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Characteristics and outcomes of acute pulmonary embolism among patients with polyvascular, single-vascular or no atherosclerotic disease: insights from RIETE

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Abstract

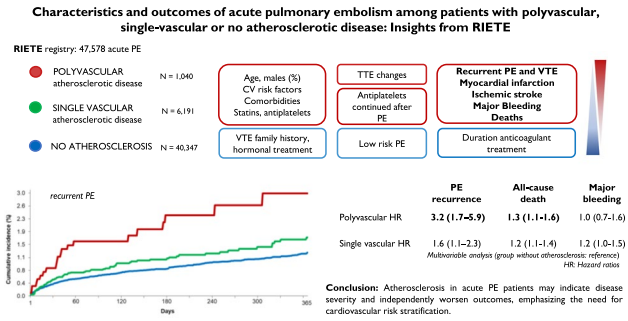
Background The role of atherosclerosis in pulmonary embolism (PE) prognosis remains uncertain. Our study assesses characteristics and outcomes of acute PE patients according to the presence and extent of atherosclerotic disease.

Methods Using data from the RIETE registry, acute PE patients were classified into three groups based on personal history: (1) polyvascular atherosclerosis, (2) single vascular atherosclerosis, and (3) no symptomatic atherosclerosis. Primary outcomes included recurrent PE and venous thromboembolism (VTE), arterial events, major bleeding, and all-cause death. Hazard ratios (HR) and Kaplan–Meier curves for clinical outcomes were estimated using Cox regression models.

Results Among 47,578 acute PE patients, 1,040 had polyvascular, 6,191 single-vascular, and 40,347 no atherosclerosis. During a median follow-up of 331 days, Adverse outcomes were more frequent in patients with atherosclerosis (vs. no atherosclerosis), rising with the number of affected vascular territories. Recurrent PE rates were 2.8, 1.6, and 1.2 per 100 patient-years in the polyvascular, single-vascular, and no atherosclerosis groups. Multivariable analysis showed a dose-dependent relationship between atherosclerosis and recurrent PE risk, with HRs of 3.2 (95% CI 1.7–5.9) and 1.6 (95% CI 1.1–2.3) for polyvascular and single-vascular disease (vs. no atherosclerosis). The risk of all-cause death followed a similar trend, with HRs of 1.3 (95% CI 1.1–1.6) and 1.2 (95% CI 1.1–1.4), respectively. Major bleeding appeared to be influenced by overall health status and antithrombotic therapy intensity.

Conclusion Atherosclerosis in acute PE patients may serve as a marker of disease severity and lead independently to adverse outcomes, highlighting the importance of cardiovascular risk stratification

Graphical Abstract



Keywords Pulmonary embolism · Venous thromboembolism · Atherosclerosis · Cardiovascular disease · Platelet aggregation inhibitors · Registries retrospective studies

Extended author information available on the last page of the article

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Introduction

Acute pulmonary embolism (PE) and atherosclerotic cardiovascular disease have traditionally been regarded as distinct conditions. Over the past decade, studies have shown that individuals with venous thromboembolism (VTE) exhibit a high prevalence of asymptomatic atherosclerosis and are characterized by a two- to three-times higher risk of developing arterial cardiovascular events compared to patients without VTE [1–7]. Moreover, patients with atherosclerosis may have a higher risk of suffering from VTE, particularly if the burden of atherosclerotic disease is larger [8–10].

The underlying mechanisms remain poorly understood. Conditions such as vasculitis, antiphospholipid syndrome, and patent foramen ovale are too rare to be the sole factors. Shared risk factors, such as older age, prothrombotic mutations, hormonal therapy, cancer, and classical cardiovascular risk factors, may predispose to both clinical manifestations [11–17]. The observation that statins and antiplatelet therapy reduce the risk of first-episode and recurrent VTE further supports a causal link [9, 18–23].

A recent retrospective analysis of German nationwide data found that patients with acute PE and symptomatic cardiovascular disease appear to have worse hospital outcomes compared to those without [24]. However, although a formal cardiovascular risk assessment is suggested in patients with PE, there is a lack of information on the characteristics and prognosis of patients with vs. without atherosclerotic disease, and whether the extent of cardiovascular burden would play a further prognostic role.

In this study from the Registro Informatizado Enfermedad TromboEmbolica (RIETE), we described the characteristics of clinical presentation, treatment, and clinical outcomes of acute PE patients with polyvascular, single vascular, or no atherosclerotic disease.

Methods

Data source

We did a patient-level analysis of the RIETE registry, an ongoing multinational multicentre registry that includes consecutive patients with acute VTE confirmed with imaging and a minimum of 3 months follow-up (NCT02832245) [25]. Data extracted from the registry undergo regular on-site monitoring, achieving an overall agreement of 95% between the registered information and patient records. In accordance with local Ethics Committee requirements, patients provided either written or oral consent to participate in the registry [25]. A statistical analysis plan was prepared before formal data analysis for this study. The Ethics Committee on Research from the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) approved the study protocol on April 7, 2017 (code IRB00002131).

Patients diagnosed with PE between February 2009 (the date when all arterial variables were included into the database) and March 2024 were recruited, irrespective of the presence or absence of concomitant deep vein thrombosis (DVT). We stratified them into three groups according to prior clinical manifestations of atherosclerosis. These included: (1) patients with polyvascular atherosclerotic disease, defined as patients with a known personal history of symptomatic atherosclerosis, encompassing two or more of the following diseases: myocardial infarction or angina, cerebrovascular disease (ischemic stroke or transient ischemic attack, regardless of etiology), or peripheral artery disease, (2) patients with single vascular atherosclerotic disease; (3) patients without a prior symptomatic atherosclerotic disease [26].

The primary objective was to provide a comprehensive description of the demographic characteristics, distribution of comorbidities, cardiovascular and thromboembolic risk factors, clinical and radiological features of PE presentation, and treatments across these three groups. Furthermore, we studied the risk of experiencing clinical outcomes, including recurrent VTE, major bleeding, arterial cardiovascular events, and disease-specific death. Major bleeding events were defined according to the ISTH criteria [27]. Anticoagulation management followed the clinical practices of each participating institution, with details on the type, dose, and duration of treatment systematically recorded. Most outcomes were classified and reported from each participant sites.

Statistical analysis

We used descriptive statistics to summarize baseline characteristics, prevalence of risk factors, comorbidities, and concomitant therapies. Data are presented either as count and percentages or in the case of continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR). Additionally, we calculated the incidence rate of adverse events during follow-up as events per 100 patient-years. Cox proportional hazard regression models were used for univariable and multivariable analyses to estimate hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI). Patients without history of atherosclerosis served as the reference group for comparative analyses. Two multivariable Cox regression models were used. Model 1 included age, sex, and anticoagulation duration. Model 2 additionally adjusted for renal failure, prior VTE, anemia, active cancer,

chronic lung and heart disease, low oxygen saturation (≤ 90%), tachycardia (heart rate > 110 bpm), diabetes, and use of antiplatelet agents and statins. Kaplan–Meier survival curves were plotted to visualize and compare time-to-event distributions across groups (VTE and PE recurrence, major bleeding, and all-cause death). Statistical analyses were conducted using SPSS.

Role of the funding source

The authors are solely responsible for the content of this work. No external funding was obtained for this study. The study statistician had full access to all the data. The corresponding author had the responsibility for submission for publication.

Results

We included a total of 47,578 patients with acute PE: of these, 1,040 had polyvascular atherosclerotic disease, 6,191 had a single vascular atherosclerotic disease, and 40,347 had no history of atherosclerotic disease.

Among patients with polyvascular disease, prior myocardial infarction or angina and prior cerebrovascular disease exceeded 70%, whereas peripheral artery disease was described in 64%. Among patients with isolated atherosclerosis, prior myocardial infarction or angina and prior cerebral ischemia exceeded 40%, whereas peripheral artery disease was described in 17%: Table 1.

Baseline characteristics

Patients with polyvascular atherosclerotic disease were older: median age was 79 (IQR: 71–84) years vs. 77 (IQR: 68–83) years among patients with single vascular atherosclerotic disease vs. 68 (IQR: 53–78) years among patients without prior symptomatic atherosclerosis. Patients with atherosclerotic disease had a higher prevalence of classical cardiovascular risk factors, such as male sex, diabetes, arterial hypertension, chronic lung disease, renal failure, atrial fibrillation, particularly if two or more territories were affected. Statins, antiplatelet agents, corticosteroids, anticoagulants (before index PE), and erythropoietin were also progressively more prevalent. The prevalence of smoking and the median body mass index at baseline appeared similar across groups; Table 1.

The prevalence of classical risk factors for VTE appeared similar across the three groups with respect to prior VTE, cancer, and recent surgery. In contrast, prolonged immobility, hormonal treatment, and family history of VTE were less prevalent with an increasing number of territories affected by atherosclerotic disease.

Presentation of acute PE and treatment

The proportion of patients with initial oxygen saturation below 90% was higher in the group of patients with polyvascular atherosclerotic disease (34% vs. 29% with single vascular atherosclerotic disease, vs. 23% with no history of atherosclerotic disease). A similar distribution was found for the proportion of patients with hypotension (4.1% vs. 3.9% vs. 3.0%). Consistently, patients with polyvascular and single vascular disease were less frequently classified as low-risk according to ESC criteria for pulmonary embolism (14% and 19%, respectively), compared to those without atherosclerotic disease (33%); Table 2.

Approximately half of the patients was screened for the presence of concomitant DVT, the distribution of which was similar across groups. Echocardiography was also performed in approximately half of the patients: key findings are summarized in Table 2, indicating a higher prevalence of patent foramen ovale, right atrium dilatation, and right ventricular hypertrophy in patients with atherosclerotic disease.

Cholesterol, LDL-C, and triglycerides levels were lower in patients with polyvascular vs. single vascular vs. no atherosclerotic disease, reflecting the prevalent use of lipid-lowering therapies.

Table 3 summarized the characteristics of initial and long-term treatment. Patients with atherosclerotic disease were more often treated with antiplatelet therapies after acute PE (23% vs. 21% vs. 2.5%, respectively), but the median length of anticoagulation was slightly lower (155 vs. 182 vs. 190 days, respectively).

Clinical outcomes

Patients with polyvascular atherosclerotic disease experienced the highest annual rates of recurrent VTE, with progressively lower rates observed in those with single-territory or no atherosclerotic disease; Table 4. Such trend was driven by recurrent PE events: 2.8, 1.6, and 1.2 per 100 patient-years among patients with polyvascular, single vascular, and without atherosclerotic disease, respectively. Similar trends were documented for myocardial infarction (2.4 vs. 0.8 vs. 0.2 per 100 patient-years), ischemic stroke (1.7 vs. 1.1 vs. 0.4 per 100 patient-years), and major bleeding (5.6 vs. 5.0 vs. 3.2 per 100 patient-years). The leading causes of bleeding were gastrointestinal and intracranial.

Patients with polyvascular disease had the highest rate of death at one year (24.6 per 100 patient-years) followed by patients with single vascular atherosclerotic disease (17.4 per 100 patient-years) and no atherosclerotic disease (9.8 per 100 patient-years). Fatal cardiovascular events, encompassing PE, myocardial infarction, and stroke, and bleeding events contributed to this trend. The cancer-specific death rate was similar across groups.

Table 1 Baseline characteristics of the study population

	Polyvascular atherosclerotic disease	Single vascular atherosclerotic disease	No history of atherosclerotic disease
Patients, N	1,040	6,191	40,347
Demographics			
Male sex, n/N (%)	672 (65)‡	3,320 (54)‡	19,085 (47)
Age (years), median (IQR)	79 (71–84)‡	77 (68–83)‡	68 (53–78)
BMI (kg/m2), median (IQR)	27 (25–30)‡	27 (25–31)	28 (25–31)
CV risk factors			
Current smoker, n/N (%)	141 (14)	706 (12)‡	5,482 (14)
Diabetes, n/N (%)	405 (39)‡	1,681 (27)‡	5,569 (14)
Arterial hypertension, n/N (%)	861 (83)‡	4,531 (74)‡	18,199 (45)
VTE risk factors			
History of VTE, n/N (%)	155 (15)	944 (15)‡	5,465 (14)
Family history of VTE, n/N (%)	10 (2.5)‡	97 (3.8)‡	1,365 (7.0)
Active cancer, n/N (%)	142 (14)*	985 (16)	6,717 (17)
Recent surgery, n/N (%)	99 (9.5)	596 (9.6)	4,211 (10)
Recent immobility ≥ 4 days, n/N (%)	340 (33)‡	1,727 (28)‡	8,068 (20)
Hormonal treatment, n/N (%)	19 (1.9)‡	108 (1.8)‡	2,763 (7.0)
Pregnancy, n/N (%)	0	4 (0.06)‡	184 (0.5)
Postpartum, n/N (%)	1 (0.1)	0	225 (0.6)
Arterial disease			
Prior MI or angina, n/N (%)	803 (77)	2,591 (42)	0
Prior ischemic stroke or TIA, n/N (%)	736 (71)	2,548 (41)	0
Peripheral artery disease, n/N (%)	668 (64)	1,052 (17)	0
Comorbidities			
Atrial fibrillation, n/N (%)	138 (20)‡	526 (12)‡	1,440 (4.9)
Chronic heart failure, n/N (%)	369 (36)‡	1,222 (20)‡	2,313 (5.7)
Chronic lung disease, n/N (%)	299 (29)‡	1,223 (20)‡	4,965 (12)
SAHS, n/N (%)	52 (5.0)†	277 (4.5)‡	1,273 (3.2)
Chronic renal failure, n/N (%)	440 (42)‡	2,131 (34)‡	7,534 (19)
Nephrotic syndrome, n/N (%)	10 (1)†	33 (0.5)	151 (0.4)
Periodic hemodialysis, n/N (%)	4 (0.4)*	13 (0.2)*	36 (0.1)
Liver cirrhosis, n/N (%)	9 (0.9)*	30 (0.5)	160 (0.4)
Liver steatosis, n/N (%)	23 (2.2)†	91 (1.5)†	431 (1.1)
Chronic liver disease (no biopsy), n/N (%)	8 (0.8)	71 (1.1)	383 (1.0)
Antiphospholipid syndrome, n/N (%)	1 (0.1)	5 (0.1)	55 (0.1)
Concomitant therapies			
Corticosteroids, n/N (%)	135 (14)‡	703 (12)‡	3,672 (9.8)
Anticoagulants, n/N (%)	72 (16)‡	318 (11)‡	1,119 (5.6)
NSAIDs, n/N (%)	82 (8.7)*	483 (8.4)‡	2,527 (6.8)
Antiplatelets, n/N (%)	724 (74)‡	3,671 (62)‡	3,956 (11)
Erythropoietin, n/N (%)	10 (1.2)*	47 (1.0)†	185 (0.5)
Statins, n/N (%)	639 (63)‡	3,039 (50)‡	7,598 (19)

Legend: BMI: body mass index; CrCl: creatinine clearance (CrCl < 50 mL/min); CV: cardiovascular; MI: myocardial infarction; NSAIDs: non-steroidal anti-inflammatory drugs; SAHS: sleep apnoea hypopnea syndrome; VTE: venous thromboembolism

Comparisons between subgroups of patients: *$p < 0.05$, †$p < 0.01$; ‡$p < 0.001$

Table 2 Clinical and radiological presentation of pulmonary embolism

	Total	Polyvascular atherosclerotic disease	Single vascular atherosclerotic disease	No history of atherosclerotic disease
Patients, N		1,040	6,191	40,347
Clinical presentation				
HR, mean ± SD		88 ± 21‡	89 ± 21‡	92 ± 20
RR, mean ± SD		22 ± 7.0‡	21 ± 6.6‡	20 ± 6.4
SBP, mean ± SD		129 ± 26	130 ± 25	129 ± 23
SBP < 90 mmHg, n/N (%)		43 (4.1)*	244 (3.9)‡	1,216 (3.0)
$SatO_2$, mean ± SD		91 ± 6.4‡	91 ± 7.2‡	92 ± 6.5
$SatO_2$ < 90%, n/N (%)	26,717	210 (34)‡	1,037 (29)‡	5,165 (23)
PE ESC risk class				
Low risk	46,673	143 (14)‡	1,140 (19)‡	13,141 (33)
Intermediate-low risk	46,673	769 (74)‡	4,342 (71)‡	22,453 (57)
Intermediate-high risk	46,673	78 (7.6)	409 (6.7)	2,695 (6.8)
High risk	46,673	43 (4.2)	244 (4.0)‡	1,216 (3.1)
Laboratory tests				
Total cholesterol, mean ± SD	18,238	158 ± 41‡	161 ± 43‡	177 ± 47
HDL, mean ± SD	12,553	42 ± 34	42 ± 67*	44 ± 31
LDL, mean ± SD,	11,645	93 ± 34‡	96 ± 38‡	110 ± 37
Triglycerides, mean ± SD	16,577	129 ± 61	132 ± 70	134 ± 71
Compression ultrasonography		**584**	**3,466**	**23,693**
Positive (DVT), n/N (%)		353 (60)	1,918 (55)‡	14,345 (61)
Proximal, n/N (%)		267 (76)	1,493 (78)	11,096 (77)
Distal, n/N (%)		66 (19)	337 (18)	2,482 (17)
Helical CT scan		**869**	**5,349**	**36,172**
Segmental and subsegmental, n/N (%)		241 (27.8)	1447 (27.1)	9566 (26)
Lobar, n/N (%)		224 (26)	1,324 (25)	9,201 (25)
Main, n/N (%)		183 (21)*	1,240 (23)	8,722 (24)
Central, n/N (%)		50 (5.8)*	372 (7.0)†	2,969 (8.2)
RV/LV ratio, mean ± SD	3,633	1.1 ± 0.37	1.1 ± 0.31*	1.1 ± 0.36
Echocardiogram		**530**	**3,111**	**20,502**
PAP mean ± SD		47 ± 15†	46 ± 17‡	44 ± 16
Persistent PFO, n/N (%)		8 (3.8)†	43 (3.7)‡	102 (1.2)
Right atrium dilatation, n/N (%)		163 (36)‡	707 (27)‡	3,795 (23)
Right ventricular hypokinesis, n/N (%)		116 (26)*	589 (23)*	3,568 (21)
Right ventricular hypertrophy, n/N (%)		39 (16)‡	147 (10)	902 (8.9)
RVDD/LVDD ratio ≥ 1.0, n/N (%)	3,611	33 (39)	156 (35)	1,085 (35)
TAPSE (mm), mean ± SD	11,187	19 ± 4.8‡	19 ± 5.1‡	20 ± 5.2

Legend: DVT: deep vein thrombosis; HDL: high density lipoprotein; HR: heart rate (beats/min); LDL: low density lipoprotein; LVDD: left ventricular diameter; PAP: pulmonary artery pressure (mmHg); PFO: patent foramen ovale; RR: respiratory rate (breaths/min); RV/LV ratio: right ventricle to left ventricle ratio; RVDD: right ventricular diameter; SatO2: oxygen saturation (%); SBP: systolic blood pressure (mmHg);; TAPSE: Tricuspid annular plane systolic excursion (mm)

Comparisons between subgroups of patients: $^{*}p < 0.05$, $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$

Univariable and multivariable time-to-event Cox regression models

Having a polyvascular or single vascular atherosclerotic disease was associated with recurrent PE and with all-cause death. This association remained significant after adjustment for age, sex, and length of anticoagulation (Model 1) and after full adjustment for several comorbidities and antiplatelet and statin use (Model 2). By increasing the number of conditioning variables, the strength of association between atherosclerotic diseases progressively increased for the outcome recurrent PE: HR 3.2 (95%CI 1.7–5.9) for polyvascular disease vs. no

Table 3 Treatment

	Polyvascular atherosclerotic disease	Single vascular atherosclerotic disease	No history of atherosclerotic disease
Patients, N	1,040	6,191	40,347
Initial treatment			
LMWH, n/N (%)	849 (82)	5,200 (84)†	33,344 (83%)
UFH, n/N (%)	78 (7.5)	452 (7.3)*	2,626 (6.5%)
DOACs, n/N (%)	62 (6.0)	236 (3.8)‡	2,219 (5.5%)
Thrombolytic, n/N (%)	8 (0.8)‡	126 (2.0)†	1,077 (2.7%)
Fondaparinux, n/N (%)	20 (1.9)	96 (1.6)	723 (1.8%)
No anticoagulant drugs, n/N (%)	4 (0.4)	20 (0.3)	92 (0.2%)
Vasopressors, n/N (%)	10 (1.0)	62 (1.0)	328 (0.8%)
ECMO, n/N (%)	1 (0.1)	6 (0.1)	51 (0.1%)
Surgical (or catheter), n/N (%)	12 (1.2)	73 (1.2)	545 (1.4%)
Long term treatment			
Median duration of anticoagulation days, median (Q1-Q3)	155 (93–329)‡	182 (96–367)‡	190 (103–374)
DOACs, n/N (%)	200 (19)‡	1,241 (20)‡	9,743 (24)
VKAs, n/N (%)	491 (47)	2,849 (46)	18,447 (46)
LMWH, n/N (%)	278 (27)	1,682 (27)	10,520 (26)
Other drugs, n/N (%)	11 (1.1)	81 (1.3)	428 (1.1)
No anticoagulant drugs, n/N (%)	13 (1.3)†	49 (0.8)‡	168 (0.4)
Surgical (or catheter), n/N (%)	2 (0.2)	13 (0.2)	66 (0.2)
Antiplatelets continued after VTE, n/N (%)	225 (23)‡	1,245 (21)‡	933 (2.5)

Legend: DOACs: direct oral anticoagulants; ECMO: extracorporeal membrane oxygenation LMWH: low-molecular-weight heparin; UFH: unfractionated heparin.

Comparisons between subgroups of patients: $^{*}p<0.05$, $^{\dagger}p<0.01$; $^{\ddagger}p<0.001$

atherosclerotic disease and HR 1.6 (95%CI 1.1–2.3) for single vascular atherosclerotic disease vs. no atherosclerotic disease in Model 2. In contrast, it progressively reduced for the outcome death: HR 1.3 (95%CI 1.1–1.6) for polyvascular disease vs. no atherosclerotic disease and HR 1.2 (95%CI 1.1–1.4) for single vascular atherosclerotic disease vs. no atherosclerotic disease in Model 2; Table 5.

Similarly to all cause death, the strength of association between polyvascular or single-vascular atherosclerosis and major bleeding progressively reduced by increasing the number of adjustment factors, particularly in patients with polyvascular disease: HR for major bleeding 1.6 (95%CI 1.2–2.2) at univariate analysis, HR 1.2 (95%CI 0.9–1.60) in Model 1, and HR 1.0 (95%CI 0.7–1.6) in Model 2. The Kaplan–Meier curve estimators illustrate the cumulative incidence of clinical events for each outcome; Table 5, Fig. 1 and Supplementary Figs. 1, 2 and 3.

Discussion

In patients with acute PE and a history of atherosclerotic disease from the RIETE registry, compared to those without atherosclerosis, we observed a higher incidence of adverse outcomes, an increased risk of recurrent PE and, albeit modestly, all-cause death, with both findings exhibiting a dose-dependent relationship with the number of arterial beds affected by atherosclerosis: Graphical abstract. Major bleeding risk was not influenced by the presence or extent of atherosclerosis, but was instead associated with the patient's overall health status and the intensity of antithrombotic therapy. These results suggest that atherosclerotic disease, particularly as its burden increases, may serve as a prognostic marker for worse outcomes in patients with acute PE or, even, be implicated in the genesis of future adverse events.

When stratifying PE patients based on the presence and extent of atherosclerosis, significant baseline differences emerged in terms of age, risk factors, comorbidities, and treatment. Patients with polyvascular atherosclerosis, and to a lesser extent those with single-vascular involvement, tended to be older, predominantly male, and had a higher burden of comorbidities, contributing to poorer health status at the time of PE diagnosis. Whether these, or atherosclerosis and its burden itself, could increase the risk of adverse outcomes in these patients was the core issue.

The higher incidence of myocardial infarction and stroke observed in patients with atherosclerosis, particularly in those with multiple arterial beds involved, is consistent with existing

Table 4 Outcomes during anticoagulation

	Polyvascular atherosclerotic disease		Single vascular atherosclerotic disease		No history of atherosclerotic disease	
	N	*Events per 100 patient-years (IC 95%)*	*N*	*Events per 100 patient-years (IC 95%)*	*N*	*Events per 100 patient-years (IC 95%)*
Patients, N	1,037		6,178		40,291	
Recurrent PE	23	2.8 (1.8–4.1)‡	88	1.6 (1.3–1.9)*	460	1.2 (1.1–1.3)
Recurrent VTE	31	3.8 (2.6–5.3)†	132	2.4 (2.0–2.8)	809	2.1 (2.0–2.3)
Major bleeding	47	5.6 (4.2–7.4)‡	281	5.0 (4.5–5.6)‡	1,214	3.2 (3.0–3.4)
Gastrointestinal	20	2.4 (1.5–3.6)‡	86	1.5 (1.2–1.9)‡	362	0.94 (0.8–1.0)
Intracranial	12	1.4 (0.8–2.4)*	66	1.2 (0.9–1.5)‡	243	0.6 (0.6–0.7)
Retroperitoneal	3	0.4 (0.1–1.0)	22	0.4 (0.3–0.6)*	83	0.2 (0.2–0.3)
Vaginal	0	0.0 (0.0–0.4)	3	0.1 (0.0–0.1)	53	0.1 (0.1–0.2)
Other hematoma	5	0.6 (0.2–1.3)	54	1.0 (0.7–1.2)	274	0.7 (0.6–0.8)
Myocardial infarction	20	2.4 (1.5–3.6)‡	46	0.8 (0.6–1.1)‡	75	0.2 (0.2–0.2)
Ischemic stroke	14	1.7 (1.0–2.7)‡	60	1.1 (0.8–1.4)‡	161	0.4 (0.4–0.5)
Limb amputation	1	0.1 (0.0–0.6)	12	0.2 (0.1–0.4)‡	8	0.0 (0.0–0.0)
Death	207	24.6 (21.4–28.1)‡	983	17.4 (16.3–18.5)‡	3,797	9.8 (9.5–10.1)
Fatal PE	22	2.6 (1.7–3.9)‡	91	1.6 (1.3–2.00)‡	270	0.7 (0.6–0.8)
Fatal bleeding	13	1.5 (0.9–2.6)‡	52	0.9 (0.7–1.2)‡	165	0.4 (0.4–0.5)
Fatal MI	8	1.0 (0.4–1.8)‡	10	0.2 (0.1–0.3)‡	14	0.0 (0.0–0.1)
Fatal ischemic stroke	5	0.6 (0.2–1.3)‡	11	0.2 (0.1–0.3)†	26	0.1 (0.0–0.1)
Disseminated cancer	31	3.7 (2.6–5.2)	224	4.0 (3.5–4.5)	1,534	4.0. (3.8–4.2)
Heart failure	23	2.7 (1.8–4.0)‡	65	1.2 (0.9–1.5)‡	148	0.4 (0.3–0.5)

Legend: DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

Comparisons between subgroups of patients: $^{*}p < 0.05$, $^{†}p < 0.01$; $^{‡}p < 0.001$

Table 5 Time-to-event Cox regression analysis

	Polyvascular disease	Single vascular artery disease	Absence of prior atherosclerotic events
Recurrent VTE			
Univariate model	1.7 (1.2–2.4)	1.1 (0.9–1.3)	Reference
Adjusted model 1	1.8 (1.3–2.7)	1.2 (1.0–1.5)	Reference
Adjusted model 2	2.2 (1.3–3.7)	1.3 (1.0–1.8)	Reference
Recurrent PE			
Univariate model	2.2 (1.4–3.3)	1.3 (1.0–1.6)	Reference
Adjusted model 1	2.4 (1.5–3.6)	1.4 (1.1–1.8)	Reference
Adjusted model 2	3.2 (1.7–5.9)	1.6 (1.1–2.3)	Reference
Major Bleeding			
Univariate model	1.6 (1.2–2.2)	1.6 (1.4–1.8)	Reference
Adjusted model 1	1.2 (0.9–1.6)	1.3 (1.1–1.4)	Reference
Adjusted model 2	1.0 (0.7–1.6)	1.2 (1.0–1.5)	Reference
All-cause death			
Univariate model	2.3 (2.0–2.7)	1.8 (1.6–1.9)	Reference
Adjusted model 1	1.4 (1.2–1.6)	1.2 (1.1–1.3)	Reference
Adjusted model 2	1.3 (1.1–1.6)	1.2 (1.1–1.4)	Reference

Legend PE: pulmonary embolism; VTE: venous thromboembolism

Adjusted model 1 (age, sex, length of anticoagulation)

Adjusted model 2 (age, sex, length of anticoagulation, renal failure (CrCl < 50 mL/min), prior VTE, anemia, cancer, chronic lung disease, chronic heart failure, Sat ≤ 90%, heart rate > 110 bpm, diabetes, antiplatelets, statins)

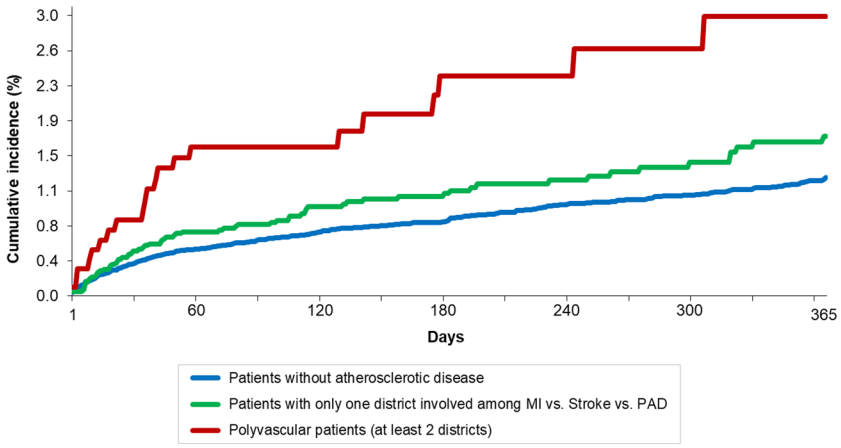

Fig. 1 Kaplan–Meier estimates for pulmonary embolism (PE) recurrences over one year. This graph depicts the cumulative incidence of PE recurrence in patients without atherosclerotic disease (blue line), with single vascular artery disease (green line), and with polyvascular disease (red line). A log-rank test revealed statistically significant differences between the groups (p-value < 0.001)

literature, where polyvascular disease is recognized as an independent risk factor for major cardiovascular events [26, 28–32].

Advanced age, combined with the high prevalence of heart failure, atrial fibrillation, and other cardiovascular and VTE risk factors in these patients, likely contributed to the heightened thrombotic risk and may have driven the increased rates of VTE and recurrent PE in these groups [14, 33]. Similarly, older age and the high prevalence of comorbidities that significantly affect prognosis, such as chronic kidney, lung, and hepatic diseases, along with heart failure, likely contributed to the higher rates of major bleeding and mortality observed in patients with atherosclerosis. Furthermore, over 20% of these patients were receiving concomitant antiplatelet and anticoagulation therapy, further elevating the risk of bleeding.

Cancer, which was equally prevalent across all groups, emerged as the leading cause of death, while PE was the primary cause of death in patients with single-vascular or no atherosclerosis and heart failure was the main cause in those with polyvascular disease.

To assess the independent contribution of atherosclerosis and its burden to adverse outcomes, we examined its association with PE recurrences, accounting for potential confounders. As additional variables were considered, the strength of this association increased, reinforcing that atherosclerosis is linked to an elevated risk of PE and VTE recurrences, particularly in patients with polyvascular disease.

This finding aligns with other studies, which have demonstrated that symptomatic atherosclerosis is associated with an increased risk of VTE [8–10, 34]. Notably, sub-analyses of the TRA2P-TIMI 50 and PEGASUS-TIMI 54 trials, which assessed different antiplatelet regimens in stable symptomatic atherosclerosis, found that the degree of atherosclerotic burden, particularly in polyvascular disease, correlated with a higher VTE risk [9]. These results are relevant, as polyvascular disease appears to increase the risk of both arterial and venous thrombosis compared to isolated atherosclerosis. In terms of recurrent VTE risk, both statins and antiplatelet agents have been shown to reduce primary and secondary VTE risks, indicating a potential role for atherosclerosis in recurrence, even in the absence of direct evidence [9, 18–20, 22, 23]. Our findings support this hypothesis, revealing a dose-dependent relationship between the number of affected arterial beds and the risk of recurrent PE and VTE. While the underlying mechanisms remain unclear, chronic systemic inflammation, endothelial dysfunction, and a prothrombotic state, common to both conditions, may contribute to this overlap [35–37].

In contrast to the strong association between atherosclerosis and recurrent VTE, the increased bleeding risk observed in the univariate analysis was not significant after full adjustment. This indicates that bleeding risk in this population is more likely related to advanced age, comorbidities, and antithrombotic therapy intensity, rather than the atherosclerotic disease burden itself.

Regarding all-cause death, while the association with atherosclerosis weakened after adjustment for confounders, it remained significant, demonstrating a modest but dose-dependent relationship, especially in patients with polyvascular disease, emphasizing its influence on outcomes in PE patients. This relationship between atherosclerosis and PE recurrence, as well as all-cause death, was further supported by our Kaplan–Meier curves, which demonstrated an increasing rate of VTE and PE recurrences and all-cause death with greater atherosclerotic burden.

Our findings underscore the importance of comprehensive cardiovascular risk assessment in all patients with acute PE, aligning with recent recommendations for cardiovascular evaluation at the three-month follow-up after PE diagnosis [38]. Also, for patients with known atherosclerotic disease, it is essential to ensure proper control of existing cardiovascular risk factors, adjusting treatment to meet guideline-recommended targets. Achieving LDL-cholesterol goals is particularly significant, as lipid-lowering therapies have been shown to reduce the risk of both primary and recurrent VTE [9, 18–23]. Additionally, PE patients with a history of symptomatic atherosclerotic

disease, particularly those with polyvascular involvement, may benefit from extended anticoagulant therapy due to their increased risk of PE and VTE recurrence. However, to minimize the risk of bleeding, concomitant anticoagulant and antiplatelet therapies should be reserved for cases with clear indications and discontinued as soon as clinically warranted. This highlights the need for an individualized treatment approach.

The findings of this study should be interpreted in the light of its limitations. The RIETE registry relies on data entered by a variety of practitioners across multiple centres, which could introduce variability in the accuracy of the data. The definition of polyvascular disease was based on symptomatic events in major arterial territories, which likely underestimates the true burden of atherosclerosis by excluding asymptomatic disease and other vascular beds not routinely captured in the registry. In addition, the observational design of this study carries an inherent risk of selection bias, as patients with more severe atherosclerosis may have been more likely to be enrolled and subjected to more intensive monitoring. Although male sex was more prevalent in patients with polyvascular disease, the interaction between sex and atherosclerosis extent was not formally analyzed, as this was beyond the primary objectives of the study. However, sex was included in all multivariable models to mitigate confounding. Despite these limitations, the large, multinational nature of the RIETE registry provides a comprehensive and globally relevant perspective on the interaction between atherosclerosis and PE.

In conclusion, we showed that atherosclerotic disease worsens the prognosis in patients with acute PE, including the risk of recurrent PE and death. These risks were higher in patients with larger burden of atherosclerosis and only partially depended on age, sex, and comorbidities. This finding suggests that especially polyvascular arterial disease in patients with acute PE may serve as a marker of disease severity and also lead independently to adverse events. As per current consensus documents, a formal cardiovascular risk stratification is recommended in patients with acute PE.

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Authors' contributions SC contributed to the concept and design of the study, interpretation of the results, writing of the manuscript, and final approval of the Article. SB, SW, MM contributed to the concept and design of the study, interpretation of the results, writing of the manuscript, and final approval of the Article. PDR, MPP, AS, ZTM, JBLS, PJM contributed to the interpretation of the results, critical revision of the manuscript, and final approval of the Article.

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Data availability The data that support the findings of our study can be accessed through the RIETE registry upon request.

Declarations

Conflict of interest The authors declare that they have no conflict of interesting regarding this work.

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