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ORIGINAL ARTICLE

Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism

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Summary. *Background:* While the primary therapy for most patients with a pulmonary embolism (PE) consists of anticoagulation, the efficacy of thrombolysis relative to standard therapy remains unclear. *Methods:* In this retrospective cohort study of 15 944 patients with an objectively confirmed symptomatic acute PE, identified from the multicenter, international, prospective, Registro Informatizado de la Enfermedad TromboEmbólica (RIETE registry), we aimed to assess the association between thrombolytic therapy and all-cause mortality during the first 3 months after the diagnosis of a PE. After creating two subgroups, stratified by systolic blood pressure (SBP) (< 100 mm Hg vs. other), we used propensity score-matching for a comparison of patients who received thrombolysis to those who did not in each subgroup. *Results:* Patients who received thrombolysis were younger, had fewer comorbid diseases and more signs of clinical severity compared with those who did not receive it. In the subgroup with systolic hypotension, analysis of propensity score-matched pairs (n = 94 pairs) showed a non-statistically significant but clinically relevant lower risk of death for thrombolysis compared with no thrombolysis (odds ratio [OR] 0.72; 95% confidence interval [CI], 0.36–1.46; P = 0.37). In the normotensive subgroup, analysis of propensity score-matched pairs (n = 217 pairs) showed a statistically significant and clinically meaningful increased risk of death for thrombolysis compared with no thrombolysis (OR 2.32; 95% CI, 1.15–4.68; P = 0.018). When we imputed data for missing values for echocardiography and troponin tests in the group of normotensive patients, we no longer detected the increased risk of death associated with thrombolytic therapy. *Conclusions:* In normotensive patients with acute symptomatic PE, thrombolytic therapy is associated with a higher risk of death than no thrombolytic therapy. In hemodynamically unstable patients, thrombolytic therapy is possibly associated with a lower risk of death than no thrombolytic therapy. However, study design limitations do not imply a causal relationship between thrombolytics and outcome.

Keywords: prognosis, pulmonary embolism, survival, thrombolysis.

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Introduction

Although most patients with an acute pulmonary embolism (PE) have an uncomplicated clinical course associated with standard anticoagulation, the overall 3-month mortality rate exceeds 15% [1]. During the first 30 days after diagnosis of a PE, right ventricular (RV) failure causes approximately half of the deaths [1,2].

Hemodynamic status remains the most important short-term prognostic factor for patients with an acute PE. A massive PE, defined by the presence of arterial hypotension or cardiogenic shock, accounts for 5% of all cases of PE and has a short-term mortality of at least 15% [3]. The high risk of death in patients with PE and associated hypotension or shock may improve the risk–benefit ratio of escalated treatment (e.g. thrombolysis) [4,5]. In the absence of large randomized clinical trials that demonstrate the benefit of thrombolytic therapy on mortality, the American College of Chest Physicians (ACCP) guidelines recommended the use of thrombolytic therapy for (i)

patients with an acute symptomatic PE and hemodynamic instability that do not have major contraindications owing to bleeding risk (Grade 2C), and (ii) selected high-risk patients without hypotension and a low risk of bleeding (Grade 2C) [4]. Although the American Heart Association (AHA) also recommends consideration of thrombolysis for patients with a submassive acute PE [2], a previous clinical trial did not demonstrate any significant mortality reduction in hemodynamically stable patients with a acute PE and RV dysfunction who received thrombolytic therapy [6].

In a large, state-wide sample of patients hospitalized for an acute PE, Ibrahim *et al.* [7] found that patients who received thrombolytic therapy had a significantly higher risk of death in the 30 days after admission in comparison to those that did not receive thrombolytics. Among the small subgroup with a relatively high predicted probability of receiving thrombolysis (the 7.5% with propensity scores > 0.057), treatment with thrombolysis did not show an increased risk. In the subgroup of patients with PE-associated systolic hypotension ($n = 1557$), thrombolytic therapy did not have a significant effect on survival [7].

Given the uncertainty surrounding survival effects of thrombolysis in patients with an acute PE, the present study was conducted to assess the association between thrombolytic therapy and all-cause mortality within each of the two subgroups, stratified by systolic blood pressure (SBP) (< 100 mm Hg vs. other), during the first 3 months after the diagnosis of an acute symptomatic PE. The study analyzed data from patients with a symptomatic acute venous thromboembolism (VTE) enrolled in an international, multicenter, prospective registry [8,9].

Methods

Study design

The present study used a retrospective cohort design to assess data from patients enrolled in the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE registry) [8,9].

Study cohort

At each participating site, RIETE investigators enrolled consecutive patients that had an acute symptomatic PE confirmed by objective testing that consisted of high-probability ventilation-perfusion (V/Q) scintigraphy [10] or positive contrast-enhanced, PE-protocol, helical chest computerized tomography (CT) [single or multi-detector CT] [11]. Alternatively, the registry considered PE present in patients with inconclusive V/Q scans or negative CT scans that also had a lower limb venous compression ultrasonography positive for proximal DVT [12]. RIETE did not enforce a diagnostic algorithm. RIETE also did not enforce a treatment algorithm, though it excluded those patients who participated in a blinded venous thromboembolism treatment trial. All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements. The RIETE coordinating center used multiple data quality control procedures to optimize data quality [9]. Briefly, participating physicians aimed to enroll consecutive eligible patients. Site investigators or designees recorded data on a computer-based case report form and submitted the forms to a centralized coordinating center through a secure website. The study coordinating center responsible for all data management assigned patients with a unique identification number to maintain patient confidentiality. The coordinating center regularly monitored the data to detect inconsistencies or errors, and sent queries to each site which required resolution by the local coordinators. During periodic visits to participating hospitals that compared medical records with the submitted data, contract research organizations also monitored data quality.

Baseline variables

Patients enrolled in RIETE had the following data from around the time of PE diagnosis collected: age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (< 30 days before a PE) major bleeding; the presence of risk factors for PE including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal or support therapy]); recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ≥ 4 days in the 2 months before PE diagnosis); surgery (defined as those who had undergone major surgery in the 2 months before a PE); echocardiographic findings (if available); and laboratory results at hospital admission that included serum creatinine, troponin and arterial oxygen tension (PaO_2).

Study outcomes

The RIETE investigators assessed mortality using medical record review, and proxy interviews when necessary. The present study used 90-day all-cause mortality as the primary outcome, and selected 30- and 15-day all-cause mortality as secondary endpoints.

Treatment and follow-up

Clinicians at RIETE-enrolling sites managed patients according to their local practice (i.e. no standardization of treatment). Most patients received initial anticoagulation with intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH), and overlap and long-term therapy with an oral vitamin K antagonist. Clinicians administered thrombolytic treatment and/or inotropic support as deemed appropriate. In general, clinicians used thrombolytic treatment of an acute PE in patients with cardiogenic shock (e.g. persistent systolic arterial pressure of < 100 mm Hg in the setting of clinical signs of organ hypoperfusion [clouded sensorium, oliguria, cold and clammy skin or lactic acidosis]). In most patients with a contraindication to or a failure (i.e.

VTE recurrence while on therapeutic doses of anticoagulation) of anticoagulant treatment, clinicians used inferior vena cava (IVC) filter therapy followed by anticoagulation if and when the contraindication resolved. RIETE recorded information related to patient outcomes through 3 months after the diagnosis of the acute PE.

Statistical analysis

We *a priori* expected that blood pressure might confound the relationship between the administration of thrombolytic therapy and mortality. Thus, we performed analyses stratified by SBP (< 100 mm Hg vs. other). We chose to select a less stringent definition for hypotension since we expected that a cutoff of 90 mm Hg would reduce even more the relatively small sample size of the propensity-matched cohorts.

We used the chi-square or Fisher's exact tests to compare categorical data between subgroups. We used the Kolmogorov–Smirnov test to assess continuous data for a normal distribution. We used two-tailed paired *t*-tests to assess normal continuous data between the propensity-matched groups, and we used the Mann–Whitney *U*-test for non-normally distributed continuous data comparisons.

As clinicians did not randomly allocate thrombolytic therapy, the patients who received thrombolysis probably systematically differed from patients who did not with respect to baseline characteristics, clinical course, clinical examination and test findings, and comorbid conditions. As these characteristics also probably had a relationship to mortality, we used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving thrombolytic therapy [13]. We used logistic regression to estimate propensity scores. We modeled the receipt of thrombolytic therapy using baseline demographic and clinical variables that had a potential relationship to the receipt of thrombolytic therapy or a clinical likelihood of influencing a decision regarding thrombolytic therapy. These variables included: patient age at time of diagnosis of PE; presence or absence of recent (< 30 days before a PE) major bleeding; and presence or absence of risk factors for PE that included active cancer (defined as newly diagnosed cancer or cancer that is being treated), recent immobility, or surgery; clinical signs and symptoms on admission, including tachycardia (heart rate ≥ 110) and hypoxemia (oxyhemoglobin saturation < 90%); and abnormal serum creatinine levels (> 2 mg dL^{-1}).

After generation of the propensity scores, we sought to estimate the reduction in 90-day overall mortality attributable to the use of thrombolysis by using a matched-paired analysis. We used a greedy matching method, in which we randomly select a treated subject. The method then selected the nearest untreated subject for matching with the treated subject within a fixed caliper width of 0.02 [14]. To assess the success of the matching procedure, we measured standardized differences (measured in percentage points) in observed confounders between the matched groups [15].We estimated the logistic regression model using generalized estimating equation (GEE) methods to incorporate the matched-pairs design [16].

For the primary outcome assessment, we also used multivariable logistic regression to determine the adjusted association of thrombolysis with 3-month mortality in the entire sample (n = 15,944). Since a significant proportion of the patients had missing echocardiographic (77%) and troponin (62%) data, we performed a sensitivity analysis that used imputed data. In order to evaluate whether troponin testing and echocardiographic findings influenced the study results, we imputed these variables' missing data using the multiple imputations by chained equation method [17], which resulted in 10 imputed data sets. We independently analyzed each of the 10 data sets. We averaged estimates of the variables to give a single mean estimate and adjusted the standard error (SE) according to the rules of Rubin [18].

To assess the robustness of the findings, we performed similar analyzes that used a different blood pressure cut-off to define the hypotensive (< 90 mm Hg) and normotensive (≥ 90 mm Hg) groups. To further address the mortality outcome, we also estimated the effect of thrombolysis on 15- and 30-day overall mortality.

We used two-tailed probability values for all analyzes. We used Stata, version 10.2 (StataCorp, College Station, TX, USA) for Windows for most analyzes, whereas we used psmatch2 in Stata 11.1 for the propensity score analyzes, and the ice system for multiple imputation of missing values [19].

Results

Of the 15 944 patients with objectively confirmed acute PE enrolled in RIETE during the study period, the eligible study cohort included 7351 men and 8593 women.

In the vast majority of patients, clinicians diagnosed PE by a positive PE-protocol CT (73%; 11 641 of 15 944 patients) or a high-probability V/Q scan (28%; 4438 of 15 944 patients). Clinicians used CCUS results to assist with the diagnosis of PE in 929 (5.8%; 95% confidence interval [CI], 5.5%–6.2%) patients with an inconclusive V/Q scans or negative CT scans. At the time of admission to the hospital, 1212 of patients (7.6%) had systolic blood pressure (SBP) levels < 100 mm Hg. Of the 15 944 patients, 15 742 patients (99%) received initial therapy with LMWH, 2251 (14%) received UFH, 470 (2.9%) received an inferior vena cava filter and 432 (2.7%) received thrombolytic therapy. Of the 432 patients that received thrombolytic therapy, 134 (31%) had SBP levels < 100 mm Hg and 298 had SBP levels ≥ 100 mm Hg.

The RIETE registry had alive/dead status information for all patients through the 3-month study follow-up period. Overall, 10.3% of patients died (1638 out of 15 944, 10.3%; 95% CI, 9.8%–10.7%). Approximately one-quarter (415 of 1638 patients, 25.3%; 95% CI, 23.2%–27.5%) of the deaths were ascribed to PE. Cancer (23.7%; 389 of 1638 patients), cardiopulmonary disease (13.6%; 223 of 1638), infection (8.1%; 133 of 1638 patients), bleeding (6.1%; 100 of 1638 patients) other miscellaneous diseases (7.6%; 125 of 1638

patients) and unknown disorders (15.4%; 253 of 1638 patients) caused the other deaths.

Of the patients who received thrombolytic therapy, 12% (52 of 432 patients; 12.0%; 95% CI, 9.0%–15.1%) died during the 3-month study follow-up period. About 10% (1586 of 15 512 patients; 10.2%; 95% CI, 9.7%–10.7%) of those who did not receive thrombolytic therapy died (absolute difference 1.8%; 95% CI of the absolute difference, −1.4% to 4.9%; $P = 0.26$) during follow-up. In the entire cohort of 15 944 patients with a acute PE, there was a trend towards increased 90-day bleeding-related mortality in patients who received thrombolytics (1.16% [95% CI, 0.38–2.68] vs. 0.61% [95% CI; 0.5–0.75]; $P = 0.16$).

Baseline patient characteristics by treatment group and systolic blood pressure

As shown in Table 1, in the hypotensive subgroup of patients (i.e. SBP < 100 mm Hg), those who received thrombolysis were younger, had fewer comorbid diseases (cancer and chronic heart disease) and more signs of clinical severity (syncope, tachycardia, hypoxemia and an elevated troponin testing) compared with those that did not receive thrombolysis. Similarly, in the normotensive subgroup of patients (i.e. SBP ≥ 100 mm Hg), those who received thrombolysis were younger, had fewer comorbid diseases (cancer, chronic heart disease, chronic pulmonary disease and recent surgery) and more signs of clinical severity (syncope, dyspnea, tachycardia, hypoxemia and an elevated troponin testing) compared with patients that did not receive thrombolysis. In the normotensive patients, those with immobility or higher creatinine levels were more likely to be treated with thrombolytics (Table 2).

Effect of thrombolytic therapy on mortality

Table 3 shows show propensity-score analysis variables and their statistics from the model. In the hypotensive subgroup of patients, those that were younger, had signs of clinical severity (tachycardia) or elevated creatinine at admission had a higher likelihood of receiving thrombolysis compared with those

Table 1 Clinical characteristics of patients with a pulmonary embolism (PE) and a systolic blood pressure < 100 mm Hg who did or did not receive thrombolysis

	Received thrombolysis $N = 134$	Did not receive thrombolysis $N = 1078$	P-value
Clinical characteristics			
Age, years (mean ± SD)	61 ± 18	68 ± 17	0.07
Age > 80 years (%)	16 (12)	292 (27)	< 0.001
Male gender (%)	63 (47)	440 (41)	0.17
Weight, kilograms (mean ± SD)	76.2 ± 16.2	71.3 ± 15.1	0.34
BMI, kilograms m^{-2}	27.4 ± 5.7	27.1 ± 5.6	0.97
Inpatients (%)	39 (29)	344 (32)	0.57
Risk factors for VTE (%)			
History of VTE	12 (8.9)	135 (12)	0.23
Cancer	20 (15)	281 (26)	0.005
Recent surgery	16 (12)	146 (13)	0.61
Immobilization for ≥ 4 days	37 (28)	383 (35)	0.07
Comorbid diseases (%)			
Chronic lung disease	11 (8.2)	129 (12)	0.25
Chronic heart disease	2 (1.5)	108 (10)	0.003
Recent major bleeding	3 (2.2)	44 (4.1)	0.30
Antiplatelet therapy*	15 (11.2)	172 (16)	0.19
NSAIDs*	4 (3.0)	61 (5.6)	0.29
Corticosteroids therapy*	4 (3.0)	92 (8.5)	0.04
Clinical symptoms and signs at presentation (%)			
Syncope	74 (55)	389 (36)	< 0.001
Chest pain	63 (47)	431 (40)	0.13
Dyspnea	112 (84)	856 (79)	0.31
Heart rate ≥ 110 min^{-1}*	87 (65)	398 (37)	< 0.001
Arterial oxyhemoglobin saturation (SaO_2) < 90%*	53 (39)	371 (34)	0.07
SBP < 90 mm Hg	82 (61)	501 (46)	0.001
Atrial fibrillation*	11 (8.2)	128 (12)	0.25
Laboratory findings			
Abnormal creatinine levels* (%)	41 (31)	311 (29)	0.69
Elevated troponin testing* (%)	51 (38)	202 (19)	0.006
Hemoglobin, g dL^{-1} (mean ± SD)*	12.9 ± 2.1	12.4 ± 2.2	0.91

SD, standard deviation; VTE, venous thromboembolism; NSAID, non-steroidal ani-inflammatory drugs; SBP, systolic blood pressure. *In the hypotensive study cohort, 4.2% of patients had unknown values for concomitant therapy, 0.9% for heart rate, 23.8% for arterial oxygen saturation, 9.5% for atrial fibrillation, 1.1% for creatinine, 53.9% for troponin, and 0.2% for hemoglobin.

Table 2 Clinical characteristics of patients with a pulmonary embolism (PE) and a systolic blood pressure ≥ 100 mm Hg who did or did not receive thrombolysis

	Received thrombolysis $N = 298$	Did not receive thrombolysis $N = 14\,434$	*P*-value
Clinical characteristics			
Age, years (mean ± SD)	58 ± 18	68 ± 16	< 0.001
Age > 80 years (%)	11 (3.7)	3318 (23)	< 0.001
Male gender (%)	152 (51)	6696 (46)	0.11
Weight (kg) (mean ± SD)	79.9 ± 17.2	74.4 ± 15.0	0.007
BMI, kilograms m^{-2}	28.7 ± 5.5	28.0 ± 5.4	0.68
Inpatients (%)	76 (25)	3805 (26)	0.72
Risk factors for VTE (%)			
History of VTE	48 (16)	2168 (15)	0.60
Cancer	37 (12)	3147 (22)	< 0.001
Recent surgery	22 (7.4)	1790 (12)	< 0.01
Immobilization for ≥ 4 days	45 (15)	3457 (12)	< 0.001
Comorbid diseases (%)			
Chronic lung disease	22 (7.3)	1876 (13)	0.005
Chronic heart disease	6 (2.0)	1111 (7.7)	< 0.001
Recent major bleeding	2 (0.7)	312 (2)	0.08
Antiplatelet therapy*	20 (6.7)	2021 (14)	< 0.001
NSAIDs*	5 (1.6)	693 (4.8)	0.02
Corticosteroids therapy*	13 (4.3)	967 (6.7)	0.13
Clinical symptoms and signs at presentation (%)			
Syncope	135 (45)	1863 (13)	< 0.001
Chest pain	157 (53)	6915 (48)	0.11
Dyspnea	268 (90)	11 685 (81)	< 0.001
Heart rate ≥ 110 min^{-1}*	120 (40)	2801 (19)	< 0.001
Arterial oxyhemoglobin saturation (SaO_2) < 90%*	95 (32)	3054 (21)	< 0.001
Atrial fibrillation*	17 (5.7)	1256 (8.7)	0.09
Laboratory findings			
Abnormal creatinine levels* (%)	68 (23)	2356 (16)	0.004
Elevated troponin levels* (%)	102 (34)	1444 (10)	< 0.001
Hemoglobin, g dL^{-1} (mean ± SD)*	13.6 ± 1.9	13.1 ± 2.0	0.77

SD, standard deviation; VTE, venous thromboembolism; NSAID, non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure. *In the normotensive study cohort, 5.0% of patients had unknown values for concomitant therapy, 2.4% for heart rate, 25.9% for arterial oxygen saturation, 10.3% for atrial fibrillation, 1.3% for creatinine, 62.9% for troponin, and 2.4% for hemoglobin.

without these characteristics. Those that had a diagnosis of cancer had a lower likelihood of receiving thrombolysis.

In the normotensive subgroup of patients, those that were younger, had signs of clinical severity (tachycardia and hypoxemia) or elevated creatinine at admission had a higher likelihood of receiving thrombolysis compared with those without these characteristics. Those that had cancer, immobilization or recent surgery had a lower likelihood of receiving thrombolysis.

Propensity analyzes of the subgroup of hypotensive patients used 94 matched pairs (94 patients from each group). The matched sample showed a good balance for each variable (Table 4). The matched analysis of the hypotensive subgroup showed a non-statistically significant trend towards a better survival for patients that received thrombolysis vs. those that did not (OR 0.72; 95% CI, 0.36–1.46; $P = 0.37$).

Propensity analyzes of the subgroup of normotensive patients used 217 matched pairs (217 patients from each group). The matched sample showed good balance for each variable (Table 4). The matched analysis of the normotensive subgroup showed a statistically significant lower survival for patients who received thrombolysis vs. those who did not (OR 2.32; 95% CI, 1.15–4.68; $P = 0.02$).

We found consistent effects of thrombolytic therapy on mortality when we also evaluated 15- or 30-day mortality. Similarly, we found consistent results when we stratified analyzes by a SBP < 90 mm Hg vs. other instead of using SBP < 100 mm Hg vs. other (Fig. 1). When we imputed missing values for echocardiography and troponin tests in the group of normotensive patients (i.e. SBP > 100 mm Hg), thrombolytic therapy did not show a significant effect on survival (Fig. 1).

Discussion

The results of the present study do not support the use of thrombolytic agents in most patients with an acute symptomatic PE. Among hemodynamically stable patients at presentation, those that received thrombolytic therapy had a statistically significant two-fold higher risk of all-cause death in the 90 days after admission when compared with those that did not receive thrombolysis. Bleeding as a result of

Table 3 Estimates and standard errors for variables included in the propensity score analysis

Variable	Estimate	SE	95% confidence limits		*z*	*P*-value
			Lower	Upper		
Systolic blood pressure < 100 mm Hg						
Age > 80 years	−1.13	0.33	−1.79	−0.48	−3.38	0.001
Previous bleeding	−0.21	0.77	−1.73	1.31	−0.27	0.79
Heart rate ≥ 110 min^{-1}	0.97	0.23	0.52	1.43	4.20	< 0.001
Cancer	−0.50	0.29	−1.07	0.07	−1.72	0.09
Surgery	−0.44	0.38	−1.18	0.30	−1.16	0.25
Immobilization	−0.36	0.25	−0.86	0.13	−1.44	0.15
Abnormal creatinine levels	0.50	0.24	0.03	0.97	2.08	0.04
Arterial oxyhemoglobin saturation (SaO2) < 90%	−0.27	0.23	−0.72	0.18	−1.19	0.24
Systolic blood pressure ≥ 100 mm Hg						
Age > 80 years	−1.98	0.31	−2.59	−1.36	−6.31	< 0.001
Previous bleeding	−1.09	1.01	−3.06	0.89	−1.08	0.28
Heart ≥ 110 min^{-1}	0.85	0.14	0.57	1.13	5.95	< 0.001
Cancer	−0.80	0.21	−1.22	−0.38	−3.71	< 0.001
Surgery	−1.01	0.33	−1.65	−0.37	−3.08	0.002
Immobilization	−0.59	0.19	−0.96	−0.22	−3.12	0.002
Abnormal creatinine levels	0.55	0.17	0.22	0.87	3.31	0.001
Arterial oxyhemoglobin saturation (SaO2) < 90%	−0.67	0.14	−0.95	−0.39	−4.72	< 0.001

Table 4 Baseline characteristics of the propensity matched pairs

Variable	Lysis (N = 94)	No lysis (N = 94)	Absolute standardized difference	
			Before matching (%)	After matching (%)
Systolic blood pressure < 100 mm Hg				
Age > 80 years	12 (12.8)	14 (14.9)	49.4	6.2
Previous bleeding	2 (2.1)	1 (1.1)	8.7	8.2
Heart rate ≥ 110 min^{-1}	59 (62.8)	60 (63.8)	59.2	2.3
Cancer	17 (18.1)	17 (18.1)	23.5	0
Surgery	9 (9.6)	6 (6.4)	12.0	10.4
Immobilization	27 (28.7)	27 (28.7)	14.0	0
Abnormal creatinine levels	35 (37.2)	35 (37.2)	19.4	0
Arterial oxyhemoglobin saturation (SaO2) < 90%	41 (43.6)	42 (44.7)	36.8	2.2
Variable	Lysis (N = 217)	No lysis (N = 217)	Before matching (%)	After matching (%)
Systolic blood pressure ≥ 100 mm Hg				
Age > 80 years	11 (5.1)	11 (5.1)	49.4	0
Previous bleeding	1 (0.5)	1 (0.5)	8.7	0
Heart rate ≥ 110 min^{-1}	88 (40.5)	88 (40.5)	59.2	0
Cancer	25 (11.5)	25 (11.5)	23.5	0
Surgery	10 (4.6)	10 (4.6)	12.0	0
Immobilization	35 (16.1)	35 (16.1)	14.0	0
Abnormal creatinine levels	51 (23.5)	51 (23.5)	19.4	0
Arterial oxyhemoglobin saturation (SaO2) < 90%	122 (56.2)	122 (56.2)	36.8	0

Values expressed as number (percentage).

thrombolysis did not completely account for the increased mortality. When we imputed data for missing values for echocardiography and troponin tests, we did not see an increased death rate associated with thrombolytic therapy in normotensive patients. For the subgroup of patients that had systolic hypotension associated with PE, those that received thrombolytic therapy had a non-statistically significant lower 90-day all-cause mortality compared with those that did not receive thrombolysis.

Patients with an acute PE have a relatively high short-term mortality rate. Although clinicians typically give thrombolysis in an attempt to decrease the risk of death from a PE, the indications for its use require further study [4,20]. Only one small randomized controlled trial has compared lytic therapy

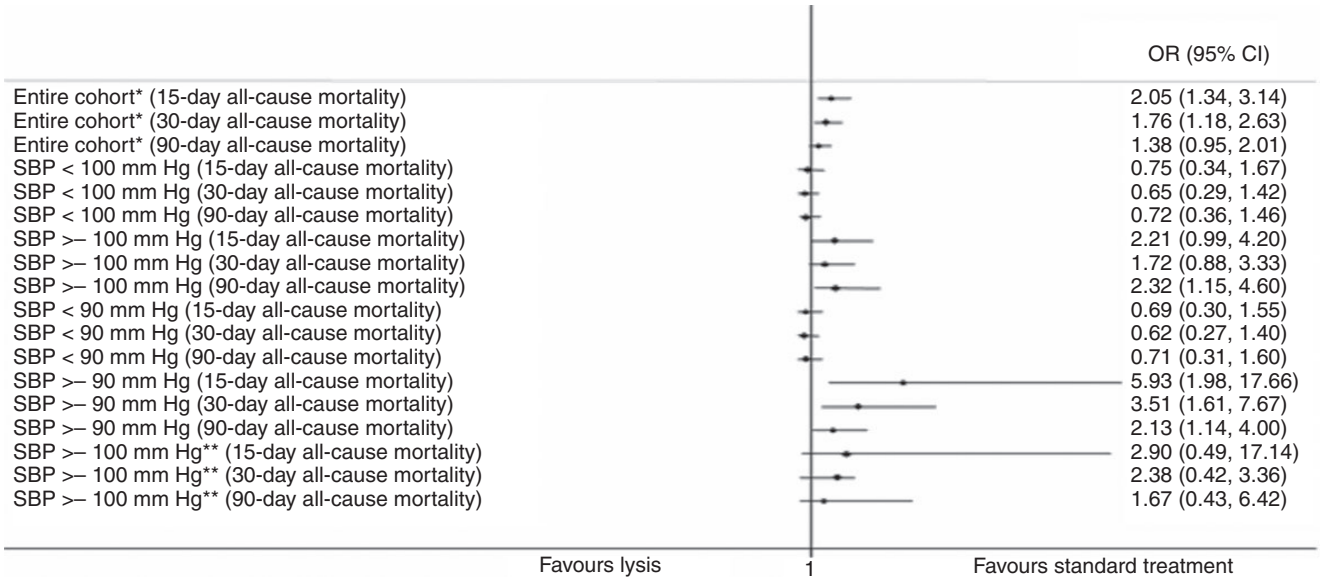

Fig. 1. Clinical outcomes after fibrinolysis for an acute symptomatic pulmonary embolism (PE). *Adjusted for age > 80 years (vs. other), SBP < 100 mm Hg (vs. other), HR ≥ 110 bpm (vs. other), previous bleeding, cancer, surgery, immobilization, abnormal creatinine levels and oxyhemoglobin saturation < 90% (vs. other). **After imputation of missing data for troponin testing and echocardiography. OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; HR, heart rate.

plus anticoagulation with anticoagulation alone in patients with a 'life-threatening' PE [21]. In the present study of a total of eight randomized patients, none of the four patients who received intrapulmonary streptokinase died, compared with four out of the four patients who received intrapulmonary heparin. One patient in each group experienced a major bleeding complication. Other randomized trials enrolled patient samples that had more heterogeneity in baseline characteristics or lower severity of illness. Pooled data from five trials that included hemodynamically unstable patients suggested that thrombolysis causes a significant reduction of the composite outcome of death *or* PE recurrence [22]. However, the pooled estimate from the trials revealed a non-statistically significant reduction in death associated with thrombolysis compared with heparin (6.2% vs. 12.7%; OR 0.47, 95% CI 0.20–1.10).

Hemodynamically stable patients with PE who do not have right ventricular dysfunction, or elevated biomarkers have a low risk of death from a PE when treated with conventional anticoagulation. In such patients, the risk of bleeding as a result of thrombolysis probably exceeds any potential benefit. A meta-analysis of nine studies of thrombolysis in heterogeneous groups of patients with PE demonstrated a pooled risk of major bleeding complications of approximately 13%, and this rate exceeded the rate of patients treated with heparin by almost 50% [23]. Moreover, a recent clinical trial did not demonstrate any significant mortality reduction in hemodynamically stable patients with an acute PE and RV dysfunction who received thrombolytic therapy [6].

The present study did not demonstrate a statistically significant lower mortality associated with thrombolytic therapy in unstable patients with PE. These results are consistent with the position of the ACCP guidelines on antithrombotic therapy, which issued a weak recommendation for administrating thrombolysis to patients with a PE and hypotension given the uncertainty of the benefit [4]. The ACCP guidelines also recommended against systemically administered thrombolytic therapy in most patients with an acute PE not associated with hypotension. Although this study showed a higher death rate in normotensive patients treated with thrombolytics for PE compared with those not treated with thrombolytics, the adverse effect of thrombolysis did not persist after we imputed values for missing echocardiographic and troponin testing results and redid the propensity score matching. Either of these findings supports the ACCP recommendation. An ongoing large, multinational, randomized trial, the Pulmonary EmbolIsm Thrombolysis (PEITHO) study (NCT00639743), aims to determine the efficacy and safety of early thrombolytic treatment in normotensive patients with RV dysfunction, as detected on an echocardiogram or CT scan, and evidence of myocardial injury, as indicated by a positive troponin test.

Some study methodological limitations may affect the findings and interpretation of the present study. Selection bias could have skewed the study sample. However, the broad range of patients with an acute symptomatic PE from multiple medical centers, countries and treatment settings enrolled in the RIETE registry decrease the likelihood of the inclusion of a skewed population in this study. In spite of the large number of patients assessed for this study from the RIETE registry, the relatively small sample size of the propensity-matched cohorts lowered the statistical power of the study and therefore raised the chance that the study would not detect a statistically significant difference in outcomes between the treatment groups (i.e. type II error). Although we accounted for many of the relevant potential confounding variables

available to us in our propensity score model, the possibility of residual confounding remains. The model likely did not capture data from all relevant variables that include the use of inotropic support and the presence of signs of shock or end-organ hypoperfusion. The study cohort may have received treatments based on certain baseline and prognostic characteristics, and this could have introduced a significant treatment bias. The selection of propensity score-matched cohorts for direct comparison allowed us to address the imbalance in distribution of characteristics that existed between patients who received and did not receive thrombolysis in the entire cohort. However, propensity score matching has its own limitations. For example, there is no consensus on what constitutes 'adequate' covariate balance between groups, and importantly, inference is valid only within the limits of the propensity-matched groups (i.e. we cannot draw conclusions for populations that are not represented in the matched groups). In addition to using the propensity scores, we used imputation for missing data and sensitivity analyzes to further address concerns of bias and to assess the robustness of the study findings. The similarity of the results from many of the sensitivity and secondary analyzes provided evidence of the robustness of the findings and further strengthened the soundness of the conclusions. Previous studies and meta-analyzes used surrogate and/or combined endpoints, whereas the present study focused on the clinically relevant question of whether thrombolysis influences all-cause mortality. Although this study did not prospectively assess the efficacy and safety of thrombolytic therapy, the population-based sample used described the effects of thrombolysis in 'real-world' clinical care and enhanced the generalizability of the findings.

In conclusion, the present study did not detect a survival advantage associated with the use of thrombolytic agents in most normotensive patients with acute symptomatic PE. Results of the sensitivity analysis with imputed data suggest that improved methods of risk stratification and additional randomized controlled trials might help to identify subgroups of patients at high risk of death that might have a favorable risk-to-benefit ratio for treatment with systemic thrombolysis.

Addendum

Study concept and design: A. Riera-Mestre, D. Jiménez, L. Moores, R.D. Yusen, M. Monreal. Acquisition of data; analysis and interpretation of data; statistical analysis: A. Riera-Mestre, D. Jiménez, A. Muriel, J.L. Lobo, L. Moores, R.D. Yusen, I. Casado, D. Nauffal, M. Oribe, M. Monreal. Drafting of the manuscript: A. Riera-Mestre, D. Jiménez, A. Muriel, L. Moores, R.D. Yusen, M. Monreal. Critical revision of the manuscript for important intellectual content: A. Riera-Mestre, D. Jiménez, A. Muriel, J.L. Lobo, L. Moores, R.D. Yusen, I. Casado, D. Nauffal, M. Oribe, M. Monreal. Study supervision: D. Jiménez, M. Monreal. The corresponding author, D. Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

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