Original Investigation

Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage
A Meta-analysis

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IMPORTANCE Thrombolytic therapy may be beneficial in the treatment of some patients with pulmonary embolism. To date, no analysis has had adequate statistical power to determine whether thrombolytic therapy is associated with improved survival, compared with conventional anticoagulation.

OBJECTIVE To determine mortality benefits and bleeding risks associated with thrombolytic therapy compared with anticoagulation in acute pulmonary embolism, including the subset of hemodynamically stable patients with right ventricular dysfunction (intermediate-risk pulmonary embolism).

DATA SOURCES PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from inception through April 10, 2014.

STUDY SELECTION Eligible studies were randomized clinical trials comparing thrombolytic therapy vs anticoagulant therapy in pulmonary embolism patients. Sixteen trials comprising 2115 individuals were identified. Eight trials comprising 1775 patients specified inclusion of patients with intermediate-risk pulmonary embolism.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted trial-level data including number of patients, patient characteristics, duration of follow-up, and outcomes.

MAIN OUTCOMES AND MEASURES The primary outcomes were all-cause mortality and major bleeding. Secondary outcomes were risk of recurrent embolism and intracranial hemorrhage (ICH). Peto odds ratio (OR) estimates and associated 95% CIs were calculated using a fixed-effects model.

RESULTS Use of thrombolytics was associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32-0.88; 2.17% [23/1061] vs 3.89% [41/1054] with anticoagulants; number needed to treat [NNT] = 59) and greater risks of major bleeding (OR, 2.73; 95% CI, 1.91-3.91; 9.24% [98/1061] vs 3.42% [36/1054]; number needed to harm [NNH] = 18) and ICH (OR, 4.63; 95% CI, 1.78-12.04; 1.46% [15/1024] vs 0.19% [2/1019]; NNH = 78). Major bleeding was not significantly increased in patients 65 years and younger (OR, 1.25; 95% CI, 0.50-3.14). Thrombolysis was associated with a lower risk of recurrent pulmonary embolism (OR, 0.40; 95% CI, 0.22-0.74; 1.17% [12/1024] vs 3.04% [31/1019]; NNT = 54). In intermediate-risk pulmonary embolism trials, thrombolysis was associated with lower mortality (OR, 0.48; 95% CI, 0.25-0.92) and more major bleeding events (OR, 3.19; 95% CI, 2.07-4.92).

CONCLUSIONS AND RELEVANCE Among patients with pulmonary embolism, including those who were hemodynamically stable with right ventricular dysfunction, thrombolytic therapy was associated with lower rates of all-cause mortality and increased risks of major bleeding and ICH. However, findings may not apply to patients with pulmonary embolism who are hemodynamically stable without right ventricular dysfunction.

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Pulmonary embolism (PE) is an important cause of morbidity and mortality with more than 100 000 US cases annually and as many as 25% of patients presenting with sudden death. Pulmonary embolism is associated with increased mortality rates for up to 3 months after the index PE event.[1] Multiple studies and meta-analyses have evaluated the role of thrombolytic therapy in PE with largely discordant results.[2-5] A randomized trial from 2002 showed improvements in a combined end point of in-hospital mortality and hemodynamic deterioration requiring escalation of treatment[2] but did not have sufficient statistical power to assess differences in mortality or intracranial hemorrhage (ICH). Meta-analyses have also been underpowered to assess the association of thrombolytic therapy with mortality.[4,5] Subsequent observational data have suggested both benefits and underuse of thrombolytic therapy in patients with high-risk PE.[6]

More recent consensus guidelines have cited a pressing need for outcomes data regarding thrombolytics from contemporary trials, especially in hemodynamically stable patients with evidence of right ventricular (RV) dysfunction (intermediate-risk PE).[7] Several recent trials have evaluated the role of thrombolytics in PE for these patients without definitive results, particularly for the end point of mortality.[8-11] Thus, we performed a meta-analysis of all randomized trials of thrombolytic therapy in PE. We aimed to ascertain associations of thrombolytic therapy with bleeding risk and potential mortality benefits, with special attention paid to the subpopulation of patients presenting with intermediate-risk PE.

Methods

A systematic review of the literature was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[12] Two authors (S.C., J.G.) identified the relevant articles by searching the following data sources: PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases (from inception through April 10, 2014), without language restrictions. The following search terms and key words were used: *pulmonary embolism* or *pulmonary thromboembolism (PTE)* (as MeSH terms), AND *thrombolytic drugs*, *thrombolytic therapy*, *clot-dissolving medication*, AND/OR *streptokinase*, *urokinase (Abbokinase)*, *tissue plasminogen activator (tPA) or recombinant tissue-type plasminogen activator (rt-PA)*, *alteplase*, *prourokinase (Umbralina)*, and *tenecteplase*. The planned analysis was registered at the PROSPERO international prospective register of systematic reviews on January 2, 2014.

Study Selection, Data Extraction, and Quality Assessment

Prespecified inclusion criteria were as follows: randomized controlled design in patients with PE evaluating thrombolytic therapy as an intervention; a comparator group that included any of the following agents: low-molecular-weight heparin (LMWH), vitamin K antagonist, fondaparinux, or unfractionated heparin; and reporting of mortality outcomes. We did not include trials that compared different thrombolytic agents against one another or different doses of the same thrombolytic drug.

Two reviewers (S.C., J.G.) independently extracted data from eligible trials using the standardized protocol. Disagreements were resolved by discussion with other authors. Risk of bias was assessed for the domains suggested by the Cochrane Handbook of Systematic Reviews,[13] specifically emphasizing sequence generation, allocation concealment, blinding, outcomes assessment, and selective reporting.

Data Synthesis and Analysis

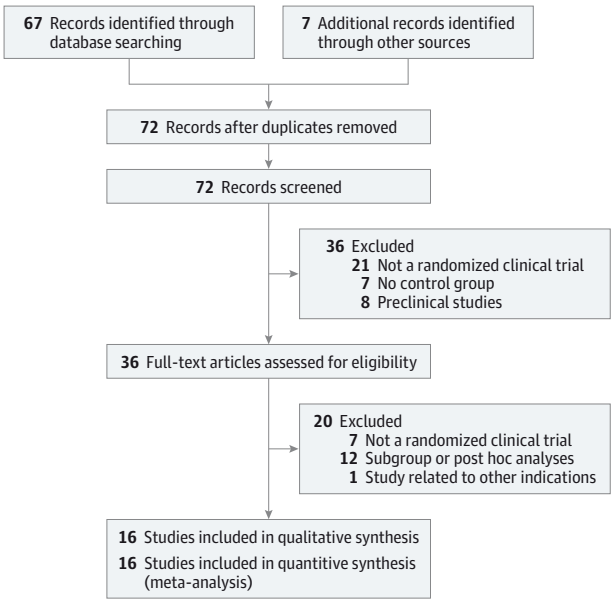
The primary efficacy outcome was all-cause mortality and the primary safety outcome was major bleeding. Secondary efficacy and safety outcomes were risk of a recurrent PE and ICH, respectively. Definitions of major bleeding were according to definitions in the individual trials with ICH included as a major bleeding end point in any trial that did not prespecify this. The outcomes data from the first available time point identified as a primary end point from each trial were incorporated into our primary analysis, noting the acute nature of intervention with thrombolytics. Several prespecified subanalyses were performed as described in the next section. Each trial patient was classified as low-risk (hemodynamically stable without objective evidence of RV dysfunction), intermediate-risk (hemodynamically stable with objective evidence of RV dysfunction), high-risk (hemodynamically unstable and/or documented systolic blood pressure <90 mm Hg), or unclassifiable (patient information not adequate to determine risk level). Objective evidence of RV dysfunction included reported abnormalities on echocardiogram, abnormalities of cardiac biomarkers (troponin and brain natriuretic peptide), or both.

Statistical Analysis

The statistical analysis was performed according to the recommendations from the Cochrane Collaboration using Review Manager Version 5.2 (Nordic Cochrane Center), WinBUGS version 1.4.3, and Stata version 11.2SE (StataCorp). As outcome proportions were expected to be low, between 2% and 3%, we calculated the Peto odds ratio (OR) estimates and associated 95% CIs using a fixed-effects model for our primary analyses.[2,14] We used the I^2 measure for heterogeneity[15] (I^2 < 25% was considered low). Bias in reporting was estimated by funnel plots (plotting of standard error of the logarithm of the OR against log of OR) and the Egger weighted regression test for evaluating heterogeneity. A 2-sided P < .05 was considered statistically significant. We calculated the number needed to treat (NNT) and harm (NNH) from the Peto OR using the following formula: NNT = 1/[CEP − {OR/(1/CEP − 1) + OR}], where CEP stands for control event proportion.[14]

We evaluated the mortality and major bleeding outcomes in the 8 studies that specified therapy for hemodynamically stable PE with objective assessment of RV function as criteria for inclusion. In addition, a prespecified analysis was planned to evaluate the primary outcomes for trials published after 2009 (to evaluate the most updated randomized evidence). A priori, another planned exploratory analysis involved the outcomes in patients older than 65 years (trials

Figure 1. Search Strategy and Study Selection



where the mean age of participants in the thrombolytic group was >65 years), as worse outcomes with thrombolytics in elderly patients have been suggested by a recent large randomized trial of the issue.[8] Prespecified analyses were performed excluding the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial, as this was the only included trial administering thrombolytic therapy through a catheter-directed (as opposed to systemic) approach. A sensitivity analysis was performed to analyze outcomes from the longest available follow-up points in trials reporting mortality at multiple time points to ensure no significant changes in overall mortality comparisons.

We also performed a weighted absolute risk difference analysis (as is used for assessment of benefit-harms trade-off analysis)[13] to compare the potential associations of mortality reduction with thrombolysis against the possible associations of risk of ICH. Additionally, we performed a net clinical benefit analysis of thrombolytic therapy in PE. We calculated the short-term mortality (Tm) prevented by thrombolytic therapy minus the short-term risk of ICH (Ti) induced by thrombolytic therapy. The latter was multiplied by a weighting factor of 0.75, indicating that a single ICH event had three-fourths of the effect of a single mortality. This weighting factor was based on data demonstrating the likelihood of death and serious disability due to ICH.[16] The weighting factor was chosen to provide a conservative estimate of potential benefits associated with thrombolytic therapy. The following equation illustrates this definition: net clinical benefit = $(Tm_{anticoagulants} - Tm_{thrombolytics})$ − weighing factor × $(Ti_{thrombolytics} - Ti_{anticoagulants})$.

Metaregression analyses were prespecified for the primary outcomes with the baseline covariate of systolic blood pressure, noting the emphasis in current guidelines on thrombolytic use in patients with hypotension. However, this covariate was available and accurate in only 6 of 16 trials, limiting the utility of this prespecified analysis.

In our initial analyses, we excluded trials with 0 events in both groups as is the recommendation of the Cochrane Collaboration.[13] To further account for 0-event trials, we performed subsequent Bayesian random-effects meta-analysis fitted in a Poisson model. For the Bayesian random-effects analysis, "vague" or noninformative priors were used to yield results that are not too different from conventional statistical analysis. We checked and confirmed convergence and lack of autocorrelation after a 10 000 simulation burn-in phase. Next, we based direct probability statements on an additional 500 000 simulation phase to identify the best and most representative data, assuming comparable interstudy variances for all treatment effects for the same outcomes. We used deviance and the deviance information criterion to appraise model fit.

Finally, to confirm validity of our findings, we performed trial sequential analysis (TSA)[17-20] with 5% risk of a type I error, which is the standard in most meta-analyses and systematic reviews. We calculated our monitoring boundaries according to the required information size to detect or reject an intervention effect of a 12%, 25%, and 40% relative risk reduction for mortality or increase of 75%, 87%, and 100% for major bleeds with a risk of a type II error of 20% (power of 80%). We used TSA version 0.9 beta for these analyses.[21]

Results

Our search identified 72 potentially eligible RCTs with 16 RCTs (n = 2115) meeting our inclusion criteria[2,3,8-11,22-31] (**Figure 1**). Two hundred ten patients (9.93%) had low-risk PE, 1499 (70.87%) had intermediate-risk PE, 31 (1.47%) had high-risk PE, and 385 (18.20%) could not be classified regarding risk (**Table 1**).

Thrombolytic therapy in PE was associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32-0.88; NNT, 59; 95% CI, 31-380) (**Figure 2**). There was a 2.17% (23/1061) mortality noted in the thrombolytic therapy cohort and a 3.89% (41/1054) mortality noted in the anticoagulant cohort at a mean duration of follow-up of 81.7 days. Thrombolytic therapy was associated with a greater risk of major bleeding compared with anticoagulant therapy (OR, 2.73; 95% CI, 1.91-3.91; NNH, 18; 95% CI, 13-27) (eFigure 1 in the Supplement). There was a 9.24% (98/1061) rate of major bleeding in the thrombolytic therapy cohort and a 3.42% (36/1054) rate in the anticoagulation cohort. Thrombolysis demonstrated an association with greater ICH rate (OR, 4.63; 95% CI, 1.78-12.04; 1.46% [15/1024] vs 0.19% [2/1019]; NNH, 78; 95% CI, 48-206) (eFigure 2 in the Supplement) and lower risk of recurrent PE (OR, 0.40; 95% CI, 0.22-0.74; 1.17% [12/1024] vs 3.04% [31/1019]; NNT = 54) (eFigure 3 in the Supplement). All outcomes were associated with negligible heterogeneity (I^2 < 25%). No publication bias was observed with the funnel plots or the Egger regression test (P = .47 for mortality and P = .82 for major bleeds) (eFigures 4, 5A, and 5B in the Supplement). Bayesian random-effects meta-

analysis was congruent with results of the primary analysis for mortality (median OR, 0.51; 95% credible interval, 0.18-0.89), major bleeds (median OR, 2.47; 95% credible interval, 1.41-4.62), ICH (median OR, 3.02; 95% credible interval, 1.68-14.72), and recurrent PE (median OR, 0.31; 95% credible interval, 0.20-0.82).

In a subgroup analysis of patients older than 65 years, there was a nonsignificant association with lower mortality (OR, 0.55;

Table 1. Baseline Characteristics of Trials

Source	No. of Patients	Randomized Treatment	Comparator	Major Bleeding Criteria	Follow-up, d	PE Risk, No. (%)				Age, Mean (Range or SD), y	Male, No. (%)
						Low	Mod	High	Unclear		
UPETSG,[31] 1970	160	Urokinase (2000 U/lb, then 2000 U/lb/h for 12 h)	Heparin	Hematocrit drop >10 points, ≥2 units PRBCs	14	[a]	[a]	14 (8.75)	146 (91.25)	45 (<50), 55 (>50)[b]	92 (57.3)
Tibbutt et at,[28] 1974	30	Streptokinase (600 000 U over 30 min through PA catheter followed by 100 000 U/h IV for 72 h)	Heparin	Not prespecified	3	[a]	[a]	7 (23.3)	23 (76.67)	48.73 (25-71)	15 (50)
Ly et al,[25] 1978	25	Streptokinase (250 000 IU loading dose, then 100 000 IU/h for 72 h)	Heparin	Not prespecified	10	[a]	4 (16)	2 (8)	19 (76)	53.2 (23-70)	11 (44)
Marini et al,[26] 1988	30	Urokinase (800 000 IU for 12 h/d for 3 d or 3 300 000 IU for 12 h)	Heparin	Not prespecified	7	[a]	[a]	[a]	30 (100)	53 (23-72)	18 (60)
Levine et al,[22] 1990	58	Alteplase (0.6 mg/kg of ideal body weight)	Heparin	ICH, RP, transfusion of ≥2 units PRBCs, Hgb drop >2 g/dL	10	[a]	[a]	[a]	58 (100)	61.5 (2.7)	29 (54.54)
PIOPED,[27] 1990	13	Alteplase (40-80 mg)	Heparin	Not prespecified	7	[a]	[a]	[a]	13 (100)	58.46 (15.81)	9 (55.55)
Dalla-Volta et al,[23] 1992	36	Alteplase (100 mg)	Heparin	ICH, any transfusion	30	[a]	[a]	0	36 (100)	64.68 (12.5)	12 (33)
Goldhaber et al,[2] 1993	101	Alteplase (100 mg)	Heparin	ICH, need for surgery	14	55 (49.5)	56 (50.4)	0	0	58.54 (17)	44 (44)
Jerjes-Sanchez et al,[24] 1995	8	Streptokinase (1 500 000 IU)	Heparin	Not prespecified	1-3	0	0	8 (100)	0	51 (22.9)	5 (63)
Konstantinides et al,[3] 2002	256	Alteplase (100 mg)	Heparin	ICH, fatal, Hgb drop >4 g/dL	30	155 (60.5)	80 (31.25)	0	21 (8.2)	62.08 (10.47)	122 (47.6)
TIPES,[29] 2010	58	Tenecteplase (30-50 mg)	Heparin	ICH, fatal, need for transfusion, need for surgery	7	0	58 (100)	0	0	68.1 (1.85)	13 (22.4)
Fasullo et al,[11] 2011	72	Alteplase (100 mg)	Heparin	ICH, fatal, any transfusion	180	0	72 (100)	0	0	55.97 (16.12)	41 (56.94)
MOPETT,[10] 2012	121	Alteplase (50 mg)	Heparin/ enoxaparin	Not prespecified	840	0	82 (67.7)	0	39 (32.23)	58.5 (9.5)	55 (45.45)
ULTIMA,[30] 2013	59	Alteplase (max dose 20 mg into PA over 16 h)	Heparin	ICH, spinal, joint, RP, pericardial, Hgb drop >2 g/dL with transfusion	90	0	59 (100)	0	0	63.01 (13.51)	28 (47.46)
PEITHO,[8] 2014	1005	Tenecteplase (30-50 mg)	Heparin/ LMWH/ fondaparinux	ICH, life-threatening, fatal, need for transfusion	30	0	1005 (100)	0	0	66.15 (15.29)	473 (47.06)
TOPCOAT,[9] 2014	83	Tenecteplase (dose not reported)	LMWH	ICH, need for surgery, Hgb drop >2 g/dL with transfusion	5	0	83 (100)	0	0	55.44 (14)	49 (59.0)

Abbreviations: Hgb, hemoglobin; ICH, intracranial hemorrhage; IV, intravenously; LMWH, low-molecular-weight heparin; Mod, intermediate risk (hemodynamically stable with objective evidence of right ventricular dysfunction); max, maximum; NA, not available; PA, pulmonary artery; PE, pulmonary embolism; PRBCs, packed red blood cells; RP, retroperitoneal.

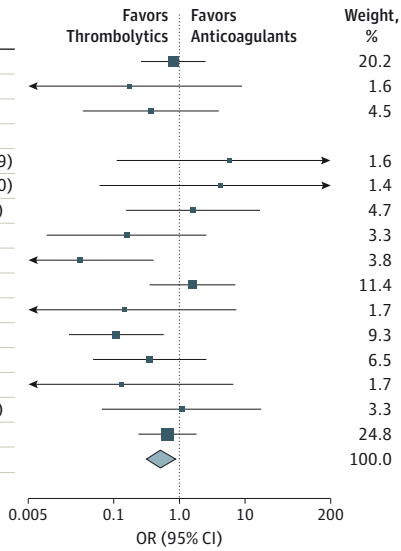
[a] Cannot exclude potential patients in this category.

[b] Precise ages of patients not provided; 50.6% of patients were younger than 50 years and 49.4% of patients 50 years or older.

Figure 2. Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

Source	Thrombolytics No. of Events	Thrombolytics No. of Patients	Anticoagulants No. of Events	Anticoagulants No. of Patients	OR (95% CI)	Weight, %
UPETSG,[31] 1970	6	82	7	78	0.80 (0.26-2.49)	20.2
Tibbutt et al,[28] 1974	0	13	1	17	0.17 (0.00-8.94)	1.6
Ly et al,[25] 1978	1	14	2	11	0.37 (0.03-3.96)	4.5
Marini et al,[26] 1988	0	20	0	10	Not estimable	
Levine et al,[22] 1990	1	33	0	25	5.80 (0.11-303.49)	1.6
PIOPED,[27] 1990	1	9	0	4	4.24 (0.06-296.20)	1.4
Dalla-Volta et al,[23] 1992	2	20	1	16	1.61 (0.15-16.82)	4.7
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)	3.3
Jerges-Sanchez et al,[24] 1995	0	4	4	4	0.03 (0.00-0.40)	3.8
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)	11.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)	1.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)	9.3
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)	6.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)	1.7
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)	3.3
PEITHO,[8] 2014	6	506	9	499	0.66 (0.24-1.82)	24.8
Total	23	1061	41	1054	0.53 (0.32-0.88)	100.0

Heterogeneity: $\chi^2_{14} = 16.51$; $P = .28$; $I^2 = 15\%$
Overall effect: $z = 2.45$; $P = .01$



Evaluated using the Peto method of meta-analysis. The standard practice in meta-analysis of odds ratios (ORs) and risk ratios is to exclude studies from the meta-analysis where there are no events in either group.[13] A 0-cell or continuity correction was not used based on recommendations regarding calculation of a Peto OR for studies with 0 events in only 1 group.[13] MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial; UPETSG, Urokinase Pulmonary Embolism Trial Stage 1.

Table 2. Absolute Risk Metrics of Outcomes of Major Interest

Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (0.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age >65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Major bleeding (5)[a]	87/673 (12.93)	27/658 (4.10)	NNH = 11	<.001
Age ≤65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT = 51	.09
Major bleeding (11)[a]	11/388 (2.84)	9/396 (2.27)	NNH = 176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Abbreviations: ICH, intracranial hemorrhage; NNH, number needed to harm; NNT, number needed to treat; PE, pulmonary embolism.

[a] Per individual trial criteria with ICH also included for any trials that did not prespecify this.

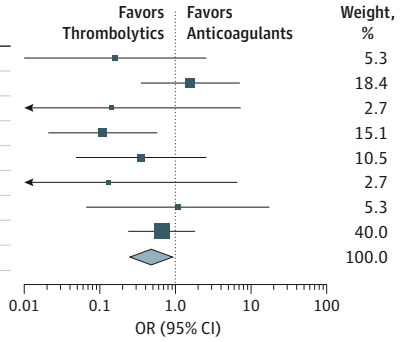
95% CI, 0.29-1.05; 2.08% [14/673] vs 3.65% [24/658]); however, there was an association with greater risk of major bleeds (OR, 3.10; 95% CI, 2.10-4.56; 12.93% [87/673] vs 4.10% [27/658]) (**Table 2**). In patients 65 years and younger, there was no association with increase in major bleeding (OR, 1.25; 95% CI, 0.50-3.14; 2.84% [11/388] vs 2.27% [9/396]). For the 1 trial that did not clearly state the age of the participants,[31] we included the trial in the age group older than 65 years in the primary analysis because the majority of patients were noted to be older than 50 years. We excluded the trial altogether on a further sensitivity assessment of bleeding (OR, 2.91; 95% CI, 1.94-4.37) and then repeated a bleeding analysis with the entire trial included in the group 65 years and younger (OR, 1.73; 95% CI, 0.96-3.12) with no significant deviation from the primary results noted in either case.

In a prespecified analysis performed of the 8 trials (n = 1775) specifically enrolling only patients who were hemodynamically stable with objective assessments of RV function, thrombolysis was associated with lower mortality (OR, 0.48; 95% CI, 0.25-0.92; 1.39% [12/866] vs 2.92%

Figure 3. Odds of Mortality in Patients With Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

Source	Thrombolytics No. of Events	Thrombolytics No. of Patients	Anticoagulants No. of Events	Anticoagulants No. of Patients	OR (95% CI)	Weight, %
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)	5.3
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)	18.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)	2.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)	15.1
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)	10.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)	2.7
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)	5.3
PEITHO,[8] 2014	6	506	9	499	0.66 (0.24-1.82)	40.0
Total	12	866	26	889	0.48 (0.25-0.92)	100.0

Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$
Overall effect: $z = 2.22$; $P = .03$



Evaluated using the Peto method of meta-analysis. The standard practice in meta-analysis of odds ratios (ORs) and risk ratios is to exclude studies from the meta-analysis where there are no events in either group.[13] A 0-cell or continuity correction was not used based on recommendations regarding calculation of a Peto OR for studies with 0 events in only 1 group.[13] MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial.

[26/889]) (**Figure 3**) and greater major bleeding rate (OR, 3.19; 95% CI, 2.07-4.92; 7.74% [67/866] vs 2.25% [20/889]) when compared with anticoagulation (Table 2). Associations with lower mortality were derived largely from use of thrombolytics for patients with intermediate-risk PE in the contemporary era (2009-2014) (OR, 0.39; 95% CI, 0.19-0.82; 1.99% [14/702] vs 4.02% [28/696]). There was no statistically significant difference in mortality between the 8 trials prespecifying enrollment of patients who were hemodynamically stable with objective assessment of RV function vs those enrolling all-comers without specific assessment of the RV (test for subgroup differences: $P_{\text{interaction}} = .64$, $I^2 = 0\%$) (eFigure 6 in the Supplement).

Findings from prespecified analyses excluding the sole included trial of catheter-directed thrombolysis, ULTIMA,[30] mirrored the primary and secondary efficacy and safety outcomes in both the primary analysis and the subanalysis of patients with intermediate-risk PE. With the exclusion of ULTIMA, the primary efficacy end point remained significantly lower with thrombolytics (OR, 0.54; 95% CI, 0.33-0.91). With the exclusion of ULTIMA, the analysis of trials of intermediate-risk PE revealed a persistent association with lower mortality (OR, 0.50; 95% CI, 0.26-0.96). Major bleeding remained associated with use of thrombolytics in each case.

A further sensitivity analysis including the outcomes from the longest available mortality follow-up for individual trials showed findings consistent with the overall results. Thrombolytic therapy across all trials was associated with lower all-cause mortality (OR, 0.57; 95% CI, 0.36-0.91), and similar results were seen in the subgroup of intermediate-risk PE trials (OR, 0.55; 95% CI, 0.32-0.97).

A weighted absolute risk difference assessment performed to weigh relative harms/benefits of ICH and mortality showed that associations with lower mortality seen with thrombolysis were comparable with associations of risk of potential ICH (weighted risk difference, 0%; 95% CI, −2% to 1%) (eFigure 7 in the Supplement). The net clinical benefit analysis comparing associated mortality benefits vs ICH risks of thrombolytic therapy demonstrated a net clinical benefit of 0.81% (95% CI, 0.65% to 1.01%). This analysis weighted the effect of an ICH event as 0.75 times that of a mortality event. The same analysis was performed on patients enrolled in the 8 trials evaluating patients with intermediate-risk PE. In this analysis, the net clinical benefit for thrombolytic therapy was 0.62% (95% CI, 0.57% to 0.67%).

For the primary analysis of all 16 trials, TSA crossed the O'Brien-Fleming boundaries to indicate existing "firm evidence" of a 12% relative reduction in mortality (diversity-adjusted OR, 0.56; 95% CI, 0.35-0.91) and 75% relative increase in major bleeds (diversity-adjusted OR, 2.68; 95% CI, 1.88-3.82) as available from current randomized data (eFigures 8 and 9 in the Supplement). Firm evidence has not yet accumulated from randomized trials for a relative risk reduction in mortality of 40% or increase in bleeding risk of 100%.

Discussion

Our systematic review and meta-analysis demonstrate lower associated mortality with thrombolytic use in PE. Furthermore, evidence from more recent trials of patients with intermediate-risk PE corroborates results reported here. This suggests potential mortality benefit with thrombolytic therapy in patients with hemodynamically stable PE with RV dysfunction in contemporary clinical practice. To our knowledge, this is the first analysis of thrombolysis in PE that has sufficient statistical power to detect associations with a meaningful mortality reduction. However, the optimism regarding this clinical advantage must be tempered by the finding of significantly increased risk of major bleeding and ICH associated with thrombolytic therapy, particularly for patients older than 65 years.

The 6 trials conducted since the last systematic Cochrane review[32] of the topic are responsible for two-thirds (1398/2115) of all randomized patients in the medical literature.[32] Our

inclusion of the latest trials[8-11,29,30] is reflective of contemporary clinical practice patterns, and our results contradict the prior Cochrane review,[32] as well as multiple guidelines that have not included the most recent data.[33,34] Prior guidelines indicated that mortality advantages of thrombolytics in patients with intermediate-risk PE may be difficult to demonstrate in randomized trials given the relatively low event rates seen in this population and the difficulty and expense of organizing such trials.[35] If the results of our meta-analysis are confirmed by future randomized clinical trials, there may be a shift in the treatment of selected patients with intermediate-risk PE using thrombolytics. It is important to consider that mortality rates in the anticoagulant group in our analysis of intermediate-risk PE patients were at the lower end of mortality rates previously described in epidemiologic literature.[36-38] Further study is needed to confirm our findings over longer follow-up.

Enthusiasm regarding a potential mortality advantage observed in the current analysis of thrombolytic agent use in intermediate-risk PE needs to be tempered with pragmatism, especially in view of the significant associations with major bleeding noted. Although some prior studies have found comparable risk of major bleeding among elderly and nonelderly patients,[39] our results show a significantly higher associated risk of major bleeding in populations older than 65 years (although the current analysis remains limited by availability of only the mean ages of the individual trial populations). Attenuation of the bleeding risk in individuals 65 years and younger may suggest a stronger case for consideration of thrombolysis in those patients. These findings are consistent with reports from the Pulmonary Embolism Thrombolysis (PEITHO) trial, the largest randomized trial of thrombolytic therapy in PE, which showed higher rates of bleeding outcomes in elderly patients older than 75 years.[8] It should be noted that all included trials specified standard exclusion criteria for thrombolytic therapy, including recent major surgery or trauma; active or recent bleeding; intracranial trauma, hemorrhage, or mass; severe uncontrolled hypertension; pregnancy; and recent stroke or transient ischemic attack, among others. Hence, the current results should not be applied to patients who are thought to be at unusually elevated risk for bleeding or ICH.

Risk stratification models for bleeding in all patients, but especially the elderly, are warranted to identify the individuals at the highest risk of hemorrhagic complications[40,41] with thrombolytic therapy. Future research should also be directed toward concomitant use of other medications, especially the "novel oral anticoagulants" in conjunction with thrombolytics in patients with hemodynamically stable PE.[42] Additionally, research should focus on standardization of dosages of thrombolytics and method of administration (peripheral intravenous vs catheter-directed therapy into the pulmonary arteries) to accrue maximal clinical benefits with minimization of bleeding risk.

Our study has limitations. Definitions for hemodynamic instability or shock, major bleeding, and minor bleeding were not standardized, and in some instances, no definition was provided. Primary outcomes were reported at varying time intervals. Varying doses and types of thrombolytic therapy were used across the 16 included analyses. The width of the confidence interval for an individual study depends to a large extent on the sample size, while width of a confidence interval for a meta-analysis depends on the precision of the individual study estimates and on the number of studies combined.[13] Although the relatively wide confidence intervals for some of our analyses may be considered to weaken the conclusions, we have attempted to overcome that issue with robust sensitivity analyses congruent with overall outcomes and TSA that corroborate that further randomized evidence is unlikely to change the overall conclusions derived with the present level of evidence. Only a single, small included study evaluated the use of catheter-directed thrombolysis, and the overall results did not materially change with exclusion of this trial. Therefore, the results of the present study should be interpreted in the context of systemic thrombolysis through a peripheral intravenous catheter. Both the reported efficacy and safety outcomes are not necessarily generalizable to therapy with catheter-directed thrombolysis. Our study does not suggest a benefit of treatment of low-risk PE with thrombolytic therapy because less than 10% of our examined population had objective evidence of this. The lack of availability of patient-level data across the 16 trials precluded a full evaluation to identify patient characteristics associated with the maximal clinical benefits and the highest risks.

Conclusions

Thrombolytic therapy was associated with lower all-cause mortality in patients with PE, including the subset of patients with hemodynamically stable PE associated with RV dysfunction. The associated risks of major bleeding and ICH were significantly elevated with thrombolytic therapy, although there may be reduced harm in patients younger than 65 years. Results reported here should not be construed to apply to patients with low-risk PE.

ARTICLE INFORMATION

Author Contributions: Dr Giri had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kadakia, Mukherjee, Giri.
Acquisition, analysis, or interpretation of data: Chatterjee, Chakraborty, Weinberg, Wilensky, Sardar, Kumbhani, Mukherjee, Jaff, Giri.
Drafting of the manuscript: Chatterjee, Sardar, Mukherjee, Giri.
Critical revision of the manuscript for important intellectual content: Chakraborty, Weinberg, Kadakia, Wilensky, Sardar, Kumbhani, Mukherjee, Jaff, Giri.
Statistical analysis: Chatterjee, Giri.
Administrative, technical, or material support: Chakraborty, Giri.
Study supervision: Kadakia, Wilensky, Kumbhani, Mukherjee, Jaff, Giri.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Jaff reported having served as a consultant to AstraZeneca; having received support from EKOS Corporation, Embolitech, Boston Scientific, and Cordis Corporation; and being a board member for VIVA Physicians, a 501(c)(3) not-for profit education and research organization. Dr Wilensky reported being a member of the scientific advisor boards of Cardiostem, GenWay, Soteria, and Vascular Magnetics and having equity interest in Johnson & Johnson. No other disclosures were reported.

REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38(4)(suppl):S495-S501.

2. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341(8844):507-511.

3. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347(15):1143-1150.

4. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110(6):744-749.

5. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. *J Am Coll Cardiol*. 2002;40(9):1660-1667.

6. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. *Am J Med*. 2012;125(5):465-470.

7. Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123(16):1788-1830.

8. Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402-1411.

9. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12(4):459-468.

10. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol*. 2013;111(2):273-277.

11. Fasullo S, Scalzo S, Maringhini G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. *Am J Med Sci*. 2011;341(1):33-39.

12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-W94.

13. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions [version 5.1.0, updated March 2011]. http://handbook.cochrane.org/. Accessed December 20, 2013.

14. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27(5):335-371.

15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

16. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med*. 2007;120(8):700-705.

17. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*. 2008;61(1):64-75.

18. Higgins JP, Whitehead A, Simmonds M. Sequential methods for random-effects meta-analysis. *Stat Med*. 2011;30(9):903-921.

19. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86.

20. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol*. 2008;61(8):763-769.

21. Thorlund K, Engstrøm J, Wetterslev J, et al. *User Manual for Trial Sequential Analysis (TSA): Copenhagen Trial Unit*. Copenhagen, Denmark: Centre for Clinical Intervention Research; 2011:1-115.

22. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest*. 1990;98(6):1473-1479.

23. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism: Plasminogen Activator Italian Multicenter Study 2. *J Am Coll Cardiol*. 1992;20(3):520-526.

24. Jerjes-Sanchez C, Ramírez-Rivera A, Arriaga-Nava R, et al. Streptokinase and heparin vs heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227-229.

25. Ly B, Arnesen H, Eie H, Hol R. A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. *Acta Med Scand*. 1978;203(6):465-470.

26. Marini C, Di Ricco G, Rossi G, Rindi M, Palla R, Giuntini C. Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: a randomized clinical trial. *Respiration*. 1988;54(3):162-173.

27. PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED Investigators. *Chest*. 1990;97(3):528-533.

28. Tibbutt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *Br Med J*. 1974;1(5904):343-347.

29. Becattini C, Agnelli G, Salvi A, et al; TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res*. 2010;125(3):e82-e86.

30. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129(4):479-486.

31. The Urokinase Pulmonary Embolism Trial. Urokinase pulmonary embolism trial: phase 1 results: a cooperative study. *JAMA*. 1970;214(12):2163-2172.

32. Dong BR, Hao Q, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2009;(3):CD004437.

33. Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e419S-e494S.

34. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing [CG144]. National Institute for Health and Care Excellence. http://guidance.nice.org.uk/CG144. Accessed May 27, 2014.

35. Weinberg I, Jaff MR. Accelerated thrombolysis for pulmonary embolism: will clinical benefit be ULTIMAtely realized? *Circulation*. 2014;129(4):420-421.

36. Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J*. 2008;29(12):1569-1577.

37. Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. *Chest*. 2001;120(1):120-125.

38. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116(4):427-433.

39. Goldhaber SZ. Thrombolysis in pulmonary embolism: a large-scale clinical trial is overdue. *Circulation*. 2001;104(24):2876-2878.

40. Meneveau N, Bassand JP, Schiele F, et al. Safety of thrombolytic therapy in elderly patients with massive pulmonary embolism: a comparison with nonelderly patients. *J Am Coll Cardiol*. 1993;22(4):1075-1079.

41. Ruíz-Giménez N, Suárez C, González R, et al; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism: findings from the RIETE Registry. *Thromb Haemost*. 2008;100(1):26-31.

42. Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297.