Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

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Aim	Thrombolytic therapy induces faster clot dissolution than anticoagulation in patients with acute pulmonary embolism (PE) but is associated with an increased risk of haemorrhage. We reviewed the risks and benefits of thrombolytic therapy in the management of patients with acute PE.
Methods and results	We systematically reviewed randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation with anticoagulation alone in patients with acute PE. Fifteen trials involving 2057 patients were included in our meta-analysis. Compared with heparin, thrombolytic therapy was associated with a significant reduction of overall mortality (OR; 0.59, 95% CI: 0.36–0.96). This reduction was not statistically significant after exclusion of studies including high-risk PE (OR; 0.64, 95% CI: 0.35–1.17). Thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation (OR: 0.34, 95% CI: 0.22–0.53), PE-related mortality (OR: 0.29; 95% CI: 0.14–0.60) and PE recurrence (OR: 0.50; 95% CI: 0.27–0.94). Major haemorrhage (OR; 2.91, 95% CI: 1.95–4.36) and fatal or intracranial bleeding (OR: 3.18, 95% CI: 1.25–8.11) were significantly more frequent among patients receiving thrombolysis.
Conclusions	Thrombolytic therapy reduces total mortality, PE recurrence, and PE-related mortality in patients with acute PE. The decrease in overall mortality is, however, not significant in haemodynamically stable patients with acute PE. Thrombolytic therapy is associated with an increase of major and fatal or intracranial haemorrhage.
Keywords	Pulmonary embolism • Thrombolytic therapy • Systematic review

Introduction

Pulmonary embolism (PE) is a common disease occurring in 60–112 per 100 000 people/year.[1,2] According to prospective cohort studies, the case fatality rate in the acute phase ranges from 7 to 11%.[3–5] Nevertheless, acute PE represents a wide spectrum of clinical presentations with varying clinical outcomes. To guide the management of acute PE, the European Society of Cardiology[6] and the American Heart Association[7] have proposed a three-level risk stratification scheme based on haemodynamic status and the presence of right ventricular dysfunction (RVD) or myocardial injury. High-risk (or massive) PE is defined as an acute PE with sustained systemic arterial hypotension. Intermediate-risk (or submassive) PE is defined by the presence of RVD or injury in the absence of arterial hypotension. Finally, low-risk PE is defined by the absence of hypotension and of markers of RVD or injury.

In 1970, the first randomized trial comparing urokinase with heparin for patients with PE was published[8] and 7 years later,

streptokinase was approved by the US Food and Drug Administration (FDA) for the treatment of high-risk PE. Since then, thrombolytic therapy has been shown to induce faster clot dissolution and haemodynamic improvement compared with heparin alone.[9–13] However, more than three decades later, the role of thrombolytic therapy in the treatment of patients with non-high-risk PE remains controversial. Previous meta-analyses have failed to demonstrate a positive impact of thrombolytic treatment on total mortality and suggested an increase in major haemorrhage.[14–16] These studies were limited by the relatively small number of patients included in randomized trials.

Current guidelines recommend thrombolytic therapy for patients with high-risk PE in the absence of contraindications.[6,7,17] Thrombolysis is not recommended on a routine basis for patients with intermediate-risk PE but may be considered following individual risk-to-benefit analysis. More recently, further evidence regarding the role of thrombolytic therapy for patients with acute PE was published,[13,18] including the large multicentre PEITHO trial.[19]

We performed a systematic review and meta-analysis of randomized controlled trials comparing anticoagulation plus systemic thrombolysis with anticoagulation alone for patients with acute PE. We also sought to identify potential subgroups of patients with a favourable risk−benefit ratio and planned to separately analyse studies according to their criteria of PE severity.

Methods

Search strategy, study selection, data extraction, and analysis were performed according to a pre-defined protocol.

Search strategy

Two authors (C.M. and G.J.) systematically searched Medline, Embase and the Cochrane Controlled Trials registry using the following key words: (*pulmonary embolism* AND [*thrombolysis* OR *thrombolytic therapy* OR *streptokinase* Or *urokinase* OR *tenecteplase* OR *desmoteplase* OR *reteplase* OR *tissue plasminogen activator*]) The detailed search strategy is available in Supplementary material online and was last updated on 16 February 2014. To ensure a comprehensive literature search, we examined reference lists from retrieved articles and reference literature (guidelines and systematic reviews) and questioned experts in PE for possible published or unpublished missing studies.

Study selection and data extraction

We included randomized controlled trials comparing a thrombolytic agent [streptokinase, urokinase, recombinant tissue plasminogen activator (alteplase), desmoteplase, reteplase, or tenecteplase] administered systemically by the i.v. route and heparin (unfractionated or low-molecular-weight heparin) with heparin alone in patients with acute PE. Studies comparing two regimens of thrombolytic therapy, and those using mechanical thrombectomy along with thrombolytic treatment or local catheter-delivered thrombolysis, were excluded. Two investigators (C.M. and G.J.) independently evaluated studies for possible inclusion. Non-relevant studies were excluded based on title and abstract. For potentially relevant studies, full-text was obtained and two investigators (C.M. and G.J.) independently assessed study eligibility and extracted the data on study design, patient characteristics, and outcomes. Disagreement about study inclusion or data extraction was resolved by consensus or by discussion with a third author (A.P.).

Outcomes and measurements

The primary efficacy outcome was early all-cause mortality (in hospital or within 30 days of inclusion). Three secondary efficacy outcomes were considered: recurrent PE confirmed by a validated diagnostic examination; death related to PE and the combination of all-cause death or clinical deterioration requiring rescue treatment (vasopressors, mechanical ventilation, cardio-pulmonary resuscitation, systemic rescue thrombolysis, or embolectomy).

Two safety outcomes, major bleeding and fatal or intracranial haemorrhage, were analysed. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH)[20] when sufficient information was available. In the other cases, definitions from the original studies were used. Two authors (C.M. and G.J.) independently extracted the patient characteristics and outcomes from retrieved studies.

Study quality assessment

Quality of included studies was assessed using quality criteria developed by Jadad *et al.*[21] evaluating the quality of randomization, blinding and handling of exclusion and attrition. Two investigators (C.M. and G.J.) assessed study quality independently. Disagreements were resolved by consensus.

Data analysis

All analyses were performed on data reported according to the intention-to-treat principle. Pooled odds ratios (ORs) were obtained using the Mantel−Haenszel method given the small sample size in some studies and the low prevalence of events.[22] A continuity correction of 0.5 was applied for studies without event in one arm. Fixed effect models were used because of the low heterogeneity. The significance level was set at 0.05. The heterogeneity was measured by the I^2 statistic.[23] Potential heterogeneity factors were explored by pre-specified subgroup analyses including: studies excluding high-risk PE, studies including (not exclusively) high-risk PE, studies limited to intermediate-risk PE (defined by the presence of RVD on imaging studies, and/or by elevated cardiac biomarkers), studies including low- and intermediate-risk PE, exclusion of older patients, and the type of thrombolytic agent used. For the safety outcomes, subgroup analyses were performed according to the type of a diagnostic procedure (invasive vs. non-invasive). *Post hoc* supplementary subgroup analyses were performed to explore the impact of the length of follow-up (14 days or less vs. 15−30 days) and the time from the onset of symptoms to inclusion (superior or inferior to 1 week). Finally, we performed a meta-regression to explore a potential variation of the odds ratios over time using the logarithm of the odds ratios over years of publication.

Sensitivity analyses were conducted to check the robustness of the pooled ORs by removing each study one-by-one, by excluding lower quality studies (Jadad score <4) and by applying several continuity corrections (correction from 0.01 to 0.5 by step of 0.1) and treatment arm correction.[24] Additionally, an exact method was applied. The advantage is to account for studies without event in both arms. Publication bias was assessed using inspection of the funnel plot, Egger's test, and the trim and fill method.[25] The R package 'meta: Meta analysis with R, version 1.6-1' and StatXact-8.0.0 (Cytel, Inc., Cambridge, MA, USA) was used for these analyses.

Results

Study selection and characteristics

The search retrieved a total of 4338 references, among which 940 duplicates were identified. Of the 3398 remaining articles, 3169
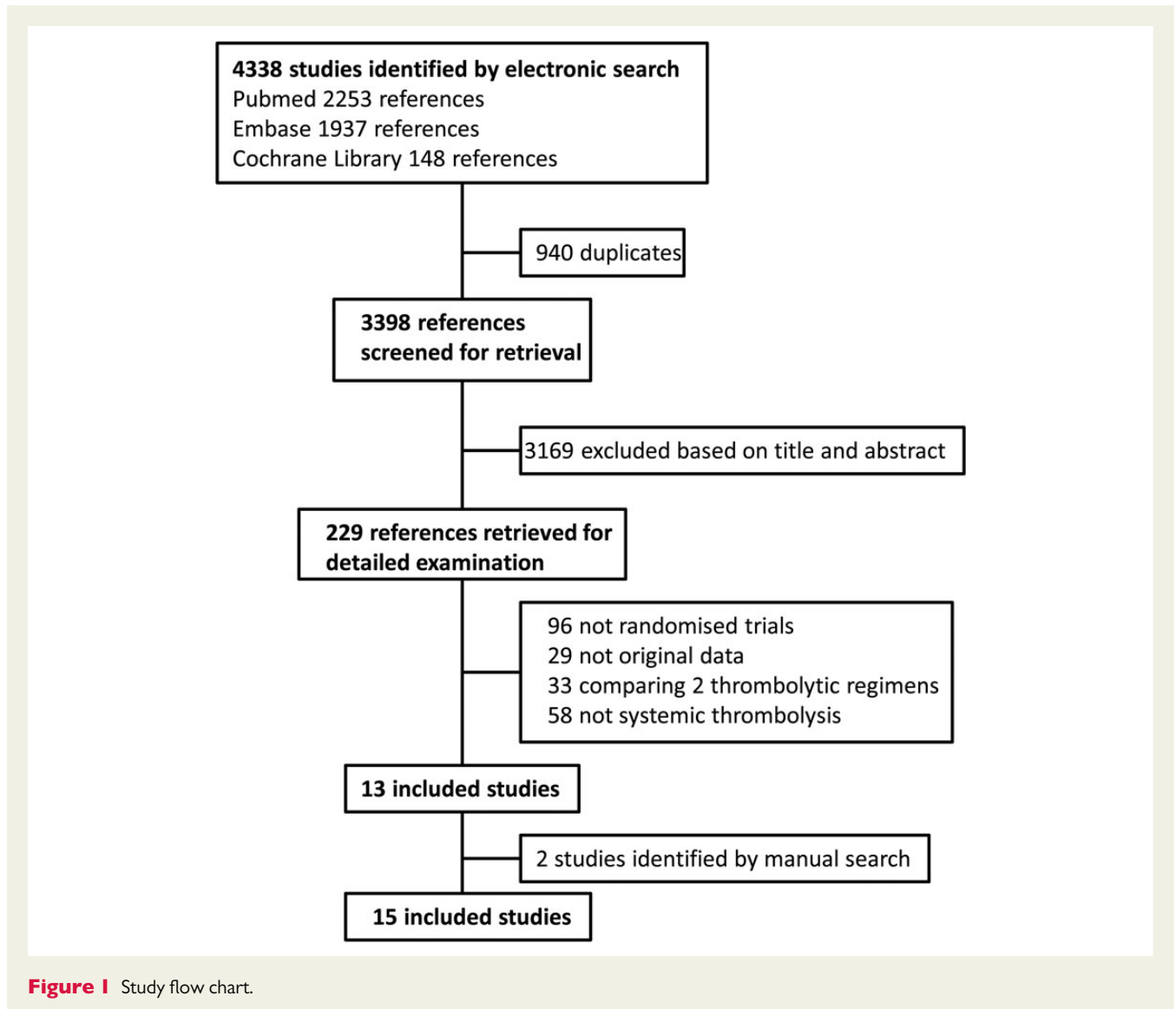
Figure 1 Study flow chart.

were excluded based on title and abstract (*Figure 1*). Full-text was obtained for the remaining 229 articles. Of these, 29 did not contain original data, 58 did not study systemic thrombolysis, 96 were non-randomized trials, 33 compared two thrombolytic regimens, and 13 satisfied the inclusion criteria. Two additional studies were identified by manual search.[19,26] Inter-readers agreement was high (Kappa coefficient 0.99). The main characteristics of the included studies are displayed in *Table 1*.

Study quality/risk of bias

The quality of randomization was considered adequate in nine studies (Supplementary material online, *Table S1*). Both patients and investigators were blinded to the treatment arm in eight studies. Among the 15 included studies, 11 were considered of good quality (Jadad score 4–5), one of fair quality, and three of poor quality. Inclusion criteria differed among studies: four studies [8,19,27–29] included patients with high-risk PE, and three specifically included patients with intermediate-risk PE [10,13,19](*Table 1*). Six studies used an upper age

limit as an exclusion criteria and the mean age of included patients varied from 53[30] to 68 years.[10] Bleeding complications could be extracted according to the ISTH definition in all studies but three[8,29,31] in which data were extracted according to the authors' definition of major haemorrhage. Finally, the outcome 'death or treatment escalation' was extracted from the case description available in the published studies, but this outcome was specifically predefined in only five studies.[8,10,19,26,31]

Overall mortality

All 15 studies including 2057 patients reported early (≤30 days) all-cause mortality. The reported mortality was 2.3% (24/1033) in the thrombolysis group and 3.9% (40/1024) in the control group. Thrombolytic therapy was associated with a significant reduction of early mortality (pooled OR: 0.59; 95% CI: 0.36–0.96, $P = 0.03$; *Figure 2*). No heterogeneity was observed among studies ($I^2 = 0$%). After exclusion of studies including high-risk PE, treatment effect was similar, but statistical significance was lost (OR: 0.64; 95% CI:

Table I Characteristics of included studies

| First author and year of publication	Number of patients	Eligibility	Severity criteria	High-risk PE included	Thrombolysis	Control	Age limit (years)	Follow-up[a]	Invasive angiography	Primary endpoint
Becattini (2010)	58	Acute PE<10 days	RVD	No	Tenecteplase 30−50 mg plus heparin	Heparin	85	30 days	No	24 h RVD[b]
Dalla Volta (1992)	36	Acute PE<10 days	Miller score >11	No	Alteplase 100 mg/2 h plus heparin	Heparin	80	30 days	100%	Pulmonary perfusion[c]
Dotter (1979)	31	Acute PE	No	Yes	Streptokinase 2−11 MIU 18−72 h	Heparin	No	7 days	100%	Pulmonary perfusion[c]
Fasullo (2011)	72	Acute PE<6 h	RVD	No	Alteplase 100 mg/2 h plus heparin	Heparin	75	10 days	No	RVD[b]
Goldhaber (1993)	101	Acute PE<14 days	No	No	Alteplase 100 mg/2 h plus heparin	Heparin	No	14 days	21%	RVD[b]
Jerjes-Sanchez (1995)	8	Acute PE<14 days	Massive	Yes	Streptokinase 1.5 MIU/2 h	Heparin	No	In-hospital	No	RVD, pulmonary perfusion[d]
Kline (TOPCOAT) (2013)	83	Acute PE	RVD or hypoxaemia	No	Tenecteplase 30−50 mg/2 h plus enoxaparin	LMWH	No	5 days	NA	Composite clinical outcome
Konstantinides (MAPPET) (2002)	256	Acute PE<4 days	RVD or pHTA	No	Alteplase 100 mg/2 h plus heparin	Heparin	80	30 days/ in-hospital	16%	Death or treatment escalation
Levine (1990)	58	Acute PE<14 days	No	No	Alteplase 0.6 mg/kg/2 min	Heparin	No	10 days	67%	Pulmonary perfusion[d]
Ly (1978)	20	Acute PE<5 days	>1 lobe[d]	Yes	Streptokinase 72 h	Heparin	70	10 days	100%	Pulmonary perfusion[c]
Marini (1988)	30	Acute PE<7 days	>9 segments[d]	No	Urokinase 2.4−3.3 MIU /12−72 h	Heparin	72	7 days	100%	Pulmonary perfusion[d]
Meyer (PEITHO) (2014)	1005	Acute PE<15 days	RVD and elevated troponin	No	Tenecteplase 30−50 mg plus heparin	Heparin	No	7 days	1.4%	Death or haemodynamic collapse
Sharifi (2013)	121	Acute PE<10 days	≥2 lobes[d]	No	Alteplase 50 mg/ 2 h + heparin	Heparin or LMWH	No	In-hospital	No	Pulmonary hypertension[b]
Stein (PIOPED) (1990)	13	Acute PE<7 days	≥ 1 lobe or ≥ 2 segments[d]	No	Alteplase 40−80 mg/ 40−90 min + heparin	Heparin	No	7 days	100%	Pulmonary perfusion[c]
UPET (1970)	160	Acute PE<5 days	No	Yes	Urokinase 12 h	Heparin	No	14 days	100%	Pulmonary perfusion[c,d]

PE, pulmonary embolism; RVD, right ventricular dysfunction; LMWH, low-molecular-weight heparin; MIU: million units, NA, not available, pHTA, pulmonary hypertension.
[a]Follow-up for overall mortality.
[b]Echocardiography.
[c]Pulmonary angiography.
[d]Based on ventilation-perfusion scintigraphy.
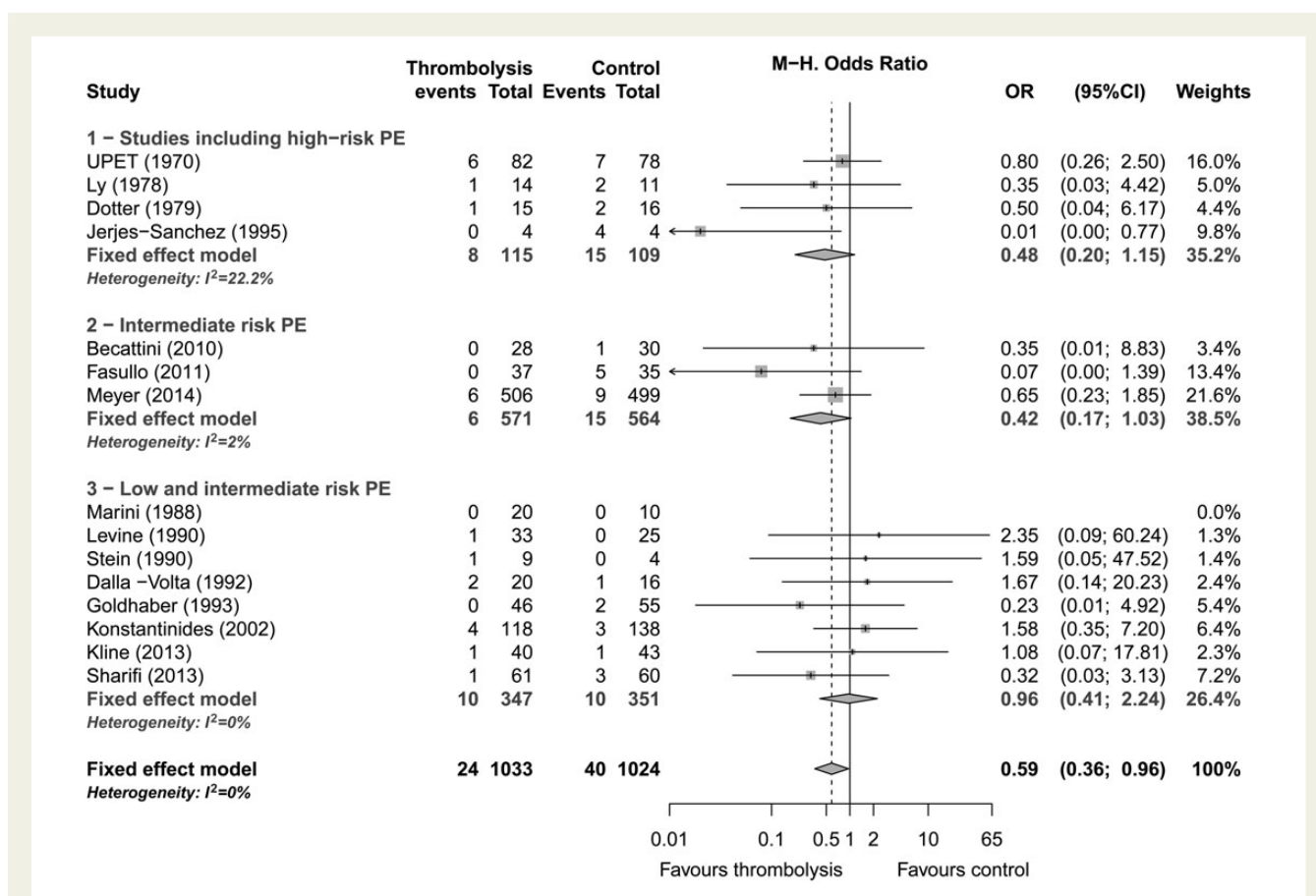
Figure 2 Early mortality by pulmonary embolism severity, Forest plot.

Table 2 Efficacy outcomes, subgroup analyses

|	All studies			Studies including[a] High-risk PE	Intermediate-risk PE	Low and intermediate-risk PE	Group difference
	OR (95% CI)	P-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P-value
Mortality	0.59 (0.36 to 0.96)	0.034	0	0.48 (0.20 to 1.15)	0.42 (0.17 to 1.03)	0.96 (0.41 to 2.24)	0.36
PE mortality	0.29 (0.14 to 0.60)	<0.001	0	0.15 (0.03 to 0.78)	0.17 (0.05 to 0.67)	0.63 (0.20 to 1.97)	0.23
Death or treatment escalation	0.34 (0.22 to 0.52)	<0.001	0	0.18 (0.04 to 0.79)	0.37 (0.20 to 0.69)	0.35 (0.18 to 0.66)	0.67
PE recurrence	0.50 (0.27 to 0.94)	0.031	0	0.97 (0.31 to 2.98)	0.25 (0.06 to 1.03)	0.46 (0.17 to 1.21)	0.33

[a]Not exclusively.

0.35−1.17). The pooled ORs were similar in studies including high-risk PE (OR: 0.48; 95% CI: 0.2−1.15) and studies including only intermediate-risk PE (0.42; 95% CI: 0.17−1.03), whereas the pooled OR was close to one in studies including both low- and intermediate-risk PE (0.96; 95% CI: 0.41−2.24) (Table 2 and Figure 2). Subgroup analysis based on the thrombolytic regimen did not show any significant differences between alteplase (OR: 0.64; 95% CI: 0.29−1.41), tenecteplase (OR: 0.65; 95% CI: 0.26−1.64) or older thrombolytics (OR: 0.48; 95% CI: 0.20−1.15) (P = 0.86).

Pulmonary embolism-related mortality

Pulmonary embolism -related mortality was reported in 13 studies,[8,10−13,19,26−32] including 1776 patients (Supplementary material online, Figure S1). The reported PE-related mortality was 0.6% (6/890) among patients allocated to thrombolytic therapy and 3.0% (27/886) in the control group. Thrombolytic treatment was associated with a significant reduction of PE-related mortality (OR: 0.29; 95% CI: 0.14−0.60, P < 0.001) and no heterogeneity was detected (I^2 0%). No significant difference was found
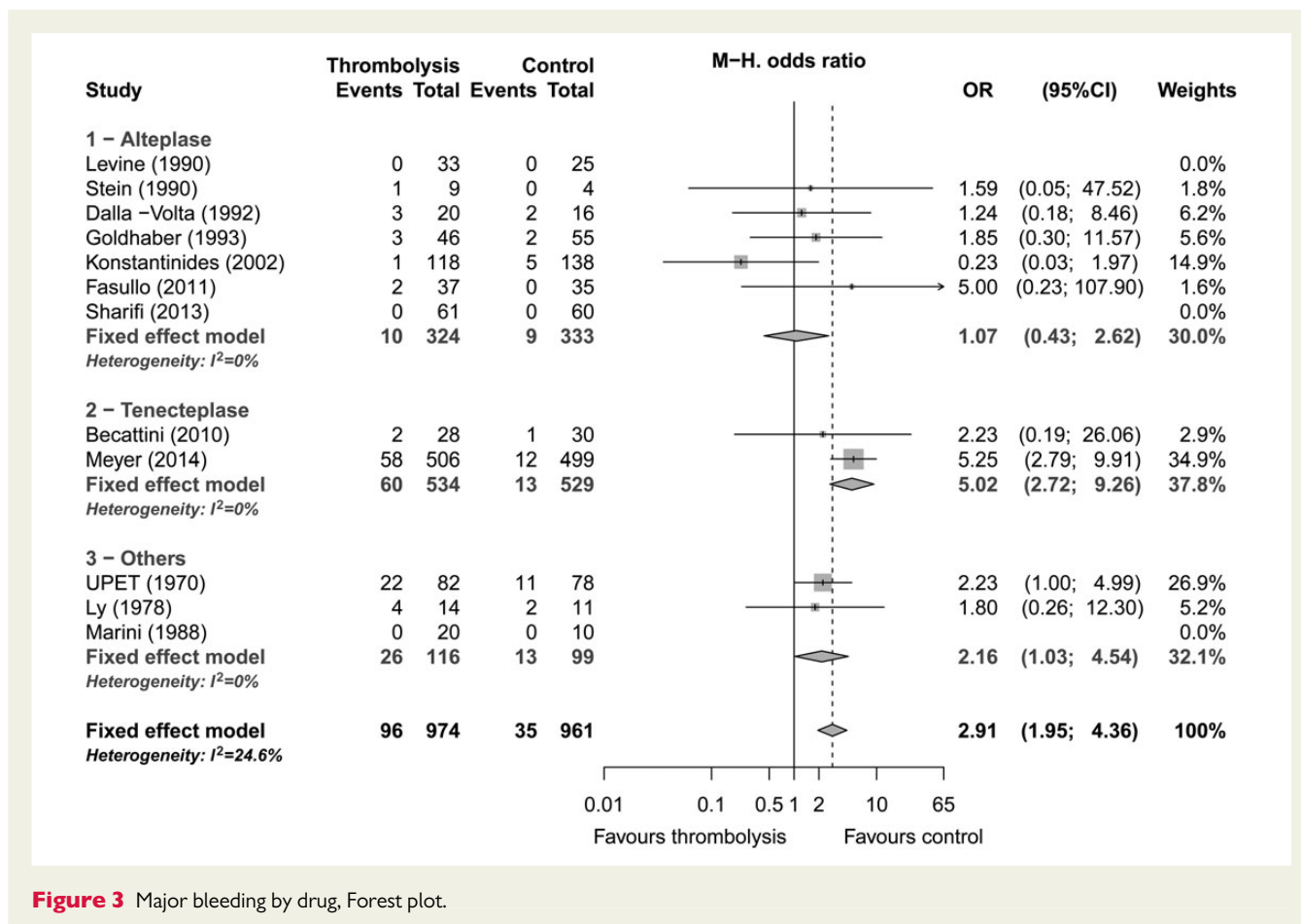
Figure 3 Major bleeding by drug, Forest plot.

according to the thrombolytic regimen ($P = 0.61$) or the severity of PE ($P = 0.23$).

Death or need for treatment escalation

This outcome was available in nine studies including 1639 patients (Supplementary material online, *Figure S2*). It was pre-defined in five studies (1474 patients)[10,13,19,26,31] and obtained based on the detailed description of complications in the remaining four studies (185 patients).[12,27–29] Death or treatment escalation were reported in 3.6% (29/808) of the patients allocated to thrombolytic therapy and 10.2% (85/831) in the control group. Thrombolytic therapy was associated with a significant reduction of this outcome (OR: 0.34; 95% CI: 0.22–0.52, $P < 0.001$). The result was similar when the analysis was restricted to the five studies in which the outcome was pre-defined[10,13,19,26,31] (OR: 0.37; 95% CI: 0.24–0.59, $P < 0.0001$). No heterogeneity was detected ($I^2 = 0\%$). No significant difference was found according to the thrombolytic regimen ($P = 0.54$) or the severity of PE ($P = 0.67$).

Pulmonary embolism recurrence

Pulmonary embolism recurrence was reported in 11 studies,[8,10–13,18–19,28,30–32] including 1928 patients (Supplementary material online, *Figure S3*). The reported incidence of PE recurrence was 1.3% (13/966) among patients allocated to thrombolytic therapy

and 2.9% (28/962) in the control group. Thrombolytic therapy was associated with a statistically significant reduction of PE recurrence (OR; 0.50; 95% CI: 0.27–0.94, $P = 0.03$). No heterogeneity was detected ($I^2 = 0\%$). No significant difference was found according to the thrombolytic regimen ($P = 0.39$) or the severity of PE ($P = 0.33$).

Major bleeding

Major bleeding was reported in 12 studies (1935 patients) and was present in 9.9% (96/974) of patients allocated to thrombolytic therapy and 3.6% (35/961) of the control group. Thrombolytic treatment was associated with a significantly increased risk of major bleeding (OR: 2.91; 95% CI: 1.95–4.36, $P < 0.0001$; *Figure 3*). Low amount of heterogeneity was detected ($I^2 = 25\%$). Subgroup analysis did not show any differences between studies using invasive vs. non-invasive diagnostic procedures. Subgroup analysis based on thrombolytic agent suggested a lower risk of major bleeding in studies using alteplase compared with tenecteplase (*Table 3*). Nevertheless, this subgroup difference was not significant after exclusion of the study by Konstantinides *et al.*[31] which used a more restrictive definition of major haemorrhage. Finally, the association between thrombolytic therapy and the risk of major bleeding was lower in studies using an upper age limit (OR: 1.13; 95% CI: 0.47–2.71) than in studies including older patients (OR: 3.71; 95% CI: 2.32–5.92) ($P = 0.02$).

Intracranial or fatal haemorrhage

Intracranial or fatal haemorrhage was reported in 12 studies including 1864 patients (Supplementary material online, *Figure S4*). The reported incidence of fatal or intracranial haemorrhage was 1.7% ($n = 16/933$) in the thrombolysis group and 0.3% ($n = 3/931$) in the control group. Thrombolytic treatment was associated with a significantly increased risk of fatal or intracranial haemorrhage (OR: 3.18; 95% CI: 1.25–8.11, $P = 0.008$). Subgroup analysis based on thrombolytic agent suggested a lower risk of intracranial or fatal haemorrhage in studies using alteplase compared with tenecteplase (*Table 3*). The risk of fatal or intracranial haemorrhage was lower in studies with an upper age limit (OR: 1.82; 95% CI: 0.37–8.93) than those without (OR: 4.11; 95% CI: 1.25–13.5), but this difference was not statistically significant ($P = 0.42$).

Other potential sources of heterogeneity

There were no significant differences between studies using a time from the onset of symptoms superior or inferior to 1 week except for the outcome major bleeding. The risk of major bleeding was higher in studies using a longer time of symptoms before inclusion. Similarly, no significant differences were observed according to the length of follow-up except for the outcome major bleeding. The risk of major bleeding was higher in studies using a shorter follow-up. The results of these analyses are provided on Supplementary material online, *Tables S4* and *S5*. Finally, the meta-regression of the logarithms of the odds ratios over years of publication did not detect any
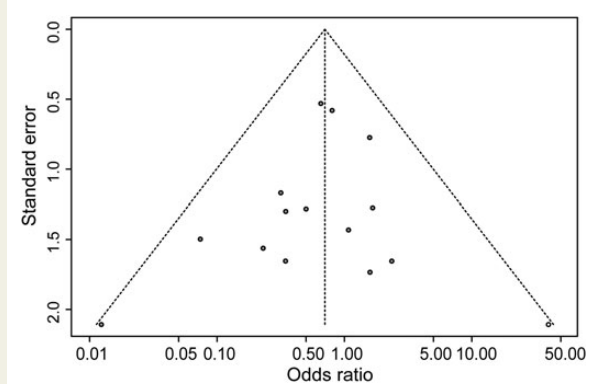
Figure 4 Early mortality, Funnel plot of included studies.

significant interaction between these variables for any of the outcomes (Supplementary material online, *Table S6*).

Sensitivity analyses

Excluding studies one by one did not significantly alter the effect of thrombolysis with regard to the overall mortality, but statistical significance was lost after exclusion of the study by Jerjes-Sanchez et al.[27] (OR: 0.66, 95% CI: 0.40–1.11, $P = 0.09$) or the study by Fasullo et al.[13] (OR: 0.65, 95% CI: 0.39–1.08, $P = 0.12$). Similarly, statistical significance was lost after deletion of a single study[12,13,18,19] for the outcome PE recurrence without major alteration of the treatment effect size (OR; ~0.55). The outcomes of PE-related mortality and death or treatment escalation were not sensitive to a specific study. The study by Meyer et al.[19] contributed importantly to the outcomes of major bleeding and fatal or intracranial haemorrhage: the ORs were reduced (1.66; 95% CI: 0.96–2.88 and 1.53; 95% CI: 0.48–4.87) and statistical significance was lost after omission of this study.

The pooled ORs were robust regarding the continuity correction for all outcomes except for intracranial or fatal haemorrhage: the OR reached 4.67 (95% CI: 1.46–14.92, $P = 0.009$) for a continuity correction of 0.1. The use of an exact method to combine odds ratios across studies provided similar estimates except for intracranial or fatal haemorrhage: the OR reached 5.18 (95% CI: 1.47–27.88, $P < 0.004$).

When only studies with good quality (Jadad score 4 or 5) were combined, the OR for the outcome overall mortality was unchanged (0.61; 95% CI: 0.36–1.06) but the statistical significance was lost ($P = 0.08$). The results were similar for the secondary outcomes.

Publication bias

The inspection of funnel plots revealed potential publication bias, especially for PE recurrence and death or treatment escalation ($P = 0.02$ for both, Egger's test). Missing studies for the funnel plots to be symmetrical (trim and fill method) would be studies with low precision and ORs in favour of controls. One missing study was detected for the outcome overall mortality (*Figure 4*) (study symmetrical to Jerjes-Sanchez) and three studies for the outcome PE recurrence. If these missing studies were added, the ORs for the outcomes overall mortality and PE-related mortality remained in favour of thrombolytic treatment but were not significantly different from 1 (0.69, 95% CI: 0.40–1.19 and 0.84, 95% CI: 0.44–1.60). For the other outcomes, the ORs were slightly modified and remained significantly different from 1.

Table 3 Safety outcomes, subgroup analyses

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

Discussion

Evidence from currently available randomized trials suggests that thrombolytic treatment reduces overall mortality of patients with acute PE. Although the estimated treatment effect corresponded to a 41% relative risk reduction of overall mortality, the benefit of thrombolytic therapy for patients with acute PE could not be definitely established. This observation deserves several comments:

First, the robustness of our primary result was limited, since statistical significance was lost after exclusion of the study by Jerjes-Sanchez *et al.*[27] This small size, open-label trial included only patients with high-risk PE and was limited by gross imbalance between-groups, the four patients allocated to heparin treatment having been admitted for an acute episode of unstable PE despite previous therapeutic anticoagulation. Nevertheless, even after exclusion of this trial, a trend towards decreased all-cause mortality was observed (OR: 0.65; 95% CI: 0.39−1.08). Second, early mortality is relatively uncommon among patients with acute PE, particularly those with non-high-risk PE. Therefore, considering a mortality of 3.9% in the control group, a 41% relative risk reduction would lead to an absolute mortality risk reduction of only 1.6% in our overall population. Our subgroup analyses suggest a possible correlation between PE severity and treatment effect. The pooled ORs were similar in studies including (not exclusively) high-risk PE and studies restricted to intermediate-risk PE with an estimated mortality risk reduction ∼55%, whereas the OR was suggestive of an absence of benefit in studies including only low- and intermediate-risk PE. However, these subgroup analyses were limited by a lack of statistical power and some between-groups overlap in terms of PE severity.

On the other hand, the mortality benefit of thrombolytic therapy may be underestimated because of the possibility to administer rescue thrombolysis to clinically deteriorating patients allocated to anticoagulant therapy; it is likely that some of these patients might have died without rescue treatment. Rescue thrombolysis was actually administered in 4.6 and 23% of control patients in the two largest randomized trials in this meta-analysis,[19,31] and its use was restricted to patients with secondary haemodynamic collapse in PEITHO.[19] However and despite reasonable equipoise on the efficacy of thrombolysis in intermediate-risk PE, a randomized trial not allowing for emergency escalation of treatment (such as rescue thrombolysis) would certainly be considered ethically unacceptable. When treatment escalation was combined with all-cause mortality, the pooled OR was slightly lower and statistically significant in all PE severity subgroups and sensitivity analyses.

The benefits of thrombolytic therapy must be weighed against the risk of haemorrhagic complications. The rate of major bleeding complications reported in our meta-analysis in patients allocated to thrombolytic therapy (9.9%) is similar to that reported by Wan *et al.*[15] (9.1%) and Dong *et al.*[14] (10.4%). In contrast to our meta-analysis, these previous reports failed to demonstrate a significant association between thrombolytic therapy and major bleeding. This difference appears to result mainly from the inclusion of the PEITHO trial in our meta-analysis, which included more patients than all other studies together and a higher proportion of elderly patients with a higher bleeding risk. Interestingly, our subgroup analysis suggested a higher risk for both major bleeding and fatal or intracranial haemorrhage in patients treated by tenecteplase compared

with those treated with alteplase, probably because two of the three studies using tenecteplase[10,19] had the oldest populations of all 15 studies included in this meta-analysis. As also previously reported by others,[33] the inclusion of older patients was associated with an increased risk of bleeding in our analysis (Supplementary material online, *Table S3*).

Given the non-negligible risks of systemic thrombolytic treatment and the relatively low risk of early mortality among patients with acute PE, research has recently focused on minimization of thrombolysis-related risks by dose reduction,[18] a strategy of catheter-delivered, ultrasound-assisted administration of thrombolytic treatment,[34] and the identification of intermediate-risk patients with a potentially favourable risk-to-benefit ratio for thrombolytic therapy. Identification of intermediate-risk patients based on RVD and/or laboratory biomarkers was performed in three studies[10,13,19] with a trend towards reduced mortality of borderline significance. Right ventricular dysfunction and laboratory markers of myocardial injury have been widely validated as adverse prognostic markers in patients with PE.[35−39] However, the observed mortality rate in the control group (2.6%) in studies including intermediate-risk PE[10,13,19] was lower than reported in large cohort studies of unselected PE patients[3,40] which may have limited the conclusiveness of this subgroup analysis. This low mortality rate might be explained by the selection criteria of randomized trials and probably also by the close monitoring of the patients included in the trials on intermediate-risk PE. Since most of the studies included PE patients with a wide spectrum of severity, an individual data meta-analysis is warranted to specifically assess treatment benefit in patients with intermediate risk PE, or to identify a subgroup of patients with a favourable risk−benefit ratio.

The present study has several potential limitations. As previously discussed, and despite the inclusion of large recent randomized trials, the power of our analysis remains low because of the low incidence of the primary outcome leading to the loss of statistical significance in some subgroup and sensitivity analyses and to a loss of precision of treatment effect estimate in subgroup analyses Nevertheless, the present meta-analysis included more than twice as many patients as previous reports allowing for a more precise estimate of treatment effect and the selection of a robust primary outcome. Previous meta-analyses frequently reported combined outcomes of variable clinical significance,[15] complicating the risk-to-benefit estimation of thrombolytic therapy. Systematic reviews and meta-analyses depend on the quality of included studies. Although the quality of the majority of the studies included in this review was considered good, important differences in inclusion criteria, thrombolytic regimens and dosing, and PE severity were present among studies, limiting the generalization of our conclusions.

Conclusion

Systemic thrombolytic therapy is associated with a significant reduction of overall mortality in patients with PE, but this reduction is not statistically significant after exclusion of studies including high-risk PE. Thrombolytic therapy significantly reduces PE-related mortality, the combined outcome of death or treatment escalation and symptomatic PE recurrence, but is associated with an increase in fatal, intracranial, or major haemorrhage. Owing to this narrow risk−benefit ratio, further analysis based on individual data is warranted to identify which

subgroup of patients with non-high-risk PE might benefit from thrombolytic therapy.

Authors' contributions

A.P. conceived the study and participated to the analysis interpretation and article redaction by critically revising the study protocol and the article draft. C.C. participated to the study conception and article redaction by critically revising the study protocol and article draft and performed the statistical analysis. C.M. conceived the study, wrote the protocol draft, performed the literature search, extracted the data, made the statistical analysis and wrote the article draft. G.J. performed the literature search and extracted the data and participated to the study conception, analysis interpretation, and article redaction by critically revising the study protocol and article draft. G.M. participated to the study conception, analysis interpretation, and article redaction by critically revising the study protocol and the article draft. M.L. participated to the study conception, analysis interpretation, and article redaction by critically revising the study protocol and the article draft. O.S. participated to the study conception, analysis interpretation, and article redaction by critically revising the study protocol and the article draft. S.K. participated to the study conception, analysis interpretation, and article redaction by critically revising the study protocol and the article draft. All authors approved the final version of the article.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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