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Clinical research study

TREATMENT OF RIGHT HEART THROMBI ASSOCIATED WITH ACUTE PULMONARY EMBOLISM

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HIGHLIGHTS

The optimal management of right heart thrombi in patients who present with acute symptomatic pulmonary embolism lacks clarity.

Right heart thrombi may not warrant riskier interventions than standard anticoagulation.

Our findings provide a rationale for further trials to assess the efficacy and safety of reperfusion therapy for right heart thrombi associated with pulmonary embolism.

ABSTRACT

Background: Evidence-based recommendations do not adequately address the treatment of right heart thrombi in patients who present with acute symptomatic pulmonary embolism.

Methods: This study included patients who had acute pulmonary embolism associated with right heart thrombi and participated in the RIETE registry. We assessed the effectiveness of anticoagulation versus reperfusion treatment for the outcomes of all-cause mortality, pulmonary embolism-related mortality, recurrent venous thromboembolism and major bleeding rates through 30 days after initiation of pulmonary embolism treatment. We used propensity score matching to adjust for the likelihood of receiving reperfusion treatment.

Results: Of 325 patients with pulmonary embolism and right heart thrombi, 255 (78%; 95% confidence interval [**CI**], 74-83%) received anticoagulation and 70 (22%; 95% CI, 17-26%) also received reperfusion treatment. Propensity score-matched pairs analyses did not detect a statistically lower risk of all-cause death (6.2% vs. 14%, *P* = 0.15) or pulmonary embolism-related mortality (4.7% vs. 7.8%; *P* = 0.47) for reperfusion compared with anticoagulation. Of the patients who received reperfusion treatment, 6.2% had a recurrence during the study follow-up period, compared to 0% of those who received anticoagulation (*P* = 0.049). The incidence of major bleeding events was not statistically different between the two treatment groups (3.1% vs. 3.1%; *P* = 1.00).

Conclusions: In patients with pulmonary embolism and right heart thrombi, no significant difference was found between reperfusion therapy and anticoagulant therapy for mortality and bleeding. The risk of recurrences was significantly higher for reperfusion therapy compared with anticoagulation. Right heart thrombi may not warrant riskier interventions than standard anticoagulation.

Abstract word count: 253

Key words: Pulmonary embolism; right heart thrombi; treatment; anticoagulation; thrombolysis.

INTRODUCTION

Pulmonary embolism ranks high among the causes of cardiovascular mortality (1, 2). Haemodynamic decompensation after acute pulmonary embolism most strongly predicts pulmonary embolism-related poor outcome (3). Alternatively, patients who do not have hypotension and evidence of right ventricular dysfunction have a low short-term mortality rate. Though coexisting right heart thrombi do not commonly occur in patients who have acute symptomatic pulmonary embolism, studies have validated right heart thrombi as predictor of poor outcome (4-6).

Management options for patients who have pulmonary embolism associated with right heart thrombi include anticoagulation, systemic or catheter-directed thrombolysis, and surgical embolectomy (7). Though the European Society of Cardiology (**ESC**) guidelines suggest the use of thrombolysis for patients with acute symptomatic pulmonary embolism and coexisting right heart thrombi (8), studies have not clearly determined which patients with pulmonary embolism and right heart thrombi would benefit from reperfusion treatment. In the absence of randomized clinical trials that assess the effects of reperfusion therapy plus anticoagulation versus anticoagulation alone for right heart thrombi associated with pulmonary embolism, investigators may use observational studies to examine and infer treatment effects. Though retrospective observational studies may suffer from various types of bias, propensity scores may reduce the impact of any imbalance in pre-treatment patient characteristics and may address concerns about confounding.

Given the lack of data supporting the efficacy and safety of reperfusion therapy in patients with acute pulmonary embolism and right heart thrombi, we conducted this study of data collected for the Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**) Registry (9). The study compared outcomes during the first month after treatment for an acute symptomatic pulmonary embolism in patients that had coexisting right heart thrombi for those who receive reperfusion treatment (i.e., thrombolysis, surgery) with a propensity matched cohort of those who did not.

METHODS

Study design

Previous publications have shown the design, methods and main results of the large international contemporary RIETE registry (10-13). Eligibility for this study consisted of objectively diagnosed acute symptomatic pulmonary embolism, coexisting right heart thrombi, and treatment with reperfusion therapy followed by anticoagulation or anticoagulation alone. We used a Registry enrolment dates of January 1, 2001, through December 15, 2015. Pulmonary embolism confirmation by objective testing consisted of high probability ventilation-perfusion scintigraphy (14), or positive contrast-enhanced, pulmonary embolism-protocol, helical chest computerized tomography for pulmonary embolism (15). Right heart thrombi were diagnosed with the use of echocardiographic examination. Reperfusion treatment included administration of (systemic or catheter-directed) thrombolysis or cardiac surgery around the time of pulmonary embolism diagnosis because of coexisting right heart thrombi. All patients provided written or oral consent for participation in the Registry in accordance with local ethics committee requirements.

Covariates of interest

Patients enrolled in RIETE had data collected from around the time of pulmonary embolism diagnosis that included but was not limited to: age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to pulmonary embolism) major bleeding; presence of risk factors for pulmonary embolism 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 prior to pulmonary embolism diagnosis), surgery (defined as those who had undergone major surgery in the 2 months prior to pulmonary embolism); clinical signs and symptoms on admission,

including heart rate and systolic blood pressure; and laboratory results at hospital admission that included hemoglobin, platelet count and serum creatinine.

Outcome measures

We identified all-cause mortality through 30 days following the diagnosis of pulmonary embolism as the primary endpoint, and 30-day pulmonary embolism-related mortality, recurrent venous thromboembolism, and major bleeding as secondary endpoints. The RIETE investigators used medical record review to assess vital status. For patients that died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those following a clinically severe pulmonary embolism, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal pulmonary embolism. The RIETE investigators defined recurrent deep vein thrombosis as a new noncompressible vein segment, or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography (16); recurrent pulmonary embolism as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography of the chest (15); and major bleeding episodes as those that required a transfusion of at least 2 units of blood, were retroperitoneal, spinal or intracranial, or were fatal (17).

Statistical analysis

We used chi-square or Fisher's exact tests to compare categorical data between groups. We used the Shapiro-Wilk test to assess continuous data for a normal distribution. We used two-tailed unpaired t-tests to compare normally distributed continuous data between two unpaired groups, and we used the Mann-Whitney U test for non-normally distributed continuous data comparisons. We used multivariate adjustment for the simplified Pulmonary Embolism Severity Index (18), and recent bleeding, to see if reperfusion treatment was an

independent significant predictor of all-cause mortality in the entire sample (n = 325).

Since clinicians did not randomly allocate reperfusion therapy, the patients who received reperfusion treatment likely systematically differed from patients who did not with respect to baseline characteristics, clinical course, clinical examination and test findings, and comorbid conditions. We used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving reperfusion therapy (19). We used logistic regression to estimate propensity scores. We modeled the log odds of the probability that a patient received reperfusion therapy by using baseline demographic and clinical variables (see Baseline variables for definitions) that were previously shown to be associated with mortality or treatment selection. These variables included: the simplified Pulmonary Embolism Severity Index (age > 80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate $\geq$ 110 beats/minute, systolic blood pressure < 100 mm Hg, and oxyhemoglobin saturation < 90%), recent bleeding, immobilization and concomitant deep vein thrombosis.

After generation of the propensity scores, we sought to estimate the reduction in 30-day overall mortality attributable to the reperfusion treatment by using a greedy matched-paired analysis that has a 1:1 matching algorithm and does not allow for replacements. We randomly selected a patient in the reperfusion therapy group and then matched that patient with the nearest patient in the anticoagulant group within a fixed caliper width of 0.15 (0.25 of the standard deviation of the logit of the propensity score) (20). To assess the success of the matching procedure, we measured standardized differences (measured in percentage points) in observed confounders between the matched groups (21). We estimated the reperfusion therapy effect using generalized estimating equation (**GEE**) methods to incorporate the matched-pairs design, and adjusted for those covariates that remained unbalanced after matching (22).

We used psmatch2 for the propensity score analyses, and we used Stata, version 14.1 (StataCorp, College Station, Texas) for Windows, for all other analyses.

RESULTS

During the 15-year study period, we identified a total of 325 (2.6%; 95% confidence interval [**CI**], 2.3-2.9%) patients who had objectively confirmed symptomatic PE and coexisting right heart thrombi (**Figure 1)**. Of these, 255 (78%; 95% CI, 74-83%) received anticoagulation alone and 70 (22%; 95% CI, 17-26%) received anticoagulation plus reperfusion treatment (systemic thrombolysis, 58 [17.9%; 95% CI, 13.8-22.5%]; surgery, 12 [3.7%; 95% CI, 1.9-6.4%]).

Patients who received reperfusion therapy differed significantly from those who received anticoagulation in preexisting medical conditions, and in relevant clinical, physiologic and laboratory parameters. As shown in **Table 1**, patients who received reperfusion therapy were older, and had a higher prevalence of high-risk simplified Pulmonary Embolism Severity Index, immobilization, and concomitant deep vein thrombosis compared to those who received anticoagulation alone. Patients who received reperfusion treatment were also more hemodynamically compromised than patients who received anticoagulation alone, with lower systolic blood pressure, higher heart rate, and more frequent hypoxemia, syncope, and right ventricle hypokinesis (**Table 1**). However, the two treatment groups had similar proportions of male gender, congestive heart failure, history of venous thromboembolism, cancer, surgery, and recent bleeding.

Outcome

Outcome data were available for all patients through the 30-day study follow-up (**Table 2**). Of the 28 of 325 patients that died (8.6%; 95% CI, 5.8% to 12.2%), 17 (17 of 325 patients; 5.2%; 95% CI, 3.1% to 8.2%) died from pulmonary

embolism, and 11 (11 of 325 patients; 3.4%; 95% CI, 1.7% to 6.0%) died from other causes.

Four deaths (4 of 70 patients; 5.7%; 95% CI, 1.6% to 14.0%) occurred in the reperfusion therapy group, whereas 24 deaths (24 of 255 patients; 9.4%; 95% CI, 6.1% to 13.7%) occurred in the anticoagulation group (absolute difference 3.7%; 95% CI of the absolute difference, -5.9% to 9.6%; P = 0.33). After adjustment by the simplified Pulmonary Embolism Severity Index and recent major bleeding, a multivariable showed a non-significant trend toward lower risk of all-cause death for reperfusion treatment compared with sole anticoagulant treatment (odds ratio [**OR**], 0.34; 95% CI, 0.10-1.11; *P* = 0.08) (**Table 3**).

Though pulmonary embolism-related mortality within 30-days of pulmonary embolism diagnosis occurred more frequently in patients who received anticoagulation (5.5% versus 4.3%; absolute difference [**AD**] 1.2%; 95% CI of the AD, -7.7% to 6.1%; P = 0.69), reperfusion therapy did not independently predict 30-day pulmonary embolism-related mortality in a multivariable model (**Table 3**).

Fatal and nonfatal recurrent venous thromboembolism within 30-days of pulmonary embolism diagnosis occurred in 4 patients (5.7%; 95% CI, 1.6% to 14.0%) who received reperfusion therapy, and in 2 patients (0.8%; 95% CI, 0.1% to 2.8%) who received sole anticoagulation therapy (AD 4.9%; 95% CI of the AD, 0.4% to 14.0%; *P* <0.01) (**Table 2**).

Overall, 15 of the 325 patients (4.6%; 95% CI, 2.6% to 7.5%) suffered a major bleeding episode. Three bleeds (3 of 70 patients; 4.3%; 95% CI, 0.9% to 12.0%) occurred in the group of patients receiving reperfusion therapy, whereas 12 bleeds (12 of 255 patients; 4.7%; 95% CI, 2.4% to 8.1%) occurred in the group who received anticoagulation (AD 0.4%; 95% CI of the absolute difference, -8.4% to 5.2%; P =0.88).

Propensity score-matched cohorts

The matching of patients presenting with acute pulmonary embolism and right heart thrombi yielded 64 patients treated with reperfusion procedures and 64 patients treated with anticoagulation. This model showed good to excellent discrimination with an AUC of 0.71. The standardized differences of less than 10% for all matched variables supported the assumption of balance between treatment groups in observed confounders (**Figure 2**).

Reperfusion therapy did not have a significantly lower mortality than non-reperfusion treatment in the matched cohort of patients with pulmonary embolism and right heart thrombi (6.2% vs. 14.1%; risk difference, 7.8%; 95% CI, –4.2% to 20.0%; *P* = 0.15) (**Table 4**). Reperfusion therapy did not have a significantly different risk of pulmonary embolism-related mortality in comparison to non-reperfusion therapy (4.7% vs. 7.8%; risk difference, 3.1%; 95% CI, -7.4% to 13.9%; *P* = 0.47). Of the patients who received reperfusion treatment, 6.2% had a venous thromboembolism recurrence during the study follow-up period in comparison to 0% of those who solely received anticoagulation (*P* = 0.049). The two treatment groups had the same proportion of patients who had a major bleeding event (3.1% vs. 3.1%; *P* = 1.00) (**Table 4**).

DISCUSSION

In this study of treatment propensity matched cohorts of patients who had acute symptomatic pulmonary embolism and coexisting right heart thrombi, we found no difference in short-term survival and major bleeding between the group that had reperfusion therapy and the group that only received anticoagulant therapy. However, reperfusion therapy was associated with a higher risk of recurrent venous thromboembolism than sole anticoagulation therapy.

Limited and conflicting data, all from non-randomized studies, support reperfusion therapy over anticoagulation in patients who have acute pulmonary embolism and coexisting right heart thrombi. For 119 patients with mobile right heart thrombi, the prospective multicenter European Cooperative Study on the

clinical significance of right heart thrombi found that short-term mortality was excessive (64%) in patients who received anticoagulation alone, compared with patients who received thrombolysis (40%) or surgery (27%) (23). In contrast, patients who enrolled in the International Cooperative Pulmonary Embolism Registry (**ICOPER**) with acute pulmonary embolism and coexisting right heart thrombi did not show differences in survival between the heparin, thrombolytic, and surgical treatment groups (23.5%, 20.8%, and 25.0%, respectively) (5). Our study did not demonstrate a significantly lower mortality associated with reperfusion therapy compared with anticoagulation alone. The absence of a detectable survival benefit of the reperfusion therapy may reflect an undersized study population and the limited power of the study to detect a difference in outcomes between the groups. However, assuming that reperfusion might have conferred a benefit in a larger study population, it seems reasonable to conclude that this benefit would have been relatively small.

Our study found a higher risk of recurrent venous thromboembolism associated with reperfusion therapy in comparison to sole anticoagulation. A previous trial that assessed the efficacy and safety of thrombolytic therapy in patients with acute deep vein thrombosis found that 9 (9%; 95% CI, 4.2-16.4%) patients who received systemic thrombolysis experienced subsequent symptomatic pulmonary embolism, whereas no recurrent pulmonary embolism occurred in patients that only received conventional anticoagulant therapy (24). In a retrospective study that used hospital discharge data, patients who received thrombolytics had a lower case fatality rate if they also received an inferior vena cava filter (25). It should be noted that these findings represent non-randomized data that may have been subject to bias; whether or not an inferior vena cava filter enhances safety for patients undergoing thrombolysis is not clear.

Putting our findings into context with other published studies, the data suggest that anticoagulation alone might be adequate treatment for most patients with pulmonary embolism and coexisting right heart thrombi. Reperfusion therapies might therefore be reserved for patients who have acute symptomatic pulmonary embolism and associated hypotension or shock, irrespective of the

presence or absence of coexisting right heart thrombi. Since patients with acute pulmonary embolism and coexisting right heart thrombi have a worse outcome when compared to those without right heart thrombi (26), a Pulmonary Embolism Response Team might assist with rapid mobilization of the necessary resources to provide the most appropriate care (27).

This study of the very large RIETE Registry has several limitations. The retrospective analysis of observational data may lack some clinical details that may be important determinants of patient selection and outcomes. Confounding may have affected the results of this observational study. We used propensity-score matching to make the patient groups comparable according to the measured confounders, and we successfully eliminated the observed differences. However, residual confounding may still have occurred. The relatively small sample size of patients who had pulmonary embolism associated with right heart thrombi and the fairly low event rates resulted in wide confidence intervals and a decreased ability to detect a significant association between treatment strategy and outcomes.

In conclusion, the results of this study of patients presenting with acute symptomatic pulmonary embolism and coexisting right heart thrombi suggest that there is no significant difference in mortality and major bleeding outcomes between reperfusion therapy and anticoagulant therapy. In addition, the risk of recurrent venous thromboembolism may be significantly higher for reperfusion therapy in comparison to sole anticoagulation. Well-designed studies should be carried out to further assess the efficacy and safety of reperfusion therapy for right heart thrombi associated with pulmonary embolism.

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Declaration of interests

None to be disclosed.

Author contributions

Study concept and design: Barrios, Chavant, Jimenez, Monreal

Acquisition of data; analysis and interpretation of data; statistical analysis: Barrios, Chavant, Jimenez, Bertoletti, Rosa-Salazar, Muriel, Viallon, Fernandez-Capitan, Yusen, Monreal

Drafting of the manuscript: Barrios, Chavant, Jimenez, Yusen, Monreal

Critical revision of the manuscript for important intellectual content: Barrios, Chavant, Jimenez, Bertoletti, Rosa-Salazar, Muriel, Viallon, Fernandez-Capitan, Yusen, Monreal

Study supervision: Jimenez, Monreal

The corresponding author, David 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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Table 1. Clinical characteristics of patients who received reperfusion or anticoagulant therapy

	Received reperfusion therapy N = 70	*Did not receive reperfusion therapy N = 255*	*P value*
Clinical characteristics			
Age, years (mean ± SD)	58.8 ± 17.1	65.7 ± 17.1	<0.01
Age >80 years, n (%)	5 (7.14%)	52 (20.4%)	0.01
Male gender, n (%)	33 (47.1%)	116 (45.5%)	0.81
Weight, kilograms (mean ± SD)	77.4 ± 1.8	75.9 ± 1.0	0.38
Risk factors for venous thromboembolism			
History of venous thromboembolism, n (%)	11 (15.7%)	43 (16.8%)	0.82
Cancer, n (%) †	12 (17.1%)	61 (23.9%)	0.23
Recent surgery, n (%) ‡	9 (12.7%)	29 (11.3%)	0.73
Immobilization for ≥ 4 days, n (%) §	26 (37.1%)	55 (21.6%)	<0.01
Comorbid diseases			
Chronic lung disease, n (%)	17 (24.3%)	37 (14.5%)	0.05
Chronic heart disease, n (%)	14 (20%)	46 (18.0%)	0.71
Recent major bleeding, n (%)	2 (2.9%)	14 (5.5%)	0.29
Clinical symptoms and signs at presentation			
Syncope, n (%)	37 (53.6%)	61 (24.6%)	<0.001
Chest pain, n (%)	42 (60%)	111 (44.6%)	0.02
Dyspnea	63 (90%)	216 (85.4%)	0.32
Heart rate ≥110/minute, n (%)	48 (68.6%)	60 (23.5%)	<0.001
Arterial oxyhemoglobin saturation (SaO2) <90%, n (%)	35 (50%)	68 (26.7%)	<0.001
Systolic blood pressure <100 mm Hg, n (%)	35 (50%)	68 (26.7%)	<0.001
Concomitant deep vein thrombosis, n (%)	41 (58.6%)	110 (43.1%)	0.02
Simplified Pulmonary Embolism Severity Index			
Low risk, n (%)	12 (17.1%)	81 (31.8%)	0.02
High risk, n (%)	58 (82.9%)	7146 (68.2%)	0.02
Echocardiography and cardiac biomarkers			
Right ventricle hypokinesis, n (%)	53 (79.1%)	104 (46.8%)	<0.001
Tricuspid annular plane systolic excursion, mm (mean ± SD)	18.2 ± 7.6	17.3 ± 5.3	0.55
Elevated troponin, n (%) (220)	34/58 (58.6%)	80/162 (49.4%)	0.23
Brain natriuretic peptide >100 pg/mL, n (%) (48)	8/9 (88.9%)	34/39 (87.2%)	0.89

Laboratory findings			
Abnormal creatinine levels (>2 mg/dL), n (%)	22 (31.4%)	62 (25.6%)	0.33
Hemoglobin, g/dL (mean ± SD)	12.9 ± 1.8	13.5 ± 9.8	0.62

Abbreviations: SD, standard deviation.

† Active or under treatment in the last year.

‡ In the previous month.

§ Immobilized patients defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to pulmonary embolism diagnosis.

Table 2. 30-day clinical events after diagnosis and treatment of acute symptomatic pulmonary embolism and coexisting right heart thrombi

	All patients N = 325	*Received reperfusion therapy N = 70*	*Did not receive reperfusion therapy N = 255*	*P value*
Primary outcome, n (%)				
All-cause death	28 (8.6%)	4 (5.7%)	24 (9.4%)	0.33
Pulmonary embolism-related death	17 (5.2%)	3 (4.3%)	14 (5.5%)	0.69
Secondary outcomes, n (%)				
Recurrent pulmonary embolism	6 (1.8%)	4 (5.7%)	2 (0.8)	<0.01
Major bleeding	15 (4.6%)	3 (4.3%)	12 (4.7%)	0.88

Table 3. Reperfusion therapy as determinant of outcome in 325 patients who had acute symptomatic pulmonary embolism and right heart thrombi

Event	*Unadjusted OR (95% CI)*	*P value*	*Adjusted OR* (95% CI)*	*P value*
All-cause mortality	0.58 (0.19-1.74)	0.33	0.34 (0.10-1.11)	0.08
Pulmonary embolism-related mortality	0.77 (0.21-2.76)	0.69	0.48 (0.12-1.92)	0.30
Recurrent venous thromboembolism	7.67 (1.37-42.77)	0.02	8.20 (1.35-49.61)	0.02
Major bleeding	0.90 (0.24-3.30)	0.88	0.70 (0.17-2.80)	0.62

Abbreviations: OR, odds ratio; CI, confidence interval.

*Multivariate adjustment for the simplified Pulmonary Embolism Severity Index (18), and recent bleeding.

Table 4. Adjusted clinical outcomes for propensity-matched cohorts

30-day outcome	*Reperfusion n/total n (%)*	*No reperfusion n/total n (%)*	*OR (95% CI)*	*P value*
Death	4/64 (6.2%)	9/64 (14.1%)	0.40 (0.11-1.40)	0.15
Pulmonary embolism-related death	3/64 (4.6%)	5/64 (7.8%)	0.58 (0.13-2.55)	0.47
Recurrent venous thromboembolism	4/64 (6.2%)	0/64 (0%)	-	0.049
Major bleeding	2/64 (3.1%)	2/64 (3.1%)	1.00 (0.13-7.38)	1.00

Abbreviations: OR, odds ratio; CI, confidence interval.

Figure 1. Patient Eligibility Flow Diagram.

Figure 2. Covariable balance for selected variables before (circles) and after (triangles) matching, contrasting characteristics of patients undergoing reperfusion therapy or sole anticoagulant therapy. Values on the horizontal axis represent the percent standardized difference.

Figure 1.

PE, pulmonary embolism

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RHT, right heart thrombi

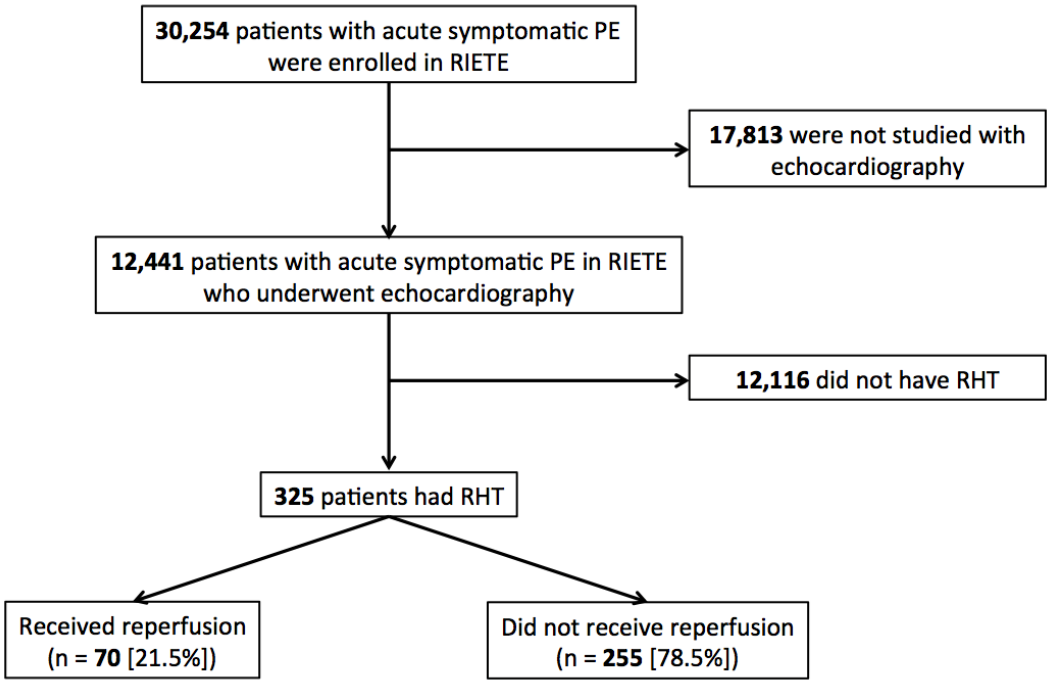
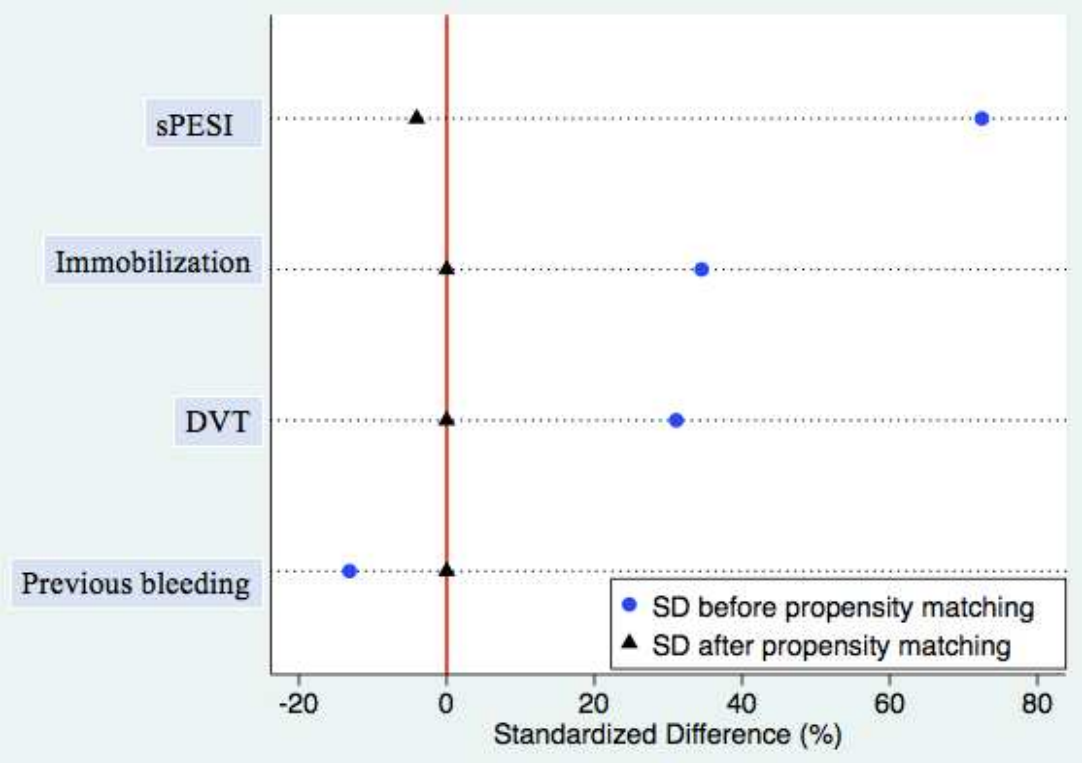


Figure 2.



Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index; DVT, deep vein thrombosis; SD, standardized difference.

HIGHLIGHTS

The optimal management of right heart thrombi in patients who present with acute symptomatic pulmonary embolism lacks clarity.

Right heart thrombi may not warrant riskier interventions than standard anticoagulation.

Our findings provide a rationale for further trials to assess the efficacy and safety of reperfusion therapy for right heart thrombi associated with pulmonary embolism.