 6 days after treatment							
Fasullo 2011	37	30 (4)	35	37 (5)		67.35%	-7[-9.1,-4.9]
Taherkhani 2014	25	31.5 (9.1)	25	34.5 (9.2)		32.65%	-3[-8.07,2.07]
Subtotal ***	**62**		**60**			**100%**	**-5.69[-9.37,-2.02]**
Heterogeneity: Tau^2=4.08; Chi^2=2.04, df=1(P=0.15); I^2=50.97%							
Test for overall effect: Z=3.04(P=0)							
8.8.5 Discharge after treatment							
Fasullo 2011	37	21 (2)	35	29 (5)		100%	-8[-9.78,-6.22]
Subtotal ***	**37**		**35**			**100%**	**-8[-9.78,-6.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.82(P<0.0001)							
8.8.6 3 months after treatment							
Fasullo 2011	37	14 (31)	35	21 (6)		100%	-7[-17.18,3.18]
Subtotal ***	**37**		**35**			**100%**	**-7[-17.18,3.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.35(P=0.18)							
8.8.7 6 months after treatment							
Fasullo 2011	37	12 (3)	35	18 (2)		50.45%	-6[-7.17,-4.83]

Favours thrombolytic -20 -10 0 10 20 Favours heparin

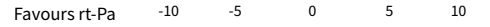


Comparison 9. Thrombolytic therapy versus heparin: haemocoagulation variables

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fibrinogen (g/L)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Less than 3 hours after treatment	2	45	Mean Difference (IV, Random, 95% CI)	-2.68 [-4.36, 1.00]
1.2 24 hours after treatment	2	114	Mean Difference (IV, Random, 95% CI)	-1.61 [-3.99, 0.76]
1.3 48 hours after treatment	1	83	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.40, 0.20]
2 D-dimer (µg/mL)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Less than 3 hours after treatment	2	45	Mean Difference (IV, Random, 95% CI)	21.04 [-4.60, 46.69]
2.2 24 hours after treatment	1	31	Mean Difference (IV, Random, 95% CI)	5.30 [2.12, 8.48]
3 Plasminogen (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 2 hours after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 24 hours after treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

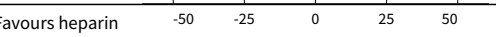
Analysis 9.1. Comparison 9 Thrombolytic therapy versus heparin: haemocoagulation variables, Outcome 1 Fibrinogen (g/L).

Study or subgroup	rt-PA N	rt-PA Mean(SD)	heparin N	heparin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
9.1.1 Less than 3 hours after treatment							
Dalla-Volta 1992	19	1.9 (1)	13	5.3 (1.6)		58.51%	-3.4[-4.38,-2.42]
PIOPED 1990	9	2.2 (1.8)	4	3.9 (1.3)		41.49%	-1.66[-3.37,0.05]
Subtotal ***	**28**		**17**			**100%**	**-2.68[-4.36,-1]**
Heterogeneity: Tau^2=1.01; Chi^2=2.98, df=1(P=0.08); I^2=66.49%							
Test for overall effect: Z=3.12(P=0)							
9.1.2 24 hours after treatment							
Dalla-Volta 1992	18	2.8 (2.1)	13	5.7 (1.7)		47.02%	-2.9[-4.24,-1.56]
Kline 2014	40	3.7 (1.6)	43	4.2 (1.5)		52.98%	-0.47[-1.14,0.2]
Subtotal ***	**58**		**56**			**100%**	**-1.61[-3.99,0.76]**
Heterogeneity: Tau^2=2.66; Chi^2=10.14, df=1(P=0); I^2=90.14%							
Test for overall effect: Z=1.33(P=0.18)							
9.1.3 48 hours after treatment							
Kline 2014	40	3.9 (1.9)	43	4.5 (1.9)		100%	-0.6[-1.4,0.2]
Subtotal ***	**40**		**43**			**100%**	**-0.6[-1.4,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.46(P=0.14)							



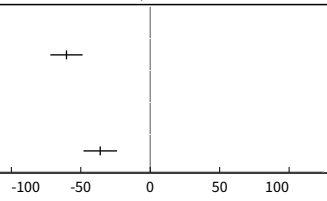
Analysis 9.2. Comparison 9 Thrombolytic therapy versus heparin: haemocoagulation variables, Outcome 2 D-dimer (µg/mL).

Study or subgroup	rt-PA N	rt-PA Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
9.2.1 Less than 3 hours after treatment							
Dalla-Volta 1992	19	15.7 (4.6)	13	6.1 (4.9)		56.65%	9.6[6.23,12.97]
PIOPED 1990	9	40 (29)	4	4 (3)		43.35%	36[16.83,55.17]
Subtotal ***	**28**		**17**			**100%**	**21.04[-4.6,46.69]**
Heterogeneity: Tau^2=299.15; Chi^2=7.06, df=1(P=0.01); I^2=85.84%							
Test for overall effect: Z=1.61(P=0.11)							
9.2.2 24 hours after treatment							
Dalla-Volta 1992	18	10.7 (4.8)	13	5.4 (4.2)		100%	5.3[2.12,8.48]
Subtotal ***	**18**		**13**			**100%**	**5.3[2.12,8.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.26(P=0)							



Analysis 9.3. Comparison 9 Thrombolytic therapy versus heparin: haemocoagulation variables, Outcome 3 Plasminogen (%).

Study or subgroup	Alteplase N	Alteplase Mean(SD)	Heparin N	Heparin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.3.1 2 hours after treatment						
Dalla-Volta 1992	19	25 (10.6)	13	85.3 (19.5)		-60.3[-71.92,-48.68]
9.3.2 24 hours after treatment						
Dalla-Volta 1992	18	52 (18.8)	13	88 (15.4)		-36[-48.06,-23.94]

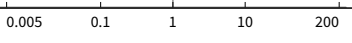


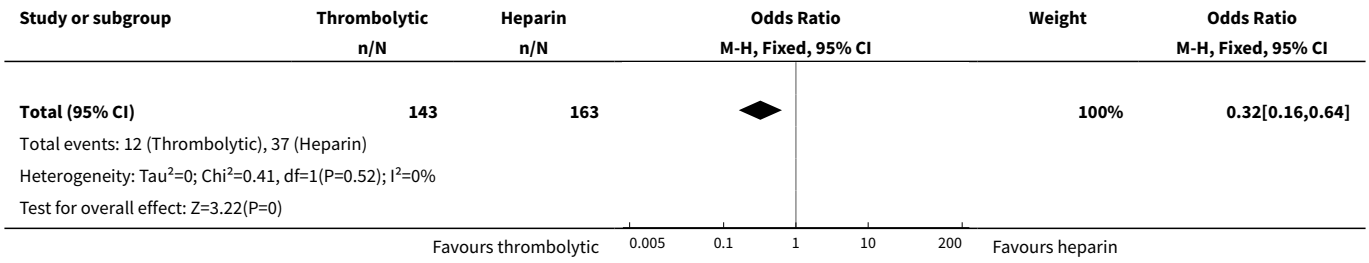
Comparison 10. Thrombolytic therapy versus heparin: other outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escalation of treatment	2	306	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.16, 0.64]
2 Hospital stay	3	230	Mean Difference (IV, Random, 95% CI)	-0.89 [-3.13, 1.34]
2.1 USAT (rt-PA) vs heparin	1	59	Mean Difference (IV, Random, 95% CI)	0.30 [-1.57, 2.17]
2.2 rt-PA vs heparin	1	121	Mean Difference (IV, Random, 95% CI)	-2.7 [-2.94, -2.46]
2.3 Streptokinase or alteplase vs enoxaparin heparin	1	50	Mean Difference (IV, Random, 95% CI)	0.0 [-0.83, 0.83]
3 Composite clinical outcome	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 All-cause death or haemodynamic decompensation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Recurrent VTE and poor functional capacity and low perception of wellness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Poor functional capacity and low perception of wellness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Recurrent VTE and low perception of wellness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

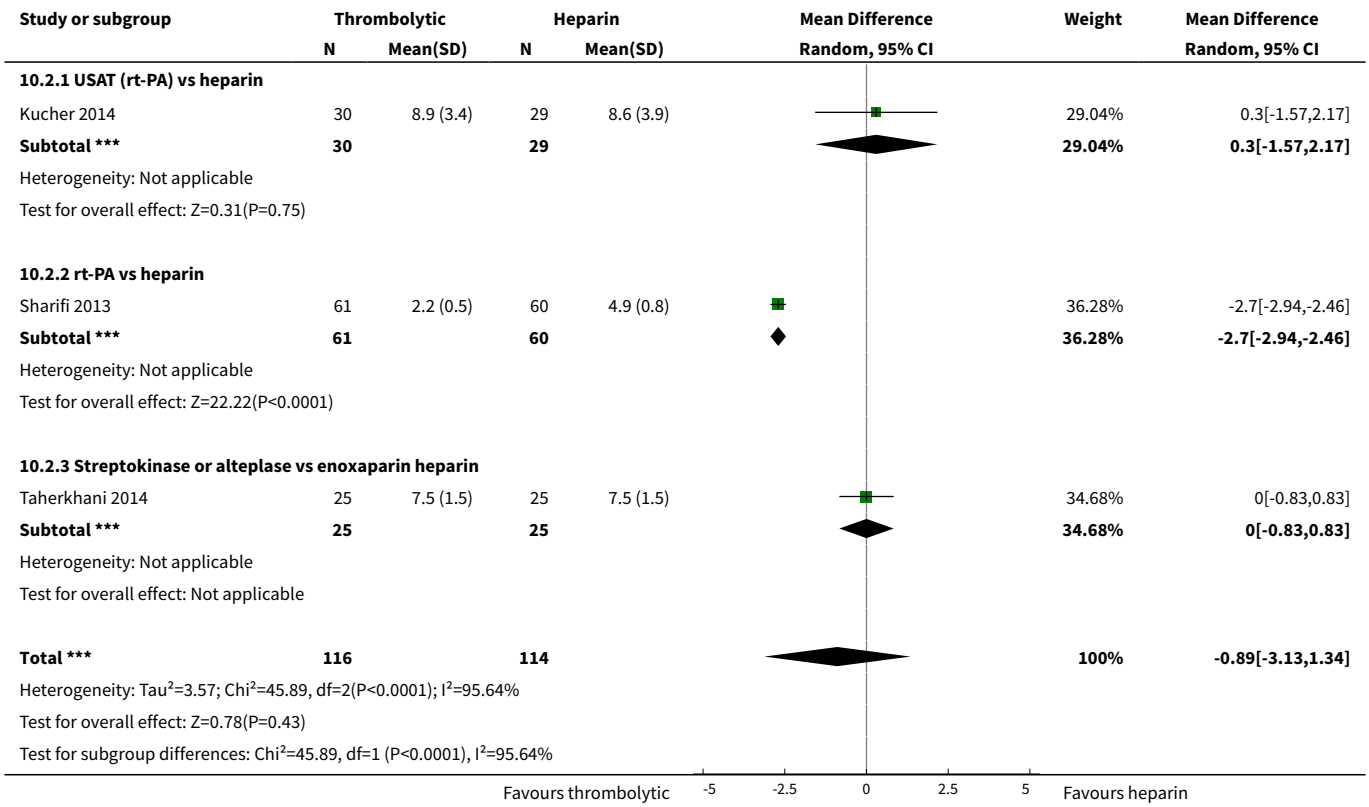
Analysis 10.1. Comparison 10 Thrombolytic therapy versus heparin: other outcomes, Outcome 1 Escalation of treatment.

Study or subgroup	Thrombolytic n/N	Heparin n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Konstantinides 2002	12/118	34/138		89.13%	0.35[0.17,0.71]
Taherkhani 2014	0/25	3/25		10.87%	0.13[0.01,2.58]

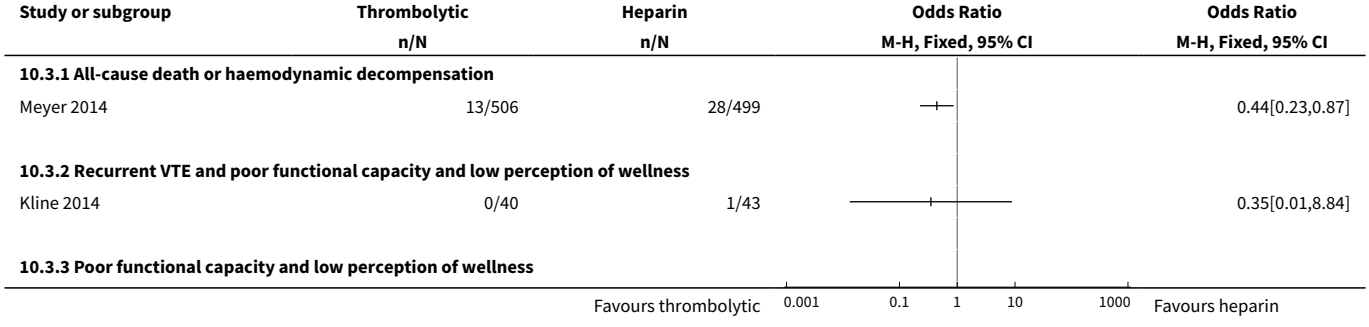


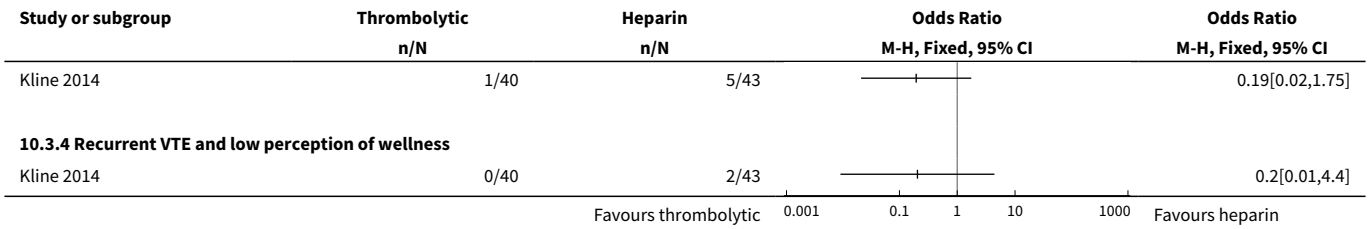


Analysis 10.2. Comparison 10 Thrombolytic therapy versus heparin: other outcomes, Outcome 2 Hospital stay.



Analysis 10.3. Comparison 10 Thrombolytic therapy versus heparin: other outcomes, Outcome 3 Composite clinical outcome.





ADDITIONAL TABLES

Table 1. American Heart Association definitions of massive, submassive, and low-risk PE

Risk classification	Definition	Short-term mortality
Massive PE	Acute PE with haemodynamically unstable manifestations such as sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolaemia, sepsis, or left ventricular dysfunction), lack of pulse, or persistent profound bradycardia (heart rate < 40 beats per minute (bpm) with signs or symptoms of shock)	25% to 65%
Submassive PE	Haemodynamically stable (without systemic hypotension (systolic blood pressure > 90 mmHg)) patients who present with either right ventricular dysfunction or myocardial necrosis (RV dysfunction (CT, BPN/proBNP, ECG changes) or myocardial necrosis (elevated troponins))	3%
Low-risk PE	Absence of hypotension, RV dysfunction, and myocardial necrosis	< 1%

BPN: B-type natriuretic peptide
CT: computed tomography
ECG: electrocardiography
PE: pulmonary embolism
RV: right ventricular

APPENDICES

Appendix 1. Database searches

Source	Search strategy	Hits retrieved
CENTRAL via CRSO	#1 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 784	130
	#2 ((lung or pulmonary) near (embol* or clot*)):TI,AB,KY 3388	
	#3 MESH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES 1582	
	#4 MESH DESCRIPTOR Fibrinolytic Agents EXPLODE ALL TREES 11397	
	#5 MESH DESCRIPTOR Plasminogen Activators EXPLODE ALL TREES 2302	
	#6 MESH DESCRIPTOR Fibrinolysis EXPLODE ALL TREES 964	
	#7 (streptokinase or urokinase or alteplase):TI,AB,KY 2846	

(Continued)

	#8 (9 thromboly* or fibrinoly*):TI,AB,KY 5077 #9 (avelizin or awelysin or celiase or distreptase or kabikinase or kabivitrum or streptase or streptodecase or apsac or anistreplase or monteplase or apsac):TI,AB,KY 216 #10 (avelizin or awelysin or celiase or distreptase or kabikinase or kabivitrum or streptase or streptodecase or apsac or anistreplase or monteplase or apsac):TI,AB,KY 216 #11 (activase or saruplase or retavase or abbokinase or abbokinase or renokinase or u-pa):TI,AB,KY 94 #12 ((clot* or thrombus) near3 (lyse or lysis or dissolv* or dissolution)):TI,AB,KY 1149 #13 (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actil-yse):TI,AB,KY 5649 #14 (anistreplase or streptodornase or pro-urokinase or prourokinase or pro-uk or lum-brokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphy-lokinase or streptase or tenecteplase or desmoteplase or retevase):TI,AB,KY 720 #15 #1 OR #2 3388 #16 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 18011 #17 #15 AND #16 852 #18 01/01/2015 TO 16/04/2018:CD 301940 #19 #17 AND #18 130	
Clinicaltrials.gov	Pulmonary Embolism | Thrombolytic Therapy OR Fibrinolytic Agents OR Plasminogen Ac-tivators OR Fibrinolysis | Last update posted from 01/01/2015 to 04/16/2018	54
ICTRP Search Por-tal	Pulmonary Embolism | Thrombolytic Therapy OR Fibrinolytic Agents OR Plasminogen Ac-tivators OR Fibrinolysis | Last update posted from 01/01/2015 to 04/16/2018	2
MEDLINE	1 exp Pulmonary Embolism/ 36003 2 ((lung or pulmonary) adj2 (embol* or clot*)).ti,ab. 35371 3 exp Thrombolytic Therapy/ 22206 4 exp Fibrinolytic Agents/ 160854 5 exp Plasminogen Activators/ 38114 6 exp FIBRINOLYSIS/ 20624 7 (streptokinase or urokinase or alteplase).ti,ab. 21720 8 (thromboly* or fibrinoly*).ti,ab. 62774 9 (avelizin or awelysin or celiase or distreptase or kabikinase or kabivitrum or streptase or streptodecase or apsac or anistreplase or monteplase or apsac).ti,ab. 606 10 (activase or saruplase or retavase or abbokinase or abbokinase or renokinase or u-pa).ti,ab. 1981 11 ((clot* or thrombus) adj3 (lyse or lysis or dissolv* or dissolution)).ti,ab. 3704 12 (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).ti,ab. 63992	250

(Continued)

	13 (anistreplase or streptodornase or pro-urokinase or prourokinase or pro-uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).ti,ab. 2539 14 1 or 2 50623 15 or/3-13 243510 16 14 and 15 9731 17 randomized controlled trial.pt. 458772 18 controlled clinical trial.pt. 92329 19 randomized.ab. 408806 20 placebo.ab. 188173 21 drug therapy.fs. 2009606 22 randomly.ab. 288659 23 trial.ab. 424894 24 groups.ab. 1784447 25 or/17-24 4182932 26 exp animals/ not humans.sh. 4446637 27 25 not 26 3615036 28 16 and 27 5424 29 (2017* or 2018*).ed. 1223989 30 28 and 29 250	
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	14 (anistreplase or streptodornase or pro-urokinase or prourokinase or pro-uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).ti,ab. 2024 15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 148573 16 3 and 15 11379 17 randomized controlled trial/ 450402 18 controlled clinical trial/ 414396 19 random$.ti,ab. 1155905 20 randomization/ 69465 21 intermethod comparison/ 223864 22 placebo.ti,ab. 220739 23 (compare or compared or comparison).ti. 331992 24 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1600366 25 (open adj label).ti,ab. 61988 26 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 156621 27 double blind procedure/ 122146 28 parallel group$1.ti,ab. 19377 29 (crossover or cross over).ti,ab. 71409 30 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 246607 31 (assigned or allocated).ti,ab. 287439 32 (controlled adj7 (study or design or trial)).ti,ab. 259032 33 (volunteer or volunteers).ti,ab. 170768 34 trial.ti. 211866 35 or/17-34 3442314 36 16 and 35 1938 37 (2017* or 2018*).em. 3287804 38 36 and 37 343 39 from 38 keep 1-343 343	
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4 (streptokinase or urokinase or alteplase).ti,ab. 14

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6 (avelizin or awelysin or celiase or distreptase or kabikinase or kabivitrum or streptase or streptodecase or apsac or anistreplase or monteplase or apsac).ti,ab. 0

7 (activase or saruplase or retavase or abbokinase or abbokinase or renokinase or u-pa).ti,ab. 3

8 ((clot* or thrombus) adj3 (lyse or lysis or dissolv* or dissolution)).ti,ab. 6

9 (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).ti,ab. 188

10 (anistreplase or streptodornase or pro-urokinase or prourokinase or pro-uk or lum-brokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphy-lokinase or streptase or tenecteplase or desmoteplase or retevase).ti,ab. 6

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16 Clinical trial.pt. 1210

17 (clinic* adj trial*).tw. 5347

18 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. 2804

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20 placebo*.tw. 3084

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22 PROSPECTIVE STUDIES/ 1065

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WHAT'S NEW

Date	Event	Description
20 September 2018	New citation required but conclusions have not changed	Searches were rerun. One article related to an included study was identified. Three new ongoing studies were added, and nine additional studies were excluded. No change was made to conclusions
20 September 2018	New search has been performed	Searches were rerun. One article related to an included study was identified. Three new ongoing studies were added, and nine additional studies were excluded

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 2, 2006

Date	Event	Description
1 September 2015	New search has been performed	Searches were rerun. Ten additional studies were included, and 15 additional studies were excluded. Three new ongoing studies were added
1 September 2015	New citation required but conclusions have not changed	Searches were rerun. Ten additional studies were included, and 15 additional studies were excluded. Three new ongoing studies were added. Review text was updated in keeping with Cochrane policy including 'Risk of bias' assessments and 'Summary of findings' tables. Conclusions were not changed
20 April 2010	New search has been performed	No new trials were found that met the review inclusion criteria. Ten additional trials were excluded. Minor amendments were made, and minor errors were corrected
11 May 2009	New citation required but conclusions have not changed	Qiukui Hao was added as a review author, and Qin Wang was removed as a review author
8 July 2008	Amended	Review was converted to new review format

CONTRIBUTIONS OF AUTHORS

Qiukui Hao: screened studies for eligibility, assessed the quality of trials, extracted and analysed data, and drafted the review.
Birong Dong: developed the protocol and assessed the quality of trials.
Jirong Yue: screened studies for eligibility, searched the reference lists of included studies, and assessed the quality of trials.
Taixiang Wu: ensured that the correct method was used during data extraction and analysis.
Guan Jian Liu: assisted with data extraction and analysis.

DECLARATIONS OF INTEREST

Qiukui Hao: none known.
Birong Dong: none known.
Jirong Yue: none known.
Taixiang Wu: none known.
Guan Jian Liu: none known.

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External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the previous version, we revised the methods of 'Assessment of risk of bias in included studies' according to the new version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We added the secondary outcomes of 'Escalation of treatment' and 'Hospital stay' because of their clinical importance in the treatment of acute pulmonary embolism with thrombolytics. We reordered

the outcomes of survival time, composite clinical outcome, QoL, and healthcare cost comparison from primary to secondary outcomes due to clinical importance. We added a subgroup analysis for massive/submassive PE because of its clinical importance in the treatment of acute pulmonary embolism. We used GRADE to assess the overall quality of the evidence according to instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we summarised this information in a 'Summary of findings' table.

NOTES

The protocol for this review was developed and published under the auspices of the Cochrane Airways Collaborative Review Group. As the scope of treatment of pulmonary embolism was considered to be better suited to the Peripheral Vascular Diseases (PVD) Group, whose scope already included prevention of pulmonary embolism, this review was passed over to the PVD Group. The PVD Group was renamed Cochrane Vascular in July 2015.

The published protocol did not specify methods used for statistical analysis. We have added details of the analysis to the full review. In addition, we have clarified the review objectives.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Fibrinolytic Agents [adverse effects] [*therapeutic use]; Hemorrhage [chemically induced] [epidemiology]; Heparin [adverse effects] [*therapeutic use]; Pulmonary Embolism [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Recurrence; Thrombolytic Therapy [adverse effects] [*methods]

MeSH check words

Humans