Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism

A Meta-Analysis of the Randomized Controlled Trials

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Background—Randomized trials and meta-analyses have reached conflicting conclusions about the role of thrombolytic therapy for the treatment of acute pulmonary embolism.

Methods and Results—We performed a meta-analysis of all randomized trials comparing thrombolytic therapy with heparin in patients with acute pulmonary embolism. Eleven trials, involving 748 patients, were included. Compared with heparin, thrombolytic therapy was associated with a nonsignificant reduction in recurrent pulmonary embolism or death (6.7% versus 9.6%; OR 0.67, 95% CI 0.40 to 1.12, *P* for heterogeneity=0.48), a nonsignificant increase in major bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46), and a significant increase in nonmajor bleeding (22.7% versus 10.0%; OR 2.63, 95% CI 1.53 to 4.54; number needed to harm=8). Thrombolytic therapy compared with heparin was associated with a significant reduction in recurrent pulmonary embolism or death in trials that also enrolled patients with major (hemodynamically unstable) pulmonary embolism (9.4% versus 19.0%; OR 0.45, 95% CI 0.22 to 0.92; number needed to treat=10) but not in trials that excluded these patients (5.3% versus 4.8%; OR 1.07, 95% CI 0.50 to 2.30), with significant heterogeneity between these 2 groups of trials (*P*=0.10).

Conclusions—Currently available data provide no evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. A benefit is suggested in those at highest risk of recurrence or death. The number of patients enrolled in randomized trials to date is modest, and further evaluation of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute pulmonary embolism appears warranted. (***Circulation*. 2004;110:744-749.)**

Key Words: embolism ■ meta-analysis ■ thrombolysis ■ heparin

Pulmonary embolism remains a major cause of morbidity and mortality in the general community, with an estimated incidence of 0.5 per 1000 people[1] and a case-fatality rate of 15% at 3 months.[2] Mortality is even higher for patients with "major" pulmonary embolism; registry data indicate in-hospital mortality of up to 30% in patients with acute pulmonary embolism who are hemodynamically unstable at presentation.[3,4]

The established treatment for acute pulmonary embolism is anticoagulation with unfractionated or low-molecular-weight heparin,[5] followed by at least 3 to 6 months of warfarin.[6] Thrombolytic therapy has also been evaluated for the initial treatment of major pulmonary embolism, but its role remains controversial.[7] Despite favorable effects of thrombolysis on angiographic, hemodynamic, and scintigraphic measures, the majority of studies comparing thrombolysis with heparin have not demonstrated a reduction in recurrent venous thromboembolism or death[8,9] but have demonstrated an increase in bleeding.[10]

Three recently published meta-analyses[11–13] and 1 large randomized trial[14] have prompted further debate about the role of thrombolysis for the initial treatment of pulmonary embolism.[15–17] Two of the meta-analyses pooled data from the same 9 randomized trials, yet they came to conflicting conclusions about the benefits of thrombolysis compared with heparin for the initial treatment of pulmonary embolism.[12,13] The randomized trial by Konstantinides et al[14] is the largest trial to date to compare thrombolysis with heparin for the initial treatment of pulmonary embolism; however, it remains underpowered to reliably detect a modest yet worthwhile reduction in pulmonary embolism or death with thrombolytic therapy compared with heparin.[14]

To further clarify the role of thrombolysis for the treatment of pulmonary embolism, we performed an updated meta-analysis of all properly randomized trials comparing thrombolysis with heparin for the initial treatment of acute pulmonary embolism.
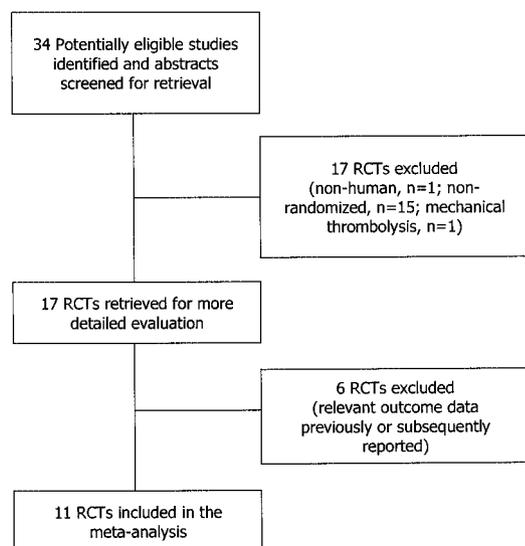
Figure 1. Process of study selection. RCTs indicates randomized, controlled trials.

Methods

A protocol was developed prospectively that detailed the specific objectives, criteria for study selection, the approach to assessing study quality, clinical outcomes, and statistical methodology.

Study Identification

We attempted to identify all relevant published and unpublished randomized trials comparing thrombolysis with heparin for the initial treatment of pulmonary embolism. We searched electronic databases (MEDLINE and EMBASE) from January 1980 to January 2003 and the Cochrane Library (2003, Issue 1) using the terms "pulmonary embolism," "thromboembolism," "thrombolysis," "fibrinolysis," "randomized controlled trial," "controlled clinical trial," and "random" in combination with generic and trade names of individual thrombolytic agents. We also hand searched bibliographies of journal articles and abstracts from major international meetings.

Study Selection

Two investigators (S.W., J.W.E.) independently evaluated studies for inclusion, and any disagreements were resolved by discussion. Criteria for inclusion were (1) proper randomization, (2) inclusion of patients with objectively diagnosed symptomatic pulmonary embolism, (3) comparison of thrombolysis with heparin for the initial treatment of pulmonary embolism, and (4) use of objective methods to assess 1 or more clinical outcomes, including pulmonary embolism, death, and bleeding.

Assessment of Study Quality

We adopted the criteria for study quality outlined by Schultz and colleagues[18] and Eikelboom et al[19] in the evaluation of studies included in the present meta-analysis. These criteria include (1) proper generation of the treatment allocation sequence, (2) proper concealment of the allocation sequence, (3) blinding of the patient and the investigator assessing clinical outcomes to treatment allocation, and (4) completeness of follow-up.

Data Extraction

Two investigators (S.W., J.W.E.) independently extracted data on study design, study quality, and the following efficacy and safety outcomes during hospitalization or within 30 days: (1) pulmonary embolism; (2) death; (3) major bleeding; (4) nonmajor bleeding; and (5) intracranial hemorrhage.

Outcomes

The primary efficacy outcome was the composite of recurrent pulmonary embolism or death. Secondary outcomes were the individual components of the primary outcome, and safety outcomes were major bleeding, nonmajor bleeding, and intracranial hemorrhage.

Statistical Analysis

We used a fixed-effects model based on the Mantel-Haenszel method for combining results from the individual trials.[20] All statistical calculations were performed with Comprehensive Meta Analysis, version 1.0.23 (Biostat; 1998). Subgroup analyses were performed to explore the treatment effect of thrombolytic therapy compared with heparin in trials that included patients with major (hemodynamically unstable) pulmonary embolism versus trials that excluded these patients.

Sensitivity analyses were conducted to explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time. We examined the effect of excluding lower-quality studies from the analysis. An inverted funnel plot of treatment effect versus study precision was created for the primary outcome to look for possible publication bias.[21] Results obtained with a fixed-effects model were also compared with those obtained with a random effects model. A probability value of less than 0.05 was considered statistically significant except for heterogeneity testing, for which statistical significance was accepted at a probability value of 0.10.[22]

Results

Study Selection

The process of study selection is outlined in Figure 1. Our search identified 700 potentially eligible citations. After their titles and abstracts were scanned, 34 were retained for further evaluation. Seventeen studies (including 1 published only in abstract form) were nonhuman, nonrandomized, and/or evaluated the use of surgical or percutaneous mechanical thrombolysis.[23–38] These studies were excluded. Six reported identical or long-term follow-up data on patients or subgroups of patients previously or subsequently included in other or more complete reports.[39–44] These studies were also excluded, which left a total of 11 studies for inclusion in the present meta-analysis.[14,45–54]

Study Design

The designs of studies included in the meta-analysis are summarized in Table 1. All 11 studies included patients with symptomatic pulmonary embolism; however, patients with major pulmonary embolism (hemodynamic instability) were eligible for inclusion in only 5 trials.[45–48,54]

Study Quality

Reporting of study quality data was incomplete. Randomized treatment allocation sequences were generated with random number tables or programs in 3 studies.[14,47,53] Information about proper concealment of the treatment allocation was provided in 5 trials.[45–47,53,54] Both patients and investigators were blinded to treatment allocation in 3 of the 11 trials.[14,50,51] The number of patients lost to follow-up was not reported in any of the trials.

TABLE 1. Design of Trials Included in the Meta-Analysis

| Trial, Year | Eligibility | n | Randomized Treatment | | Subsequent Anticoagulation | | Follow-Up* |
			Thrombolysis	Heparin	Thrombolysis	Heparin	
UPET trial, 1973	Acute PE,† symptoms ≤5 days	160	Urokinase 12 hours	Heparin	Heparin, warfarin	Heparin, warfarin	14 days
Tibbutt et al, 1974	Acute life-threatening PE†	30	Streptokinase‡ 72 hours	Heparin‡	Warfarin (started at 60 hours)	Warfarin (started at 60 hours)	72 hours
Ly et al, 1978	Acute major PE†, symptoms <5 days	25§	Streptokinase 72 hours	Heparin (7 days)	Warfarin, heparin if TCT <2× control	Heparin, warfarin	10 days
Dotter et al, 1979	Acute PE†	31	Streptokinase 18–72 hours	Heparin (5 days)	Heparin, warfarin	Heparin, warfarin	In hospital
Marini et al, 1988	Acute PE, symptoms ≤7 days	30	Urokinase, 12 hours or 3 days	Heparin (7 days)	Warfarin	Heparin, warfarin	7 days
Levine et al, 1990	Acute PE, symptoms ≤14 days	58	tPA 2 minutes	Heparin	Heparin, warfarin	Heparin, warfarin	10 days
PIOPED, 1990	Acute PE, symptoms ≤7 days	13	tPA 40 to 90 minutes	Heparin	Heparin, warfarin	Heparin, warfarin	7 days
Dalla-Volta et al, 1992	Acute PE, symptoms ≤10 days	36	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	30 days
Goldhaber et al, 1993	Acute PE, symptoms ≤14 days	101	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital or 14 days
Jerjes-Sanchez et al, 1995	Acute massive PE,† symptoms ≤14 days	8	Streptokinase 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital
Konstantinides et al, 2002	Acute PE, symptoms ≤4 days	256	tPA 2 hours	Heparin	Heparin, warfarin	Heparin, warfarin	In hospital or 30 days

UPET indicates Urokinase Pulmonary Embolism Trial; PE, pulmonary embolism; TCT, thrombin clotting time, tPA, tissue plasminogen activator; and PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

*Patients in some trials were followed up for a longer period for selected outcomes.

†Patients with major pulmonary embolism were eligible for inclusion in these trials.

‡Given as an intrapulmonary infusion.

§Therapy was not randomly allocated to 5 of the 25 patients included in the published report.

Efficacy Outcomes

Data on the primary outcome of recurrent pulmonary embolism or death are presented in Figure 2, and summary data for individual components of this outcome are presented in Table 2. Seven of the 11 trials suggested a reduction in recurrent pulmonary embolism or death with thrombolysis compared with unfractionated heparin.[45–49,53,54] The pooled estimate from all of the trials revealed a nonstatistically significant reduction in pulmonary embolism or death for thrombolysis compared with heparin (6.7% versus 9.6%; OR 0.67, 95% CI 0.40 to 1.12), with no statistical evidence of heterogeneity among the studies ($P=0.48$). Similar estimates of treatment effect were obtained for pulmonary embolism (2.7% versus 4.3%; OR 0.67, 95% CI 0.33 to 1.37) and death (4.3% versus 5.9%; OR 0.70, 95% CI 0.37 to 1.30).
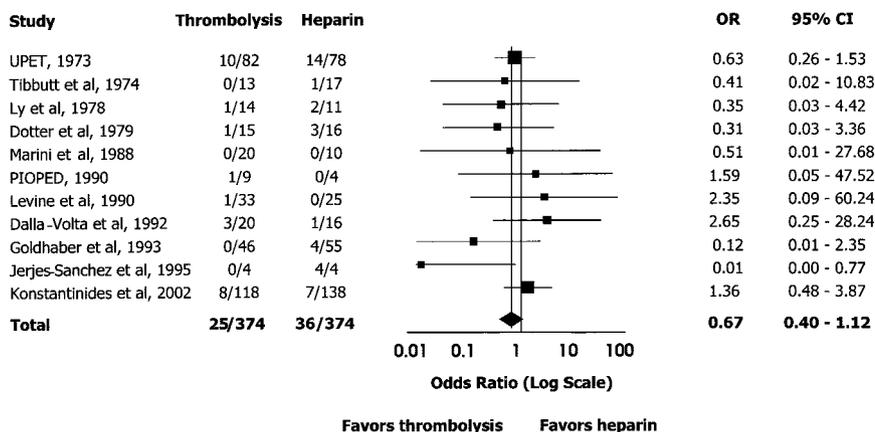
Study	Thrombolysis	Heparin		OR	95% CI
UPET, 1973	10/82	14/78		0.63	0.26 - 1.53
Tibbutt et al, 1974	0/13	1/17		0.41	0.02 - 10.83
Ly et al, 1978	1/14	2/11		0.35	0.03 - 4.42
Dotter et al, 1979	1/15	3/16		0.31	0.03 - 3.36
Marini et al, 1988	0/20	0/10		0.51	0.01 - 27.68
PIOPED, 1990	1/9	0/4		1.59	0.05 - 47.52
Levine et al, 1990	1/33	0/25		2.35	0.09 - 60.24
Dalla-Volta et al, 1992	3/20	1/16		2.65	0.25 - 28.24
Goldhaber et al, 1993	0/46	4/55		0.12	0.01 - 2.35
Jerjes-Sanchez et al, 1995	0/4	4/4		0.01	0.00 - 0.77
Konstantinides et al, 2002	8/118	7/138		1.36	0.48 - 3.87
Total	**25/374**	**36/374**		**0.67**	**0.40 - 1.12**

Odds Ratio (Log Scale)

0.01 0.1 1 10 100

Favors thrombolysis   Favors heparin

Figure 2. Recurrent pulmonary embolism or death in trials comparing thrombolysis with heparin for initial treatment of acute pulmonary embolism. UPET indicates Urokinase Pulmonary Embolism Trial; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis.

TABLE 2. Recurrent Pulmonary Embolism and Death in Patients Randomized to Thrombolysis Compared With Heparin

Outcome	Thrombolysis, n/N (%)	Heparin, n/N (%)	OR (95% CI)
Recurrent pulmonary embolism or death	25/374 (6.7)	36/374 (9.6)	0.67 (0.40–1.12)*
Recurrent pulmonary embolism	10/374 (2.7)	16/374 (4.3)	0.67 (0.33–1.37)†
Death	16/374 (4.3)	22/374 (5.9)	0.70 (0.37–1.30)‡

*Heterogeneity: $P=0.48$.
†Heterogeneity: $P=1.00$.
‡Heterogeneity: $P=0.72$.

Safety Outcomes

Pooled data for safety outcomes are presented in Table 3. Seven of the 11 trials suggested an increase in major bleeding for thrombolysis compared with heparin,[45–48,51–53] Seven of the 8 trials for which nonmajor bleeding data were available suggested an increase in nonmajor bleeding with thrombolysis compared with heparin.[45,46,48–50,52,53] The pooled data revealed a nonstatistically significant increase in major bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46) and a statistically significant increase in nonmajor bleeding (22.7 versus 10.0%; OR 2.63, 95% CI 1.53 to 4.54, number needed to harm=8).

Subgroup Analyses

Compared with heparin, thrombolytic therapy was associated with a significant reduction in pulmonary embolism or death in the 5 trials that included patients with major (hemodynamically unstable) pulmonary embolism (9.4% versus 19.0%; OR 0.45, 95% CI 0.22 to 0.92, number needed to treat=10)[45–48,54] but no benefit in the 6 trials that excluded these patients (OR 1.07, 95% CI 0.50 to 2.30; P for heterogeneity between subgroups=0.10; Table 4).[14,49–53]

Sensitivity Analyses

Deletion of individual studies did not significantly alter the primary outcome. A funnel plot of effect size versus study precision was relatively symmetrical, with a similar number of studies on either side of the summary treatment effect for pulmonary embolism or death (Figure 3). This is consistent with a lack of major publication bias. There were no meaningful differences between results obtained using the fixed versus a random effects model.

Discussion

The currently available randomized data provide no evidence of benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. However, subgroup analyses indicate a benefit of thrombolysis compared with heparin in trials that included patients with major pulmonary embolism but no benefit in trials that excluded these patients. This apparent heterogeneity of treatment effect appears to be due to an effect of thrombolytic therapy on death, the incidence of which was approximately 5-fold higher in heparin-treated patients enrolled in trials that also included patients with major pulmonary embolism. Patients at risk of dying of major pulmonary embolism are also those most likely to achieve benefit from thrombolytic therapy, because more rapid clot lysis can reverse hypotension and prevent irreversible shock that leads to death.

Registry data indicate that right ventricular dysfunction in patients with acute pulmonary embolism is associated with an increased risk of fatal outcomes,[3,55] even in patients who are hemodynamically stable,[4] and it is therefore plausible that these patients would derive benefit from thrombolytic therapy compared with heparin. Unfortunately, the majority of trials included in the present meta-analysis did not separately report the proportion of patients with right ventricular dysfunction without hemodynamic instability, and we were therefore unable to further explore this question.

Previous meta-analyses have provided conflicting conclusions about the benefits of thrombolytic therapy in patients with acute pulmonary embolism. Serra-Prat et al[11] and Thabut et al[12] reported no significant benefit of thrombolysis compared with heparin for the initial treatment of pulmonary embolism, whereas Agnelli et al[13] reported a significant reduction in recurrent pulmonary embolism and death. This may be explained, at least in part, by the inclusion of patients with clinically suspected but not objectively confirmed recurrent venous thromboembolism in one of these meta-analyses.[56] The present updated meta-analysis included only ob-

TABLE 3. Major and Nonmajor Bleeding and Intracranial Hemorrhage in Patients Randomized to Thrombolysis Compared With Heparin

Outcome	Thrombolysis, n/N (%)	Heparin, n/N (%)	OR (95% CI)
Major bleeding	34/374 (9.1)	23/374 (6.1)	1.42 (0.81–2.46)*
Nonmajor bleeding	53/233 (22.7)	22/221 (10.0)	2.63 (1.53–4.54)†
Intracranial hemorrhage	2/374 (0.5)	1/374 (0.3)	1.04 (0.36–3.04)‡

*Heterogeneity: $P=0.92$.
†Heterogeneity: $P=0.53$.
‡Heterogeneity: $P=1.00$.

TABLE 4.   Subgroup Analysis of Trials That Included Major (Hemodynamically Stable) Pulmonary Embolism Compared With Those That Excluded Patients With Major Pulmonary Embolism

Outcome	Trials That Included Patients With Major PE			Trials That Excluded Patients With Major PE			P for Heterogeneity Between Subgroups
	Thrombolysis, n/N (%)	Heparin, n/N (%)	OR (95% CI)	Thrombolysis, n/N (%)	Heparin, n/N (%)	OR (95% CI)	
Recurrent PE or death	12/128 (9.4)	24/126 (19.0)	0.45 (0.22–0.92)	13/246 (5.3)	12/248 (4.8)	1.07 (0.50–2.30)	0.10
Recurrent PE	5/128 (3.9)	9/126 (7.1)	0.61 (0.23–1.62)	5/246 (2.0)	7/248 (2.8)	0.76 (0.28–2.08)	0.71
Death	8/128 (6.2)	16/126 (12.7)	0.47 (0.20–1.10)	8/246 (3.3)	6/248 (2.4)	1.16 (0.44–3.05)	0.13
Major bleeding	28/128 (21.9)	15/126 (11.9)	1.98 (1.00–3.92)	6/246 (2.4)	8/248 (3.2)	0.67 (0.24–1.86)	0.12

PE indicates pulmonary embolism.

jectively diagnosed recurrent pulmonary embolism, and we also included data from 2 additional trials,[14,48] one of which had not yet been completed at the time of the 3 previous meta-analyses.[14]

The present study has several potential limitations. First, despite examination of the totality of the evidence by pooling results from all the available properly randomized trials, the total number of patients randomized and the number of outcome events were modest. Consequently, the present meta-analysis has limited statistical power to reliably detect clinically worthwhile differences between thrombolytic therapy and heparin or among thrombolytic agents. Second, in the only trial that demonstrated a statistically significant reduction in recurrent pulmonary embolism or death with thrombolysis compared with unfractionated heparin,[54] the time elapsed from time of onset of symptoms of the first event of pulmonary embolism was significantly shorter in patients randomized to streptokinase. Although baseline differences of this nature that occur in randomized trials are, by definition, due to the play of chance, it is possible that this difference could have accounted, at least in part, for the apparent benefit of thrombolysis in that study. However, exclusion of that study did not significantly alter our results or the conclusions of the present study. Third, definitions for hemodynamic instability or shock, major bleeding, and minor bleeding varied among the trials, and in some trials, no definition was provided. However, this does not preclude pooling of the results, because the definitions remain consistent within each trial, and it is only within the same trials that patients are directly compared with each other. Finally, meta-analysis remains retrospective research that is subject to

the methodological deficiencies of the included studies. We minimized the likelihood of bias by developing a detailed protocol before commencing this study, by performing a meticulous and exhaustive search for both published and unpublished studies, and by utilizing explicit methodology for study selection, data extraction, and data analysis. Furthermore, we considered the totality of the randomized evidence by including all relevant properly randomized trials.

Conclusions

The currently available data provide no evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. However, a clear benefit is suggested among those at highest risk of recurrence or death, in particular, patients with major pulmonary embolus who present with hemodynamic instability. Further evaluation of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute pulmonary embolism appears warranted.

Acknowledgment

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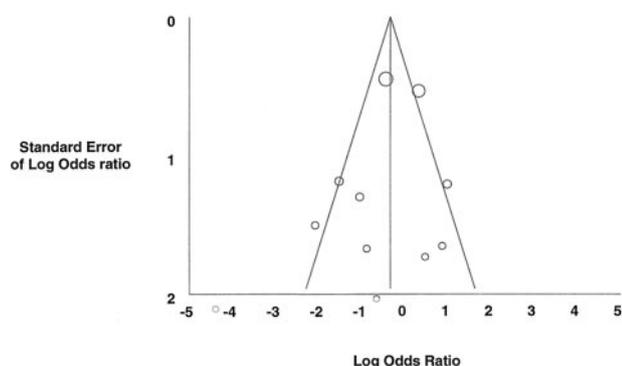

Figure 3. Funnel plot of effect size for primary outcome of recurrent pulmonary embolism or death vs study precision.

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