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REVIEW ARTICLE

Risk of recurrent venous thromboembolism after acute pulmonary embolism: Role of residual pulmonary obstruction and persistent right ventricular dysfunction. A meta-analysis

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Abstract

Background: There is conflicting evidence regarding the role of residual pulmonary obstruction (RPO) or persistent right ventricular dysfunction (RVD) after pulmonary embolism (PE) as a predictor of recurrent venous thromboembolism (VTE). The aim of this study was to assess whether RPO or persistent RVD after PE is associated with recurrent VTE.

Methods: MEDLINE and EMBASE were searched through December 2018. Studies reporting on (*a*) RPO either on computed tomography (CT) angiography or perfusion lung scan, or RVD on echocardiography or CT angiography, after therapeutic anticoagulation for the acute PE, and (*b*) recurrent VTE, were included in this meta-analysis.

Results: RPO was associated with an increased risk of recurrent VTE (16 studies; 3472 patients; odds ratio [OR] 2.22; 95% confidence interval [CI] 1.61-3.05; I^2 = 26%); the association was statistically significant for lung scan–detected RPO (11 studies; 2916 patients; OR 2.21; 95% CI 1.63-3.01) but not for CT angiography–detected RPO (five studies; 556 patients; OR 2.56; 95% CI 0.82-7.94). No significant association was found between persistent RVD and recurrent VTE (four studies; 852 patients; OR 1.62; 95% CI 0.63-4.17).

Conclusions: RPO is a predictor of recurrent VTE after a first acute PE, mainly when assessed by perfusion lung scan.

KEYWORDS

computed tomography angiography, meta-analysis, pulmonary embolism, venous thromboembolism, ventilation-perfusion scan, right ventricular dysfunction

1 | INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is regarded as a chronic disease, as it tends to recur after an acute event.[1–3] The risk of recurrent VTE is similar in patients treated for a first DVT and in those treated for a first PE (hazard ratio 1.19; 95% confidence interval [CI] 0.87-1.63).[4] However, patients with PE experience more frequent recurrence of PE and patients with DVT experience more frequent recurrence of DVT.[5,6] The risk of fatal PE is 2- to 3-fold higher after an episode of PE than after an episode of DVT.[7,8]

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Current guidelines suggest anticoagulant treatment for at least 3 months for all patients after a first VTE, and consideration of indefinite anticoagulation for patients at particularly high risk for recurrence.[9,10] The risk of recurrent VTE depends on several factors (e.g., patient features, and the presence and number of risk factors for the index event).[11] Conflicting results are currently available on the role of residual pulmonary obstruction (RPO) or persistent right ventricular dysfunction (RVD) after anticoagulant treatment as a predictor of recurrent VTE.

We performed a meta-analysis to assess the value of RPO or persistence of RVD as a predictor of recurrent VTE in patients treated with anticoagulants for PE.

Essentials

- Debated is the role of residual pulmonary obstruction (RPO) in predicting venous thromboembolism.
- Whether right ventricular dysfunction (RVD) predicts recurrent venous thromboembolism is unknown.
- 15 studies on RPO and 4 on RVD and venous thromboembolism were included in this meta-analysis.
- RPO is a predictor of recurrent venous thromboembolism when assessed by perfusion lung scan.
- RVD after acute pulmonary embolism is not associated with recurrent venous thromboembolism.

2 | MATERIALS AND METHODS

The methods used for this meta-analysis are in accordance with "Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting".[12]

2.1 | Study objectives

The primary objectives of this analysis were to assess whether there is an association between (*a*) persistent RPO or (*b*) persistent RVD and recurrent VTE in patients treated with anticoagulants for acute PE.

The secondary objectives were to assess whether there is an association between (*a*) persistent RPO or (*b*) persistent RVD and recurrent PE or all-cause death in patients treated with anticoagulants for acute PE.

2.2 | Study outcomes

The primary outcome of the study was recurrence of VTE, defined as the composite of recurrent PE and/or DVT, according to the criteria of the individual studies.

Secondary outcomes were recurrence of PE and all-cause death.

2.3 | Search strategy

We performed an unrestricted search in MEDLINE and EMBASE through December 2018. The search was performed by use of the terms "residual emboli OR residual pulmonary obstruction AND pulmonary embolism" for the RPO analyses, and "echocardiography OR right ventricular dysfunction AND pulmonary embolism" for the RVD analyses. No language restrictions were applied. Reference lists of retrieved articles and review articles were manually searched to extend our search. Only full articles were considered for analysis.

Three authors (M.G., P.C., and L.C.) independently performed the electronic search. Study selection was initially performed by review of titles. Candidate abstracts were then reviewed and selected for data retrieval, according to predetermined criteria.

2.4 | Inclusion criteria

For studies focusing on persistent RPO, the following inclusion criteria were used: (*a*) an objective diagnosis of an index acute PE, (*b*) therapeutic anticoagulation used in all patients to treat an index PE, (*c*) assessment of persistent RPO by computed tomography (CT) angiography or perfusion lung scan, and (*d*) follow-up data available on objectively diagnosed recurrence of VTE.

For studies focusing on persistent RVD, the following inclusion criteria were used: (*a*) an objective diagnosis of an index PE, (*b*) therapeutic anticoagulation used in all patients to treat an index PE, (*c*) assessment of persistent RVD on echocardiography or CT, and (*d*) follow-up data available on objectively diagnosed recurrence of VTE.

The three authors (M.G., P.C., and L.C.) independently reviewed each study by using standardized extraction forms. Disagreements were resolved through revision by an additional reviewer (C.B.) and by discussion.

Studies were included in the meta-analysis on RPO if the following data were available: numbers of patients with or without study outcome among patients with or without RPO assessed by either CT angiography or perfusion lung scan. Studies were included in the meta-analysis on RVD if the following data were available: numbers of patients with or without study outcome among patients with or without RVD assessed by either echocardiography or CT angiography.

For duplicate publications, the most recent was considered. To assess agreement between reviewers for study selection, we used the kappa statistic, which measures agreement beyond that attributable to chance.[13]

2.5 | Data extraction

For each study, the following were extracted independently by two authors: general data (study design and year of publication), patients (number, mean age, gender, and treatment for PE), and clinical outcomes (VTE recurrence or death).

For the analyses on RPO, the techniques used to assess RPO (CT angiography or perfusion lung scan), the time from the index event

to RPO assessment, the criteria used to diagnose RPO (parameters and cut-off), and the number of patients with the primary or secondary endpoints among RPO-positive or RPO-negative patients were extracted.

For the analyses on persistent RVD, the techniques used to assess persistent RVD (echocardiography or CT), the time from the index event to persistent RVD assessment, the criteria used to establish persistent RVD (parameters and cut-off) and the numbers of patients with the primary or secondary endpoints among persistent RVD-positive or RVD-negative patients were extracted.

2.6 | Statistical analysis

We determined pooled odds ratios (ORs) with 95% CIs for recurrent VTE or all-cause mortality in patients with persistent RPO (assessed by either CT angiography or perfusion lung scan) and in patients with persistent RVD (assessed by either echocardiography or CT). We planned separate analyses for: (*a*) recurrent VTE, (*b*) recurrent PE, and (*c*) all-cause death.

Sensitivity analyses were performed concerning: (*a*) methods used for the diagnosis of persistent RPO, (*b*) time from the index PE to assessment of RPO or RVD, (*c*) asymptomatic vs symptomatic recurrence of VTE, (*d*) studies only including patients treated for a first PE, and (*e*) only high-quality studies included.

Data were pooled by use of the Mantel-Haenszel method[14]; results are reported according to a fixed-effects model in the absence of significant heterogeneity, and according to a random-effects model in the presence of significant heterogeneity.[15] Correction for zero cells (0.5) was also performed. Cochran's χ^2 test and the I^2 test for heterogeneity were used to assess between-study heterogeneity.[16,17] Significant heterogeneity was considered to be present at $P < 0.10$ and $I^2 > 50\%$.

Publication bias was assessed visually by the use of funnel plots.

Statistical analyses were performed with REVIEW MANAGER release 5.3 (The Cochrane Collaboration) and STATA/SE release 10.1. The quality of observational studies was evaluated with the Newcastle-Ottawa quality assessment scale.[18] Randomized controlled trial quality was assessed by use of the Jadad score.[19] To assess the risk of bias of our study, we used the the ROBINS I tool, which was independently assessed by two authors.[20]

3 | RESULTS

3.1 | Residual pulmonary obstruction

Overall, 538 papers were found, of which 16 met the inclusion criteria (the flow diagram is shown in Figure S1).[21–36] In one study, the numbers of patients with or without RPO who had recurrent VTE events were obtained after the authors had been contacted.[35] The agreement between reviewers for study selection was good (kappa statistic of 0.85).

Table 1 shows the main features of the included studies and the methodology used for RPO assessment and definition. The number of patients included in the individual studies ranged from a minimum of 46 to a maximum of 647.

In the large majority of the studies, recurrence of PE was defined as the presence of symptoms suggesting PE associated with imaging confirmation, and recurrence of DVT was defined as the presence of symptoms suggesting DVT associated with imaging confirmation (Table 2).

Data on assessment of study quality and risk of bias are shown in Tables S1 and S3. The quality was good for the majority of the studies, and fair and poor in two studies each. The overall risk of bias of our meta-analysis was low.

Information on duration of anticoagulant treatment and the prevalence of unprovoked PE among patients with and without RPO is shown in Table S2.

3.2 | RPO and clinical outcomes

Overall, 192 of 1294 patients with RPO had recurrent VTE (14.8%; 95% CI 13.0-16.8), as compared with 176 of 2178 without RPO (8.1%; 95% CI 7.0-9.3). The presence of RPO, either on CT angiography or on lung scan, was associated with an increased risk of recurrent VTE without significant heterogeneity (16 studies; 3472 patients; OR according to the random-effects model, 2.22; 95% CI 1.61-3.05; $I^2 = 26\%$) (Figure 1).[21–36] The association was confirmed after amending for zero cells (OR 2.13; 95% CI 1.56-2.90) and after excluding from the analysis the study by Meneveau et al, in which RPO was assessed at an early stage (OR 2.11; 95% CI 1.52-2.93). Funnel plot inspection for this analysis showed no evidence of publication bias (Figure S2).

The association between RPO and recurrent VTE was confirmed in studies assessing RPO on lung scan (11 studies; 2916 patients; OR 2.21; 95% CI 1.63-3.01; $I^2 = 16\%$),[21,23,25,26,29–35] but not in studies assessing RPO on CT angiography, although there was significant heterogeneity (five studies; 556 patients; OR according to the random-effects model, 2.56; 95% CI 0.82-7.94; $I^2 = 52\%$).[22,24,27,28,36]

Sensitivity analyses were performed on the association between RPO and recurrent VTE (Table 3). These analyses confirmed the association between recurrent VTE and RPO (*a*) on lung scan regardless of the methods used for RPO assessment, (*b*) in studies assessing RPO at least 3 months after acute PE (significant heterogeneity observed in the analysis of studies assessing RPO at 3 months or earlier after acute PE was mainly related to the study of Chopard et al[30]), (*c*) after the exclusion of asymptomatic recurrence of VTE, (*d*) in patients treated for a first PE, (*e*) in high-quality studies, and (*f*) in studies with a fixed duration of anticoagulant treatment regardless of the presence or absence of RPO.

Seven studies reported on the recurrence of PE (1801 patients)[21,23,26,28,29,31,32]; recurrent PE occurred in 83 of 677 patients with RPO (12.3%; 95% CI 9.9-14.7), and in 75 of 1024 patients without RPO (7.3%; 95% CI 5.7-8.9), either on CT angiography or on lung scan. The presence of RPO was associated with an increased risk of recurrent PE (OR 2.98; 95% CI 2.00-4.44; $I^2 = 11\%$) (Figure 2A).

TABLE 1 The main features of studies reporting on the prognostic value of residual pulmonary obstruction (RPO) on computed tomography (CT) angiography or lung perfusion scan

	General features				Assessment of RPO timing and method				
Author, year	Study design	Prevalence of RPO, % (n/N)	Mean age (y)	Inclusion criteria	Time of RPO assessment	RPO assessment	Method used for RPO diagnosis	Criteria for RPO	Cut-off for RPO
Alhadad,[21]	RC	66.5 (151/227)	63	Acute PE	7.4 mo	NR	V/Q scan	Scoring segments and subsegments (total of 18 points for each lung)	NR
Meneveau,[23]	PC	24.5 (102/416)	65	Objectively confirmed acute intermediate-risk to high-risk PE	At discharge or at day 6 after the index event	Double-blind by two independent operators	V/Q scan	Meyer score	RPO ≥ 35%
Poli,[25]	PC	25.9 (61/235)	67 59	Objectively confirmed acute PE	11 mo	By a nuclear specialist	V/Q scan	Meyer score	RPO ≥ 10%
Begic,[26]	PC	17.2 (11/64)	NR	First episode of PE	6 mo	NR	V/Q scan	Scoring segments and subsegments (total of 18 points for each lung)	NR
Planquette,[29]	PC	19.3 (60/310)	69 63	First symptomatic objectively confirmed PE; age >18 y; ≥3 mo of OAC without recurrence	8.7 mo	By a blinded investigator	V/Q scan	Meyer score	RPO > 10%
Chopard,[30]	PC	29.0 (70/241)	71 57	First episode of confirmed symptomatic PE; age ≥18 y	3 mo	Double-blind by two independent operators	V/Q scan	Meyer score	RPO ≥ 15%
Meysman,[31]	PC	52.1 (24/46)	67 56	Symptomatic intermediate-risk acute PE confirmed by CTPA or V/Q scan; age ≥18 y	6 mo	By a single experienced nuclear specialist	V/Q scan	Percentage of total lung perfusion	NR
Pesavento,[32]	PC	50.0 (324/647)	70 63	First PE with or without DVT	6 mo	Centrally adjudicated by an independent commitee	Perfusion lung scan	Meyer score	RPO > 0%
Tromeur,[33]	RT	43.7 (131/300)	58	First symptomatic unprovoked objectively confirmed PE; ≥6 mo of VKAs; age ≥18 y	6 mo	Centrally adjudicated by two blinded investigators	V/Q scan	Meyer score	RPO ≥ 5%
Wan,[34]	PC	59.9 (173/289)	50	Unprovoked objectively confirmed VTE; ≥5-7 mo of anticoagulants; no recurrence of VTE during the initial treatment period	5-7 mo	Centrally adjudicated by a single experienced nuclear specialist	V/Q scan	Meyer score	RPO > 0%[a]
Villari,[35]	RC	40.0 (101/252)	69	Symptomatic objectively confirmed acute PE; age ≥18 y	6 mo	By two independent expert observers	V/Q scan	Semiquantitative scoring segments	At least two or more perfusion defects
Golpe,[22]	PC	19.8 (18/91)	68 74	Objectively confirmed acute PE; age ≥18 y	6 mo	NR	CTPA	Presence or absence of RPO	NR

(Continues)

TABLE 1 (Continued)

Author, year	General features				Assessment of RPO timing and method				
	Study design	Prevalence of RPO, % (n/N)	Mean age (y)	Inclusion criteria	Time of RPO assessment	RPO assessment	Method used for RPO diagnosis	Criteria for RPO	Cut-off for RPO
Korkmaz,[24]	RPC	47.9 (58/121)	NR	Objectively confirmed acute PE by CTPA or V/P scan	3 mo	NR	CTPA	Presence or absence of RPO	NR
Den Exter,[27]	PC	15.9 (25/157)	54 55	Acute objectively confirmed hemodynamically stable PE	6 mo	Independently adjudicated by two expert radiologists	CTPA	Qanadli obstruction index	NR
Pesavento,[28]	PC	15.2 (16/105)	64 64	First acute PE	6 mo	Centrally adjudicated by an independent commitee	CTPA	Qanadli obstruction index	NR
Ma,[36]	PC	12.2 (10/82)	50	First objectively confirmed acute PE	12 mo	Centrally adjudicated by an independent blinded radiologist	CTPA	Qanadli obstruction index	NR

Abbreviations: CTPA, CT pulmonary angiogram; DVT, deep vein thrombosis; NR, not reported; OAC, oral anticoagulant; PC, prospective cohort; PE, pulmonary embolism; RC, retrospective cohort; RPC, retrospective prospective cohort; RT, randomized trial; VKA, vitamin K antagonist; V/P, ventilation/perfusion; VTE, venous thromboembolism.

[a]In the original study, results are also provided for RPO ≥ 5% or RPO ≥ 10%.

All-cause death was reported in five studies (912 patients). Death occurred in 22 of 217 patients with RPO (10%; 95% CI 6.1-14.2) and in 44 of 695 patients without RPO (6.3%; 95% CI 4.5-8.1). The presence of RPO was not associated with an increased risk of all-cause death (OR 1.61; 95% CI 0.65-3.98; I^2 = 42% according to the random-effects model) (Figure 2B).[22,23,26,28,30]

3.3 | Persistent RVD

Our search identified 18 potentially eligible studies (Figure 1). Four studies were included in the analysis (Table 4).[22,33,37,38] The agreement between reviewers for study selection was good (kappa statistic of 0.85). The main features of studies included in this analysis and the criteria for the definition of RVD are shown in Table 4.

According to the Ottawa Quality Assessment Scale, two studies were classified as good quality and one study as fair quality. By use of the Jadad score, the randomized study was classified as high quality (Table 1).

3.4 | Persistent RVD and clinical outcomes

A non-significant association between RVD and VTE recurrence was found (four studies; 852 patients; OR 1.62; 95% CI 0.63-4.17; I^2 = 53% according to the random-effects model) (Figure 3).[22,33,37,38] After correction for zero cells, the association reached statistical significance (OR 1.87; 95% CI 0.71-4.96).

Two studies reported on the recurrence of PE and on overall mortality. The pooled analysis of these studies showed a significant association between RVD and the recurrence of PE (two studies; 524 patients; OR 3.87; 95% CI 0.53-28.26), with significant heterogeneity (I^2 = 51%).[39,40] A non-significant association was found between RVD and overall mortality (two studies; 402 patients; OR 1.72; 95% CI 0.89-3.31; I^2 = 0%).[22,37]

4 | DISCUSSION

This meta-analysis shows that RPO is associated with an increased risk of recurrent VTE in patients treated with anticoagulants for acute PE. The increase in the risk of recurrence was consistent in all sensitivity analyses for RPO assessed by lung scan, but this was not the case for RPO assessed by CT angiography. The persistence of RVD after anticoagulant treatment for acute PE seems to be associated with recurrent VTE.

We found that the risk of recurrent VTE was 2-fold higher in patients with persistent RPO than in patients without RPO. This finding is consistent with the increased risk of recurrent VTE in patients with residual vein obstruction after an episode of DVT.[41] The biological plausibility of these finding is multifactorial. The persistence of lower-limb thrombi or pulmonary emboli after the completion of an initial period of therapeutic anticoagulation could suggest a specific prothrombotic phenotype that is able to make the thrombi more resistant and stable.[42] Moreover, persistent thrombosis could facilitate

TABLE 2 Criteria for the diagnosis of recurrent venous thromboembolism in the selected studies

Author, year	Diagnosis of recurrent PE	Diagnosis of recurrent DVT	Symptomatic recurrence	Anticoagulant treatment	Thrombolytic therapy	Duration of anticoagulation
Alhadad,[21]	New objectively confirmed PE after second V/P scan	NR	Yes	All patients were treated with anticoagulation	Included	7.5 ± 4.0 mo
Golpe,[22]	New filling defect on CT scan	Non-compressible proximal vein at ultrasonography or filling defect on venography	Not specified	All patients were treated with anticoagulation	Excluded	At least 6 mo
Meneveau,[23]	New filling defect on spiral CT scan or pulmonary angiogram	NR	Yes	UFH or LMWH or fondaparinux followed by warfarin	Included	NR
Korkmaz,[24]	New filling defect on spiral CT scan	NR	Yes	UFH or LMWH followed by warfarin	Included	At least 3 mo
Poli,[25]	Intravascular filling defects on CT scan or new perfusion defect on V/Q scan	NR	Not specified	UFH or LMWH followed by warfarin	NR	At least 3 mo
Begic,[26]	New perfusion defect on V/Q scan	NR	Yes	UFH or LMWH	NR	At least 3 mo
Den Exter,[27]	New filling defect on spiral CT scan	Compression ultrasound	Yes	LMWH and warfarin	Excluded	At least 3 mo
Pesavento,[28]	New filling defect on spiral CT scan or subsegmental mismatch on V/Q scan	NR	Yes	Type of anticoagulation not specified	NR	NR
Planquette,[29]	New thrombus on CT scan or new perfusion defect on V/Q scan	DVT in a new territory or an increase of >4 mm relative to the residual diameter	Yes	NR	Included	At least 3 mo
Chopard,[30]	New defects on CT scan or V/Q scan	NR	Yes	UFH or LMWH or fondaparinux followed by warfarin	Included	At least 3 mo
Meysman,[31]	Any sign or symptom of recurrent PE	NR	Yes	UFH or LMWH followed by warfarin	Excluded	At least 6 mo
Pesavento,[32]	New filling defect on spiral CT scan or subsegmental mismatch on V/Q scan	Incompressibility of a vein segment that was initially free from thrombi or had later recanalized	Yes	UFH or LMWH or fondaparinux followed by warfarin	Included	At least 6 mo
Tromeur,[33]	Not specified	Proximal DVT	Yes	Vitamin K antagonists	Included	At least 6 mo
Wan,[34]	Any sign or symptom of recurrent PE	Any sign or symptom of recurrent DVT	Yes	UFH or LMWH followed by warfarin	NR	5-7 mo
Villari,[35]	Appearance of new perfusion defect(s)	NR	Symptomatic and asymptomatic	LMWH and vitamin K antagonists	NR	At least 6 mo
Ma,[36]	Objective diagnostic testing	Objective diagnostic testing	Not specified	LMWH followed by warfarin	NR	5.7 mo

Abbreviations: CT, computed tomography; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; NR, not reported; PE, pulmonary embolism; UFH, unfractioned heparin; V/P, ventilation/perfusion.

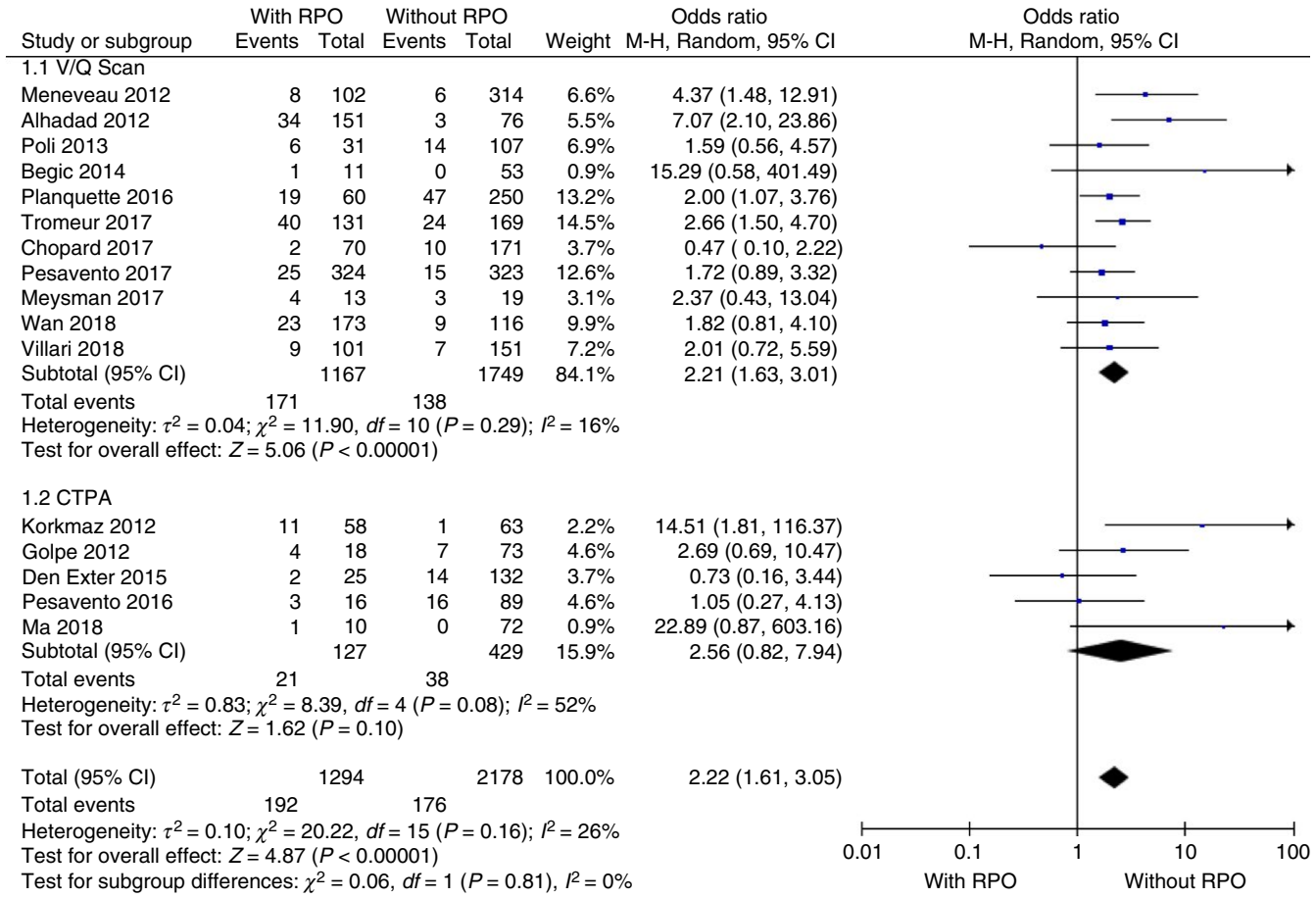

FIGURE 1 Forest plot for the incidence of recurrent venous thromboembolism based on the presence or absence of residual pulmonary obstruction (RPO) and stratified according to the instrumental test used for the diagnosis of RPO. CI, confidence interval; CTPA, computed tomography pulmonary angiogram

TABLE 3 Results of sensitivity analyses on the association between residual pulmonary obstruction (RPO) and recurrent venous thromboembolism (VTE) with the random-effects model

Subanalysis	Criteria	No. of studies; no. of patients	OR	95% CI	I^2 (%)
Methods used for RPO assessment	Meyer score	7; 2341	2.03	1.48-2.78	11
	Proportion of total lung perfusion	3; 323	5.38	2.09-13.89	0
	Qanadli score	3; 344	1.45	0.35-5.95	44
	Presence/absence of RPO (CT angiography)	3; 464	1.92	0.32-11.56	79
Time from acute PE to RPO assessment	≤3 mo	3; 778	2.89	0.49-17.21	75
	≥3 mo	14; 2920	2.00	1.50-2.65	8
	≥6 mo	13; 2694	2.14	1.63-2.79	0
Type of recurrence of VTE	Symptomatic	11; 2609	2.16	1.36-3.44	42
Inclusion criteria	First episode of PE	9; 2390	2.01	1.50-2.70	0
	Unprovoked PE	3; 841	2.28	1.49-3.49	0
Quality assessment	High-quality studies	13; 3060	1.99	1.53-2.59	0
Duration of OAC therapy	Fixed OAC duration	3; 621	2.35	1.50-3.68	0

Abbreviations: CI, confidence interval; CT, computed tomography; OAC, oral anticoagulant; OR, odds ratio; PE, pulmonary embolism.

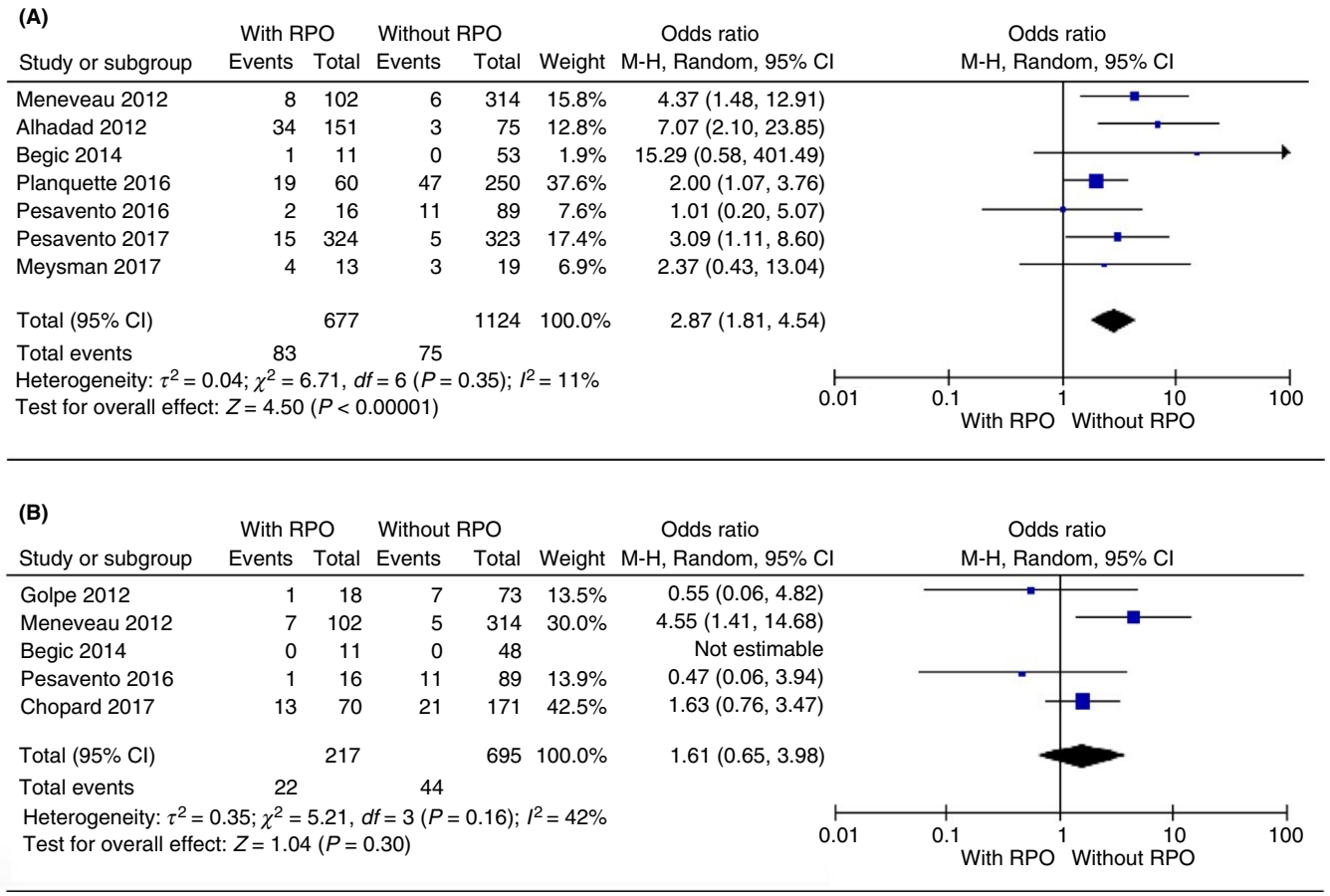

FIGURE 2 Forest plot for the incidence of recurrent pulmonary embolism (A) and all-cause death (B) based on the presence or absence of residual pulmonary obstruction RPO. CI, confidence interval

the progression to post-thrombotic syndrome, such increasing the risk of recurrent DVT.[43] A limitation of this finding is the limited accuracy of currently available algorithms for the diagnosis of recurrent VTE, in particular in patients with residual thrombi or emboli.[44] Indeed, in the presence of symptoms, the diagnosis of recurrent VTE may be challenging in patients with residual thrombi. Consensus statements have reported on criteria for discriminating between acute and chronic pulmonary artery obstruction and between acute and chronic DVT.[45,46] From this point of view, having an imaging test at an intermediate time point between the index VTE and recurrent VTE showing the persistence/resolution of the index emboli may be of use in patients with suspicion of recurrence. However, in clinical practice, only comparisons between examinations performed with the same radiologic technique can be of help in the diagnosis of recurrence.

According to the results of our analysis, RPO is predictive of recurrent VTE if it is assessed by perfusion lung scan, but not if it is asssesed by CT angiography. These results could be explained by the different sensitivities and specificities of these two techniques, mainly for detecting small peripheral perfusion abnormalities. More importantly, the evidence (number of studies and included patients) on the association between recurrent VTE and RPO on perfusion lung scan is better than that on CT angiography (11 studies and 2916 patients vs four studies and 474 patients). It is therefore conceivable that the analysis on the predictive value of RPO on CT is underpowered. However, the risk of renal toxicity associated with the administration of contrast media, the concerns about radiation exposure and the costs of CT angiography should discourage clinicians from repeating this examination for prognostic purposes after anticoagulant treatment.

In the majority of the studies, patients with RPO received a longer duration of anticoagulation than patients without RPO. Regarding the specific purpose of our meta-analysis, different treatment durations may bias the pooled estimates on the association between RPO and recurrent VTE. In order to account for this potential bias, a sensitivity analysis was performed including studies with a fixed duration of anticoagulant treatment regardless of the presence or absence of RPO. In these studies, anticoagulant treatment was withheld at the time of assessment of RPO. The sensitivity analysis confirmed the association between RPO and recurrent VTE.

According to formal evaluation, the risk of bias of our meta-analysis is low; the only concern relates to the suboptimal description of methodology in some of the selected studies, leading to potential bias in study appraisal. When assessing the individual studies, we cannot exclude the possibility that non-consecutive recruitment in some of them, and potential systematic errors in outcome

TABLE 4 Main features of studies reporting on the prognostic value of right ventricular dysfunction (RVD) on echocardiography

Author, year	Study design	Patients with RVD (N)	Patients without RVD (N)	Age (y)	Inclusion criteria	Time of RVD assessment	Criteria for RVD
Grifoni,[37]	PC	59	242	72 64	Confirmed first episode of symptomatic acute PE	At hospital discharge	At least one of the following criteria: -RV dilatation paradoxical septal systolic motion pulmonary hypertension
Poli,[38]	PC	10	213	59	Confirmed first episode of PE with or without DVT	3-6 mo	rV-rA gradient
Golpe,[22]	PC	20	81	76 69	Confirmed PE; age ≥18 y	6 mo	At least one of the following criteria: RV hypokinesis, paradoxical septal systolic motion or RV dilatation, RV systolic function with TAP <15 mm or PAP >40 mmHg
Tromeur,[33]	RT	20	207	51	First episode of a proven symptomatic unprovoked PE; at least 6 mo of VKAs; age ≥18 y	6 mo	RV/LV ratio of >0.9 or systolic pulmonary artery pressure of >50 mm Hg

Abbreviations: DVT, deep vein thrombosis; LV, left ventricular; PAP, pulmonary artery pressure; PC, prospective cohort; PE, pulmonary embolism; RT, randomized trial; RV, right ventricular; rV-rA, transtricuspidal pressure gradient; TAP, tricuspid annular plane systolic excursion; VKA, vitamin K antagonist.

measurement (difficulties in differentiating between RPO and new emboli) in the majority of them, could have generated a risk of bias. The New Ottawa Scale may not have been sensitive enough to identify these specific limits in the individual studies.

We found an association between persistent RVD and the risk of recurrent VTE that reached statistical significance after correction for zero cells. Although an increased risk of recurrent VTE is suggested by the OR in patients with persistent RVD as compared with patients without it, this increase was not statistically significant in the initial analysis in almost 1000 patients. We cannot exclude the possibility that heterogeneity in the definition of RVD could have influenced our results. Moreover, as, in this case, no "side effect" is expected for patients undergoing echocardiography, this examination could be suggested anyway for patients with RVD in the acute phase and persistent dyspnea, in order to screen for chronic thromboembolic pulmonary hypertension.

The optimal duration of anticoagulation beyond the initial 3 months after a first episode of PE remains uncertain. The decision to continue or discontinue anticoagulation after this period should be individually tailored according to the risk of recurrent VTE, and balanced against the risk of bleeding. The identification of predictors of recurrence could drive strategies for secondary prevention. Our meta-analysis shows that RPO assessed after an initial period of anticoagulant treatment is associated with increased risk of recurrence. The results of our study do not necessarily imply that anticoagulation should be prolonged in patients with RPO, but, rather, that RPO may be looked for and taken into account in the complex decision on the duration of secondary prevention of VTE.

Whether risk stratification for recurrent VTE is still a timely issue in the era of direct oral anticoagulants is to be debated. In fact, although these agents carry a reduced risk of major and intracranial bleeding, 20%-30% of VTE patients have an increased risk of bleeding or a contraindication to anticoagulation. Moreover, chronic anticoagulation could result in limitations in everyday activities in very young patients. Thus, even though a large proportion of patients will be candidates for extended secondary prophylaxis of VTE with direct oral anticoagulants, an attempt to identify low-risk patients in whom anticoagulation could be withheld is still warranted. Therefore, the assessment of RPO or persistent RVD requires validation in management studies.

There are several limitations of our study in addition to those intrinsic to the meta-analysis approach, which combines heterogeneous datasets. As an example, differences were noted regarding the methods and timing of RPO assessment, regarding the duration of anticoagulation from the index PE, which was not standardized across the included studies. In particular, different methods and different cut-off levels were also used for RPO assessment across studies evaluating perfusion lung scan for the definition of RPO. These differences could account for the different prevalences of RPO reported in the individual studies. Moreover, as all but one of the included studies involved prospective cohorts, it is conceivable that the results regarding the presence of RPO or RVD influenced

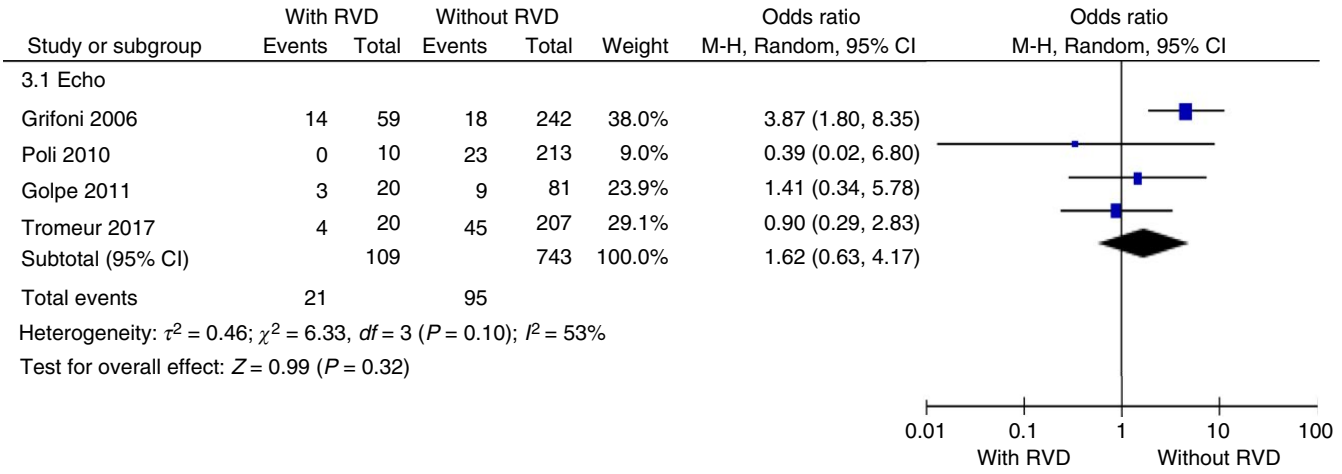

FIGURE 3 Forest plot for the incidence of recurrent venous thromboembolism based on the presence or absence of right ventricular dysfunction (RVD). CI, confidence interval

the duration of anticoagulant treatment. Finally, although a protocol for this study was prospectively developed, it has not been registered in PROSPERO.

In conclusion, we found that RPO as assessed by perfusion lung scan can be used to identify patients with a high risk of recurrent VTE after anticoagulant treatment for acute PE. However, as all meta-analyses should be regarded as hypothesis-generating, randomized studies are needed before any management strategy can be recommended concerning the duration of anticoagulant treatment or the need for imaging reassessment after an index PE.

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CONFLICT OF INTERESTS

C. Becattini reports receiving lecture fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Daiichi Sankyo. G. Agnelli reports receiving lecture fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Daiichi Sankyo. The other authors state that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

C. Becattini and M. Giustozzi conceived and designed the study. M. Giustozzi, P. Cerdà, A. Riera-Mestre and L. A. Cimini acquired clinical data. C. Becattini, M. Giustozzi and P. Cerdà performed statistical analysis, interpreted results, and drafted the manuscript. All authors performed critical revisions, and read and approved the final version of the manuscript. C. Becattini, M. Giustozzi, P. Cerdà and G. Agnelli had full access to all data in the study, and take responsibility for the integrity of the data and the accuracy of data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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