Pulmonary Embolism

Thrombolytic Therapy of Pulmonary Embolism
A Meta-Analysis

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OBJECTIVES	We sought to assess the efficacy and safety of thrombolytic therapy in patients with an acute pulmonary embolism (PE).
BACKGROUND	Thrombolytic therapy is approved for the treatment of acute PE; however, the safety and efficacy of this therapy remain debated.
METHODS	A meta-analysis of randomized, controlled trials comparing thrombolytic agents with intravenous heparin in patients with acute PE was performed. Trials were identified through a combined search of the MEDLINE, EMBASE, and Current Contents databases. Three outcome measures were assessed: 1) mortality, 2) recurrence of PE, and 3) major hemorrhage.
RESULTS	Nine trials including 461 patients were identified. Compared with intravenous heparin, thrombolytic therapy had no significant effect on mortality (relative risk [RR] 0.63, 95% confidence interval [CI] 0.32 to 1.23) or the recurrence of PE (RR 0.59, 95% CI 0.30 to 1.18), but was associated with an increased risk of major hemorrhage (RR 1.76, 95% CI 1.04 to 2.98). These results were homogeneous and largely unaffected by the formulation of thrombolytic agent, the clinical severity of PE, the extent of vascular obstruction determined radiologically, or the methodologic quality of the included trials.
CONCLUSIONS	Compared with intravenous heparin, thrombolytic therapy does not appear to have therapeutic benefit in unselected patients with acute PE, but it is associated with an increased risk of major hemorrhage. Given the small number of patients included in the randomized trials thus far, the negative results in terms of the efficacy outcomes should be interpreted with caution. Definitive evidence of the utility of thrombolytic therapy in this setting requires a large, randomized, controlled trial. (J Am Coll Cardiol 2002;40:1660−7) © 2002 by the American College of Cardiology Foundation

Pulmonary embolism (PE) is a common disorder with significant morbidity and mortality. In the U.S., PE occurs in approximately 600,000 patients and may be responsible for over 50,000 deaths annually (1,2). Standard management consists of intravenous heparin; this therapy has been shown to reduce both the recurrence of PE and mortality (3). However, the three-month mortality of this condition remains high, ranging from 10% to 17.5% (2), and is even higher in cases of massive PE (4,5).

Several randomized, controlled trials comparing thrombolytic therapy with heparin in patients with an acute PE have demonstrated more rapid clot resolution in those treated with thrombolysis (6−13). However, a significant effect of thrombolytic therapy on important clinical outcomes, including the recurrence of PE and mortality, has been difficult to demonstrate, potentially because of the small sample sizes of the aforementioned trials. Nevertheless, because of its rapid effect on pulmonary vascular resistance, thrombolytic treatment is strongly recommended

in patients with an acute PE associated with shock (2), and the use of streptokinase, urokinase, and recombinant tissue-type plasminogen activator (rt-PA) has been approved for this indication. More recently, based on studies showing that right ventricular (RV) hypokinesia, as demonstrated on the echocardiogram, is associated with an adverse clinical outcome (4,5,9,14), thrombolytic therapy has been advocated in hemodynamically stable patients with RV dysfunction (15−18). This strategy is supported by a retrospective study suggesting a beneficial effect of thrombolytic therapy on survival in this subgroup of patients (19). As 40% to 50% of patients with PE have echocardiographic evidence of RV dysfunction (5,9), these recommendations could have significant implications. Arguments against this approach include a lack of definitive evidence for the usefulness of thrombolytic therapy in this setting (1), the high cost of this treatment, and its potential for life-threatening side effects, particularly major hemorrhage (20).

In light of the limitations of the available data describing the efficacy and safety of thrombolytic therapy in patients with an acute PE, we performed a meta-analysis of randomized, controlled trials comparing thrombolysis with heparin. By combining the results of individual trials, we hoped to achieve sufficient statistical power in order to determine whether a significant treatment effect of thrombolysis truly exists. In addition, we employed sensitivity analyses to focus

Abbreviations and Acronyms

CI	=	confidence interval
PE	=	pulmonary embolism
RR	=	relative risk
RV	=	right ventricular
rt-PA	=	recombinant tissue-type plasminogen activator

on patients with severe PE and to determine whether this subgroup is more likely to achieve a benefit from thrombolytic therapy.

METHODS

This meta-analysis was conducted according to a predetermined protocol following the recommendations of the QUality Of Reporting Of Meta-analyses (QUOROM) statement (21). It was not supported by any pharmaceutical manufacturer, governmental agency, or other grants.

Data search. We reviewed all trials describing thrombolytic therapy in patients with an acute PE. Studies were identified by electronic searches of the MEDLINE (1967 to 2000), EMBASE (1974 to 2000), and Current Contents (1967 to 2000) databases. The reference lists of retrieved articles and published reviews were also searched. In addition, investigators with expertise in the field and manufacturers of thrombolytic agents were contacted for information on any missing or unpublished studies.

Inclusion and exclusion criteria. Trials were included if they met all of the following criteria: 1) planned as a prospective, randomized, controlled design; 2) published as an article or abstract; 3) included patients with an acute PE; 4) compared thrombolytic therapy with urokinase, streptokinase, or rt-PA versus heparin; and 5) described at least one of the following outcome measures: mortality, recurrence of PE, or major hemorrhage. Trials were included regardless of language and blinding. Trials that were retrospective, nonrandomized, or quasi-randomized, or that compared two thrombolytic regimens, were excluded. The decision regarding inclusion or exclusion of studies was made before analysis of the data.

Validity assessment and data extraction. Two investigators (G. T. and D. T.) independently performed the search for trials and confirmed their eligibility. The same authors extracted data independently using a structured data collection instrument, according to the recommendations of L'Abbé et al. (22). Disagreements regarding trial eligibility or data extraction were resolved by discussion.

Outcome measures. Three outcome measures were assessed to determine the safety and efficacy of thrombolytic therapy in patients with an acute PE: 1) mortality; 2) recurrence of PE demonstrated by a perfusion lung scan, pulmonary angiography, or postmortem examination; and 3) major hemorrhage (defined as intracranial or retroperitoneal hemorrhage or other bleeding requiring blood trans-

fusion or surgery). All outcome measures were assessed until the end of follow-up of each study.

Quality assessment. The methodologic quality of the included trials was scored independently by two reviewers (G. T. and D. T.) using a well-validated scale (23). This scale consists of three items describing the method of randomization, blinding, and handling of dropouts and withdrawals. Scores on the scale range from 0 to 5, with higher scores indicating better methodologic quality. Any differences in quality assessment between the authors were resolved by consensus.

Statistical analysis. All analyses were performed according to the intention-to-treat principle. For each trial, we calculated the relative risks (RRs) of the outcomes, defined as the ratio of the number of patients with the outcome to the total number of patients in the thrombolytic group, divided by the same ratio in the heparin group. Thus, a RR below 1.0 indicates a favorable effect of thrombolytic therapy. For each of the three outcome measures, we calculated a pooled RR using the Mantel-Haenszel method (fixed-effects model) (24). If significant heterogeneity ($p < 0.1$), as assessed by the chi-square test, was detected, the Der Simonian and Laird method (random-effects model) was used (25). For statistically significant differences between treatment groups, the number needed to treat (to prevent a death or case of recurrent PE) and the number needed to harm (to cause an episode of major hemorrhage) were calculated as: 1/([control group event rate] [1 − RR]). Furthermore, for each trial, we plotted the treatment effect for mortality (logarithm of RR) against the inverse of its standard error (precision). Because the precision increases with the number of trial participants, the treatment effect estimates from smaller studies scatter more widely at the bottom of the plot. Thus, the plot is expected to resemble a symmetrical, inverted funnel. Significant asymmetry in such plots may be caused by publication bias (26,27). The degree of asymmetry in the funnel plot was estimated using regression analysis (27).

Four sensitivity analyses were performed to more closely examine the impact of thrombolytic therapy on the three outcome measures. First, the effect of the type of thrombolytic agent was examined by including only trials administering rt-PA. Second, the impact of therapy in patients with a massive PE was examined. Because only one of the trials (28) examined this patient subgroup specifically, and none of the remaining trials reported the results in this subgroup separately, two post-hoc sensitivity analyses were conducted. First, we assessed the impact of therapy in studies that included patients in shock. Second, as a surrogate marker for severe PE, we examined only those trials requiring a specific extent of pulmonary vascular obstruction, as defined radiologically, for inclusion in the trial. Finally, the impact of methodologic quality was assessed by excluding trials with a methodologic quality score equal to or less than the median value (2) of the included trials.

All results are reported with their 95% confidence interval

Table 1. Characteristics of the Included Trials

Study (Year) [Ref.]	Quality Score*	Inclusion Criteria; Method of Diagnosis	Severity Assessment	Exclusion Criteria†	Treatment Regimens	Follow-up (Days)
UPET (1973) [12]	3	onset <5 days; pulmonary angiography	no restriction	—	Heparin, UK 2,000-U/lb bolus, then 2,000 U/lb per h IV for 12 h	14
Tibbutt (1974) [11]	3	life-threatening PE; pulmonary angiography	no restriction	—	Intrapulmonary heparin, intrapulmonary SK 600,000-U bolus, then 100,000 U/h for 72 h	3
Ly (1978) [6]	2	onset <5 days; pulmonary angiography	affecting >1 lobar artery	age >70 yrs	Heparin, SK 250,000-U bolus, then 100,000 U/h for 72 h	10
Marini (1988) [7]	1	onset <7 days; pulmonary angiography	>9 unperfused lung segments on perfusion lung scan	age >72 yrs, shock‡	Heparin, UK 800,000 U/d IV for 72 h, UK 3,300,000 U IV for 12 h	7
PIOPED (1990) [13]	2	onset <7 days; pulmonary angiography	occlusion of lobar artery or ≥2 segmental arteries	shock	Heparin, rt-PA 40–80 mg IV over 90 min plus heparin	7
Levine (1990) [8]	3	onset <15 days; pulmonary angiography or perfusion lung scan	no restriction	shock	Heparin, rt-PA 0.6 mg/kg IV over 2 min	10
PAIMS 2 (1992) [10]	2	onset <10 days; pulmonary angiography	Miller index >11	shock	Heparin, rt-PA 100 mg IV over 2 h	7
Goldhaber (1993) [9]	3	onset <14 days; pulmonary angiography or perfusion lung scan	no restriction	shock	Heparin, rt-PA 100 mg IV over 2 h	14
Jerjes-Sanchez (1995) [28]	2	onset <14 days; perfusion lung scan	>9 obstructed segments on perfusion lung scan or <9 segments with RV dysfunction	previous PE	Heparin, SK 1,500,000 U IV over 1 h	3

*Items assessed in the methodologic quality score include method of randomization, double-blinding, handling of dropouts, and withdrawals. †All trials excluded patients with contraindications to thrombolytic therapy. ‡Shock was defined as systolic blood pressure <90 mm Hg with or without signs of organ dysfunction, depending on the trial.
    IV = intravenous; PE = pulmonary embolism; rt-PA = recombinant tissue-type plasminogen activator; RV = right ventricular; SK = streptokinase; UK = urokinase.

(CI). A p value of <0.05 was considered significant. All statistical analyses were performed using STATA version 6.0 statistical software (Stata Corp., College Station, Texas).

RESULTS

Selection and characteristics of included trials. A total of 120 references describing thrombolytic therapy in patients with an acute PE were identified. Nine randomized, controlled trials (6–13,28) including a total of 461 patients met the inclusion criteria. No abstracts that were not subsequently published as full articles were identified. Agreement between the two reviewers for the eligibility of relevant articles was 100%.

The characteristics of the included trials, including their methodologic quality, are summarized in Table 1. The median methodologic quality score was 2 (range 1 to 3). Three studies were double-blinded (8,12,13); the remainder were unblinded (6,7,9–11,28). In six trials, the diagnosis of PE was made by pulmonary angiography (6,7,10–13), whereas it was made by either perfusion lung scan or pulmonary angiography in two trials (8,9) and by perfusion

lung scan only in one trial (28). All trials included patients with an onset of symptoms consistent with acute PE within at least 15 days before enrollment. The median time between the onset of symptoms and the initiation of treatment was <5 days in all but one study (in which the mean time was 5.9 ± 1.0 days) (8) and was not reported in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (13). All trials excluded patients with a contraindication to thrombolytic therapy, and five trials excluded patients in shock (7–10,13). Shock was defined as systolic blood pressure <90 mm Hg in all trials, but only when associated with organ dysfunction in two trials (11,12). The severity of PE, as judged by the extent of vascular obstruction on the radiograph (defined variably according to the study) (Table 1), was an inclusion criterion in five trials (6,7,10,13,28).

Thrombolytic regimens consisted of rt-PA in four trials (8–10,13), urokinase in two trials (7,12), and streptokinase in three trials (6,11,28). In one trial, thrombolytic therapy was administered through the pulmonary artery (11), whereas in the remainder of the trials, these agents were administered intravenously. The dosages of the thrombo-

Table 2. Individual Results of the Nine Included Randomized, Controlled Trials

Study (Year) [Ref.]	Patients	Mortality	Recurrence of PE*	Major Hemorrhage†
UPET (1973) [12]	78/82	7/6	12/10	11/22
Tibbutt (1974) [11]	17/13	1/0	1/0	1/1
Ly (1978) [6]	11/14	2/1	NA	2/4
Marini (1988) [7]	10/20	0/0	0/0	0/0
PIOPED (1990) [13]	4/9	0/1	0/0	0/1
Levine (1990) [8]	25/33	0/1	0/0	0/0
PAIMS 2 (1992) [10]	16/20	1/2	1/1	2/3
Goldhaber (1993) [9]	55/46	2/0	5/0	1/2
Jerjes-Sanchez (1995) [28]	4/4	4/0	NA	0/0
Total	220/241	17 (7.7%)/11 (4.6%)	19 (9.3%)/11 (4.9%)	17 (7.7%)/33 (13.7%)

*Recurrence of PE evaluated in 428 patients (heparin, n = 205; thrombolysis, n = 223). The diagnosis was made by a perfusion lung scan, pulmonary angiography, or postmortem examination. †Major hemorrhage is defined as intracranial or retroperitoneal hemorrhage or other bleeding requiring transfusion or surgery. Data are expressed as the number (%) of patients in the heparin/thrombolysis groups.

NA = not available; PE = pulmonary embolism.

lytic agents are summarized in Table 1. The dosages of heparin were adjusted to achieve a target partial thromboplastin time of 1.5 to 2.5 times the upper limit of normal in all trials.

The median follow-up of the included trials was 7 days (range 3 to 14 days). Major hemorrhage was defined as intracranial or retroperitoneal hemorrhage or overt bleeding requiring blood transfusion in all trials. Although most of the trials reported the recurrence of PE on the basis of clinical suspicion, only cases confirmed by a perfusion lung scan, pulmonary angiography, or postmortem examination were included in our analysis.

A total of 241 patients were randomized to thrombolysis and 220 to heparin alone. Their mean age ranged from 47 to 66 years, and the percentage of males ranged from 27% to 100%. Of the 461 patients enrolled in the included trials, only 24 (5.2%) presented with shock.

Evaluation of the effect of therapy. With the exception of one study (28), none of the trials showed a significant effect of thrombolytic therapy on mortality, the recurrence of PE, or major hemorrhage, as compared with administration of heparin alone (Table 2). In the lone study showing a significant reduction in mortality achieved with thrombolysis, a total of eight patients were randomized (four to thrombolytic therapy and four to heparin); all of the patients had a massive PE associated with systemic arterial hypotension. In this trial, all of the patients receiving heparin died, whereas all of those administered streptokinase recovered.

Meta-analysis. MORTALITY. This outcome measure was reported in all nine trials including a total of 461 patients (Fig. 1). There was no statistical heterogeneity among the trials for this outcome (p = 0.77). The mean mortality rates in the thrombolytic and heparin groups were 4.6% and 7.7%, respectively. The benefit of thrombolytic therapy did not reach statistical significance (RR 0.63, 95% CI 0.32 to 1.23). The sensitivity analyses (Table 3) did not reveal a significant difference in mortality between treatments when the formulation of thrombolytic agent, the clinical severity of PE, the radiologic severity of pulmonary vascular obstruction, or methodologic quality were considered.

RECURRENCE OF PE. This outcome measure was reported in seven trials including a total of 428 patients (Fig. 2). There was no statistical heterogeneity among the studies for this outcome (p = 0.58). The mean rate of recurrent PE was 4.9% in the thrombolytic group versus 9.3% in the heparin group. This difference was not statistically significant (RR 0.59, 95% CI 0.30 to 1.18). Sensitivity analyses (Table 3) did not reveal a significant difference in the recurrence of PE between treatments when the formulation of thrombolytic agent, the clinical severity of PE, the radiologic severity of pulmonary vascular obstruction, or methodologic quality were considered.

MAJOR HEMORRHAGE. The incidence of major hemorrhage was reported in all of the trials (Fig. 3). There was no statistically significant heterogeneity in this analysis (p = 1.0). Overall, thrombolytic therapy was associated with an increased risk of major hemorrhage, as compared with heparin (13.7% vs. 7.7%; RR 1.76, 95% CI 1.04 to 2.98). This difference corresponds to a number needed to harm of 17 (95% CI 7 to 325)—that is, 17 patients need to be treated with thrombolytic therapy instead of heparin to
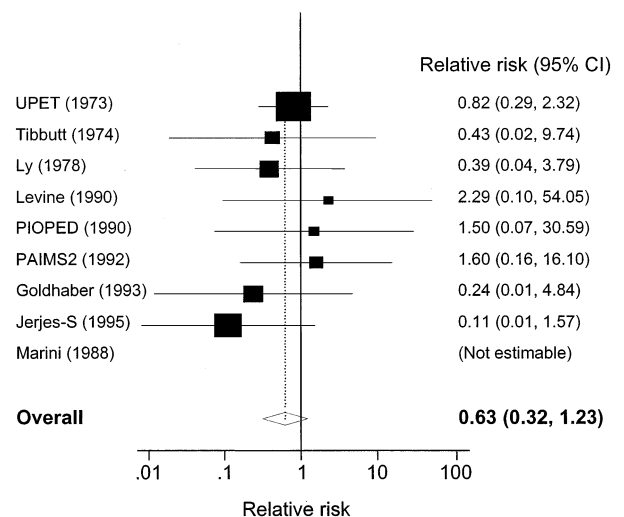

	Relative risk (95% CI)
UPET (1973)	0.82 (0.29, 2.32)
Tibbutt (1974)	0.43 (0.02, 9.74)
Ly (1978)	0.39 (0.04, 3.79)
Levine (1990)	2.29 (0.10, 54.05)
PIOPED (1990)	1.50 (0.07, 30.59)
PAIMS2 (1992)	1.60 (0.16, 16.10)
Goldhaber (1993)	0.24 (0.01, 4.84)
Jerjes-S (1995)	0.11 (0.01, 1.57)
Marini (1988)	(Not estimable)
Overall	**0.63 (0.32, 1.23)**

Figure 1. Graphic representation of the relative risk (95% confidence interval [CI]) of mortality in the thrombolysis versus heparin groups.

Table 3. Sensitivity Analyses of Thrombolytic Regimen, Clinical and Radiologic Severity of Pulmonary Embolism, and Methodologic Quality*

Criterion [Ref.]	Mortality	Recurrence of PE	Major Hemorrhage
rt-PA as thrombolytic regimen [8–10,13]	1.00 (0.28–3.60)	0.23 (0.04–1.47)	1.54 (0.45–5.26)
Patients in shock included [6,11,12,28]	0.51 (0.23–1.16)	0.76 (0.36–1.61)	1.82 (1.01–3.26)
Severity of vascular obstruction as inclusion criterion [6,7,10,13,28]	0.49 (0.16–1.46)	0.80 (0.05–11.82)	1.40 (0.49–3.99)
Methodologic score ≥3 [8,9,11,12]	0.73 (0.30–1.75)	0.58 (0.29–1.19)	1.90 (1.03–3.50)

*Items assessed in the methodologic quality score include method of randomization, double-blinding, and handling of dropouts and withdrawals. Results are reported as the relative risk (95% confidence interval) of the event in the thrombolysis group compared with the heparin group. All analyses used a fixed-effect model.
    NA = not available; PE = pulmonary embolism; rt-PA = recombinant tissue-type plasminogen activator.

cause an additional episode of major hemorrhage. In the sensitivity analyses (Table 3), this difference remained significant when only the trials randomizing patients in shock (RR 1.82, 95% CI 1.01 to 3.26) and those with high methodologic quality (RR 1.90, 95% CI 1.03 to 3.50) were considered. In trials administering rt-PA and those requiring a particular extent of pulmonary vascular obstruction for inclusion, the difference in the rates of major hemorrhage between thrombolytic therapy and heparin were not statistically significant.

FUNNEL-PLOT ANALYSIS. A plot of the logarithm of RR of mortality versus the precision for each trial is illustrated in Figure 4. The symmetry of the plot (intercept 0.15; 95% CI −1.06 to 1.37; p = 0.50) contradicts the presence of a publication bias. Similar results were obtained regardless of the outcome measure assessed (data not shown).

DISCUSSION

Acute PE is a common medical condition. Although the standard therapy—heparin—is effective, the morbidity and mortality attributable to acute PE remain high (2,5). Thrombolytic agents represent an alternative treatment with convincing biologic plausibility for a benefit. By lysing the obstructive thrombus, these agents rapidly reverse the RV

dysfunction that is associated with decreased survival in these patients (4,5,9,14). In addition, thrombolysis serves as a medical embolectomy, a benefit that could conceivably lead to a reduction in the rate of recurrent PE. Several randomized, controlled trials have compared heparin with thrombolytic agents in patients with an acute PE, but a beneficial effect of thrombolysis on important clinical outcomes—namely, survival and the recurrence of PE—has been difficult to demonstrate. This may relate to the small sample sizes of the trials thus far reported. To determine whether a treatment effect of thrombolysis truly exists, we endeavored to increase the statistical power by pooling the results of the available trials using meta-analytic techniques. Our study showed that thrombolytic therapy is not associated with a significant reduction in mortality or the recurrence of PE, as compared with heparin, when administered to unselected patients with an acute PE. However, thrombolytic therapy did lead to a near doubling in the rate of major hemorrhage, as compared with heparin alone.

Although a significant reduction in mortality and the recurrence of PE was not demonstrated in patients receiving thrombolytic agents, there was a trend in favor of this treatment. The point estimates suggest a reduction of approximately 40% for both of these outcomes in patients
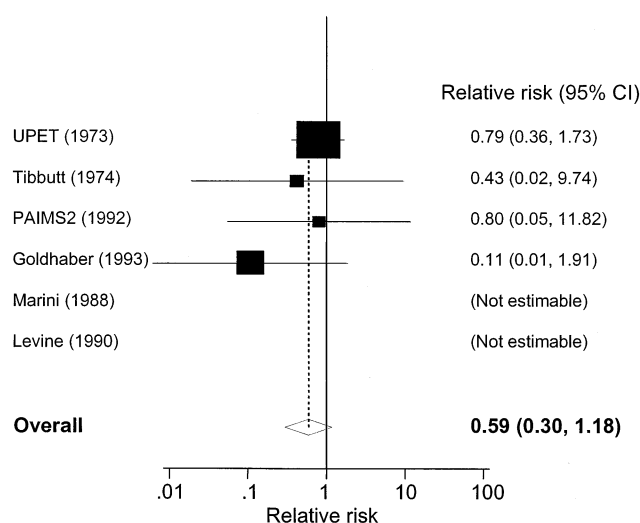

Figure 2. Graphic representation of the relative risk (95% confidence interval [CI]) of the recurrence of pulmonary embolism in the thrombolysis versus heparin groups.
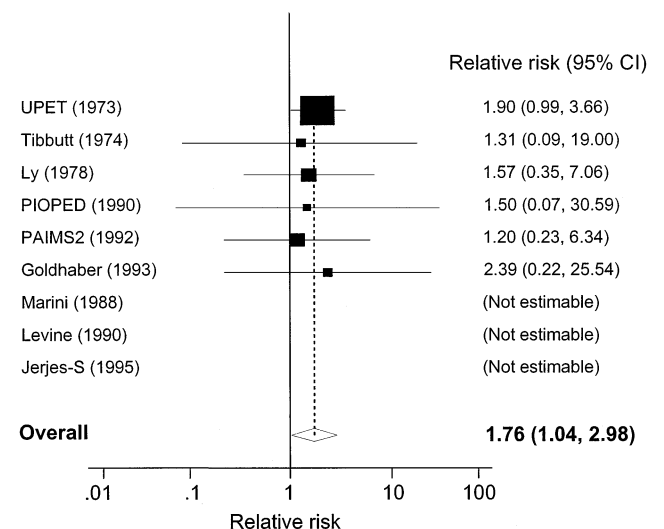

Figure 3. Graphic representation of the relative risk (95% confidence interval [CI]) of major hemorrhage in the thrombolysis versus heparin groups.
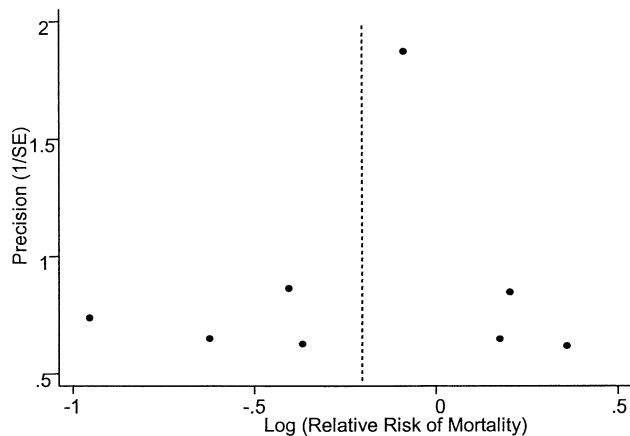
Figure 4. Funnel-plot analysis. Plot of the logarithm of the relative risk of mortality versus precision of the included trials. The study by Marini et al. (7) was excluded because the relative risk could not be calculated, as no deaths occurred in either treatment group. The funnel plot is symmetrical (intercept 0.15; 95% confidence interval −1.06 to 1.37), contradicting the presence of a publication bias.

treated with thrombolysis versus heparin. Sensitivity analyses showed that these results were robust to the formulation of thrombolytic agent used and the methodologic quality of the trials. The failure to detect a significant difference between treatments has several possible explanations. First and foremost, a difference may not exist. Alternatively, our meta-analysis may have been underpowered; despite pooling all of the randomized, controlled trials thus far published, only nine trials enrolling a total of 461 patients (241 randomized to thrombolysis) were available. Our funnel-plot analysis (Fig. 4) suggests that a publication bias—the failure of small trials to be published due to nonsignificant treatment effects—does not explain this paucity of data. The point estimates and CIs for mortality and the recurrence of PE suggest that a difference in favor of thrombolysis may become apparent if the sample size were increased. However, to demonstrate a clinically important difference between these therapies (e.g., 30% reduction in short-term mortality) would necessitate the enrollment of approximately 1,000 patients per treatment arm in a controlled trial (assuming a 15% three-month mortality rate in the heparin group and 80% power) (5,29). A potentially similar situation occurred in the early trials examining the effect of intravenous thrombolytic therapy in patients with an acute myocardial infarction. In this condition, several thousand people were enrolled in controlled trials before a convincing survival benefit of thrombolysis was demonstrated (30). Furthermore, this treatment did not become standard clinical practice until nearly 20,000 patients had been studied (30). In patients with an acute PE, only a multicenter, prospective, controlled trial will be able to definitively answer this question. For various reasons (31), and despite international calls (32), such a trial has yet to be initiated.

An alternative explanation for the failure to detect a significant difference in mortality between these treatments

may be that PE, by itself, is not the major cause of death in these patients. Indeed, in a one-year prospective study of 399 patients (29), most of the deaths were due to underlying diseases; only 2.5% died as a direct result of their PE. However, this hypothesis is not supported by the results of the International COoperative Pulmonary Embolism Registry (ICOPER) (5). In this prospective study including 2,454 patients, the overall three-month mortality rate was 17.4%; 45% of these deaths were attributed to PE. Moreover, 24% of the deaths were due to respiratory failure or sudden cardiac death; recurrent PE may have caused a large proportion of these deaths.

Although the indications for thrombolytic therapy in patients with a PE have yet to be precisely defined, the subset of patients with a "massive" PE (i.e., those with RV dysfunction and hemodynamic instability) has been the typical target for treatment. To determine whether this subgroup might be particularly likely to sustain a benefit or injury from thrombolysis, a sensitivity analysis was planned in these patients. Unfortunately, only a single trial examined this population exclusively (28), and the remainder failed to report these patients' results separately. Consequently, post-hoc sensitivity analyses were performed examining only the trials including patients in shock and those requiring a minimal extent of pulmonary vascular obstruction, as defined radiologically, for inclusion. Although these definitions are clearly not ideal surrogates for massive PE, neither analysis revealed a significant benefit of thrombolytic therapy on mortality or the recurrence of PE. However, as only 5% of the trial participants were in shock, any benefit in this subset may have been masked by a lack of benefit in the remaining patients. Interestingly, the single trial exclusively enrolling patients with a massive PE and shock was the only study to show a significant reduction in mortality with thrombolysis (28). Nevertheless, this trial included only eight patients and has been criticized on methodologic grounds (1,33). Whether thrombolytic therapy has a role in patients with RV dysfunction but stable hemodynamics is also unclear from our study. Our results are in accordance with a retrospective cohort study of 128 patients receiving thrombolysis or heparin, in which thrombolysis was associated with an improvement, as demonstrated on perfusion lung scans, but no difference in the rate of recurrent PE or mortality (34). However, in a larger study of a similar population, Konstantinides et al. (19) reported a significant reduction in mortality and PE recurrence in patients treated with thrombolysis. The same investigators have recently reported the results of a prospective, multicenter, placebo-controlled trial in which 247 patients with a major PE were randomized to rt-PA plus heparin or placebo plus heparin (35). In this study, although mortality did not significantly differ between the two groups, the rt-PA group had a less "rocky" hospital course, as compared with the placebo group. Only a large, randomized, controlled trial stratifying patients according to evidence of RV dysfunction and the

presence of hemodynamic instability will be able to definitely resolve these issues.

This meta-analysis demonstrated a significant increase in the rate of major hemorrhage in patients receiving thrombolytic therapy (13.7%) versus heparin (7.7%). This finding is in accordance with other studies (20,36). According to this analysis, for every 17 patients treated with thrombolytic therapy instead of heparin, one additional major hemorrhage can be expected. This difference remained significant regardless of the methodologic quality of the included trials and the inclusion of patients in shock. Based on the available data, we could not determine a particular patient subgroup at risk of this complication; however, advancing age, larger body mass index, and previous catheterization have been reported to increase the risk of hemorrhagic complications (36,37). Interestingly, our sensitivity analysis including only those trials administering rt-PA failed to reveal a difference between thrombolytic therapy and heparin in terms of the rate of major hemorrhage, suggesting that rt-PA may be less likely to cause bleeding, as compared with streptokinase or urokinase. However, this finding should be interpreted with caution due to the limited power of this analysis. Furthermore, a comparison of the relative risk of major hemorrhage in the trials administering rt-PA versus that of the other agents revealed a nonsignificant difference (data not shown). Moreover, direct comparisons of these agents in randomized, controlled trials have failed to demonstrate a difference in this outcome (38,39).

Our meta-analysis has several limitations—in particular and as already alluded to, the small sample size. Nevertheless, pooling of all of the currently available data by using meta-analytic techniques has allowed us to confirm a common clinical suspicion not yet substantiated in randomized, controlled trials; namely, that thrombolysis is associated with an increased risk of bleeding, as compared with heparin, in patients with an acute PE. Although meta-analysis does not replace the value of a large, well-designed, randomized trial, it is nonetheless useful when sample sizes are individually too small to detect a treatment effect and label it statistically significant (22). In this setting, there is some agreement between the overall estimates given by meta-analyses and subsequently published, large, randomized trials (40). Other limitations of meta-analysis are well known (41,42). Comparative studies yielding conflicting results are difficult to evaluate because many factors other than the administered treatments can affect the outcome(s). As in any meta-analysis, critical attention must be paid to the quality of the primary trials. In our study, all of the included trials were prospective, controlled, and randomized; all of them incorporated reasonable definitions of the main outcome measures; and the treatment effects of the trials were homogeneous. In addition, the methodologic quality of the trials, as judged by a well-validated quality score (23), did not affect the results in the sensitivity analyses. Another limitation of our meta-analysis is the failure to identify particular patient characteristics that may

predict an enhanced benefit or risk of thrombolytic therapy. Although an evaluation of treatment effects based on the presence of RV dysfunction was attempted by use of sensitivity analyses, an analysis based on individual patient data would have likely been more enlightening (43).

Conclusions. This meta-analysis revealed an increased risk of major hemorrhage in patients treated with thrombolytic therapy versus heparin for acute PE, but it did not detect a significant difference in the rate of recurrent PE or mortality. Given the small number of patients enrolled in the included trials, these negative results should be interpreted with caution due to a potential lack of statistical power. Definitive evidence of the usefulness of thrombolytic therapy in this setting requires a large, prospective, randomized, controlled trial (33).

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