# Association between reperfusion therapy and outcomes in patients with acute pulmonary embolism and right heart thrombi

*To the Editor:*

Right heart thrombi (RHT) may be detected in <4% of patients with pulmonary embolism (PE) [1], and are associated with worse outcomes [1–4]. Given the limited existing evidence, society guidelines or consensus statements have either not addressed the management of RHT, or have based their recommendations on prior case reports, case series or pooled results of case series [5–8]. It is plausible that reperfusion strategies reduce the adverse outcomes in PE patients with RHT; thrombolysis may dissolve the RHT and emboli, while thrombectomy might reduce the thromboembolic burden. Using the data from RIETE (Registro Informatizado Enfermedad TromboEmbolica), a prospective international venous thromboembolism registry, we sought to compare the outcomes of patients with PE and coexisting RHT, with *versus* without reperfusion therapy.

The design of RIETE has been described previously [9]. Institutional review board approval and informed consent were obtained at participating sites. We included patients with PE (March 2001 to September 2019) and determined the use of reperfusion therapies within 3 days from echocardiographic identification of RHT. Main outcomes were 30-day PE-related mortality (autopsy-confirmed, or death within 10 days from PE, in the absence of an alternative cause), all-cause mortality, major bleeding (events that were overt and required ⩾2 units of blood, or retroperitoneal, spinal or intracranial, or fatal), and recurrent PE.

In the primary analysis, 1:1 propensity-score matching was used, matching each patient receiving reperfusion with the nearest patient not receiving reperfusion, within a caliper width of 0.2 times the standard deviation of the log odds of the propensity score. The propensity score was derived from a group of variables thought to influence the use of reperfusion therapies and outcomes, including vital signs, age, history of heart failure and cancer.

As confirmatory analyses, we included all patients with RHT in multivariable logistic regression, assessing the association between reperfusion therapies and outcomes.

Among 42 620 patients with PE, 18 803 underwent transthoracic echocardiography with assessment of right ventricular function, of whom 443 (2.4%) had RHT. Among these 443 patients, 102 received reperfusion (thrombolytic therapy in 74, percutaneous or surgical thrombectomy in 28). After propensity-score matching, age was comparable in the two groups (59.1 *versus* 58.9 years, p=0.94), as was the history of heart failure (14.6% *versus* 15.9%, p=0.83), active cancer (14.6% *versus* 13.4%, p=0.82) and immobility (35.3% *versus* 31.7%, p=0.62). Similarly, presenting vital signs were comparable in the propensity-matched groups (heart rate 108.4 *versus* 108.7 bpm, p=0.94; systolic blood pressure 107.8 *versus* 107.3 mmHg, p=0.91; and proportion of patients with oxygen saturation <90% 39.0% *versus* 40.2%, p=0.87).

During 30-day follow-up, 40 (9.0%) patients died, including 24 (5.4%) from PE. In the propensity-matched cohort (82 pairs), use of reperfusion therapy was not associated with significantly reduced odds of 30-day PE-related mortality (OR 0.65, 95% CI 0.20–2.16; p=0.48) or all-cause mortality

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**Right heart thrombi portend worse outcomes in pulmonary embolism (PE). In propensity-matched analyses of patients from a large registry, reperfusion therapy was not associated with significantly reduced odds of all-cause or PE-related mortality.** https://bit.ly/2WRLYnq

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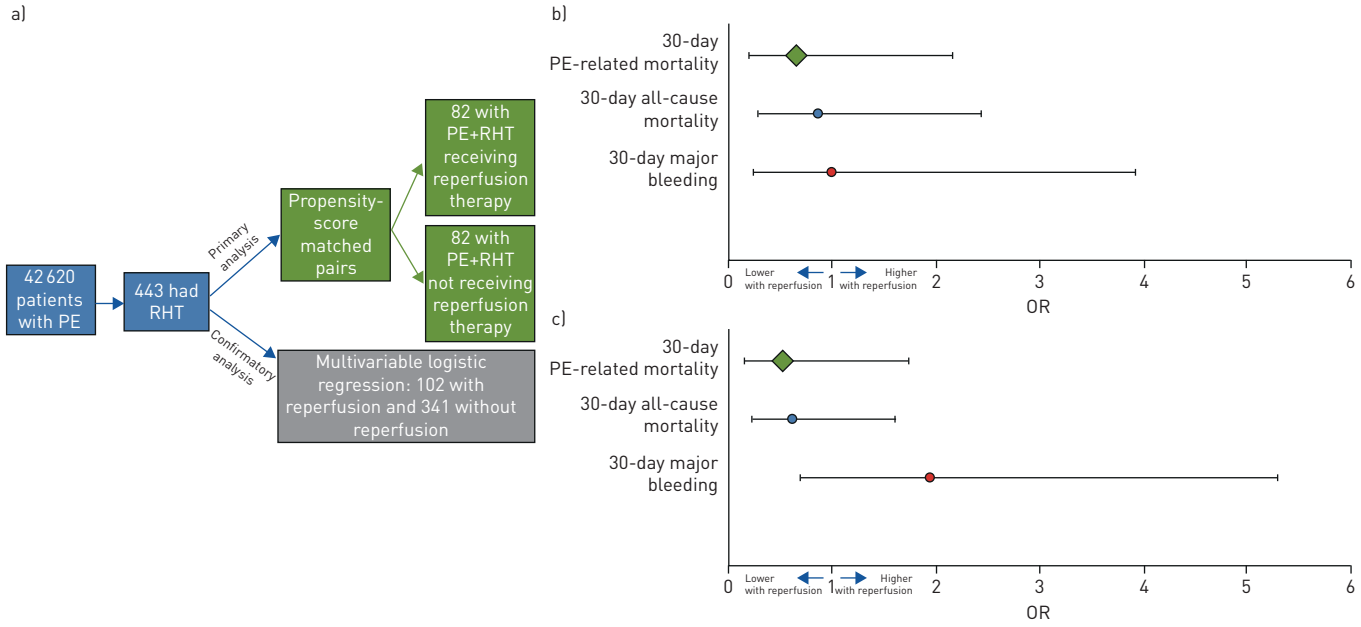


FIGURE 1 a) Cohort selection and outcomes with or without reperfusion: b) propensity-matched cohort (n=164) and c) multivariable logistic regression among all participants (n=443). Matched and adjusted for age, history of active cancer, heart failure, immobilisation, heart rate systolic blood pressure and hypoxaemia. Odds ratio could not be calculated for recurrent pulmonary embolism (PE) in both models. In the matched-pair analysis, use of reperfusion was associated with increased absolute risk (risk difference 0.08, 95% CI 0.02–0.14) for recurrent events. RHT: right heart thrombi.

(OR 0.86, 95% CI 0.30–2.43; p=0.78). The rate of major bleeding was comparable (OR 1.00, 95% CI 0.25–3.92; p=0.999). Six patients receiving reperfusion therapy and no control patients had recurrent PE (risk difference 0.08, 95% CI 0.02–0.14). Findings were consistent in multivariable logistic regression analyses of all 443 patients (figure 1). Results were similar in supplemental analyses with 1:2 propensity-score matching.

In a *post hoc* analysis, we assessed the use of thrombolytic therapy, compared with anticoagulation. In the propensity-matched cohort (62 pairs), use of thrombolytic therapy was not associated with significantly reduced odds of 30-day PE-related mortality (OR 0.54, 95% CI 0.14–2.06; p=0.37) or all-cause mortality (OR 0.84, 95% CI 0.25–2.84; p=0.78). The rate of major bleeding was comparable (OR 0.64, 95% CI 0.16–2.54; p=0.529).

In this study of patients with PE and coexisting RHT, we failed to find a significantly reduced odds of PE-related mortality with reperfusion attempt, mainly *via* thrombolytic therapy. Although this study reports the largest series of patients with RHT from a multinational registry, Type II error is still possible, similar to a prior investigation [10]. We must acknowledge that we cannot exclude a clinically meaningful, but smaller, effect size for improved outcomes with reperfusion (in the form of thrombolytic therapy). In addition, our findings do not exclude the utility of thrombolytic therapy in hemodynamically unstable patients. Such patients should be treated according to standard guideline recommendations [5, 6, 11]. However, the lack of large significant reduction in mortality and the hypothesis-generating increase in recurrent PEs in unselected patients with PE and coexisting RHT deserve further attention.

Importantly, patients with PE and coexisting RHT have an increased risk of PE-related mortality. Therefore, although we failed to show reduced mortality with reperfusion (mainly *via* thrombolytic therapy), alternative strategies, including percutaneous thrombectomy or surgical thrombectomy, require further investigations to see if they could safety improve the outcomes. In the current investigation, small numbers made it unfeasible to provide a matched comparison between patients who underwent thrombectomy *versus* patients who received anticoagulation only. Given the rarity of this condition, it is unlikely that a large trial will become available in near future. Furthermore, we did not have access to detailed thrombus characteristics, including size, morphology and mobility. Therefore, we are unable to provide subgroup analyses for the comparative efficacy or reperfusion *versus* standard anticoagulation, based on thrombus characteristics.

In conclusion, in patients with PE and coexisting RHT, use of reperfusion therapy, primarily in the form of thrombolytic therapy, was not associated with significantly lower PE-related mortality. Nevertheless,

RHT is an indicator of increased PE-related mortality. Additional studies are required to identify alternative effective treatments for this high-risk subgroup.

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