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Full Length Article

Risk of recurrent venous thromboembolism and bleeding in patients with acute isolated subsegmental pulmonary embolism

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ABSTRACT

Introduction: Approximately 10 % of all diagnosed pulmonary embolism are isolated to the subsegmental vessels. The risk of recurrent venous thromboembolism (VTE) in patients with an acute subsegmental pulmonary embolism (SSPE) managed with or without anticoagulant therapy remains poorly understood.

Methods: This is an observational cohort study including consecutive adult patients diagnosed with acute isolated SSPE between June 01, 2019, and August 31, 2022. We excluded patients with a concomitant diagnosis of deep vein thrombosis and those who had an indication for long-term anticoagulation. The primary outcome was objectively confirmed recurrent VTE.

Results: Overall, 118 patients with acute SSPE were included in the analysis. The mean (± standard deviation [SD]) age of the participants was 59 ± 17 years and 44 % of them had active cancer. Mean (±SD) duration of follow-up was 438 ± 426 days. Seventy-seven patients (65 %) were initially treated with anticoagulation, whereas 41 patients (35 %) were not. Of the 77 patients receiving anticoagulant therapy, 23 (30 %) received extended-duration anticoagulation (beyond 3 months) for secondary prevention. Overall, recurrent VTE events occurred in 6/118 (5 %, 95 % CI 2.4 to 10.7) patients. Four events (4/77 = 5.2 %, 95 % CI 2.0 to 12.6) occurred in initially treated patients. Two recurrent VTE occurred in patients initially left untreated (2/41 = 4.9 %, 95 % CI 1.4 to 16.1). Half of the recurrent VTE occurred in patients with active cancer.

Conclusions: Most patients diagnosed with an acute SSPE received anticoagulation. The incidence of recurrent VTE detected over time was relatively high, especially in patients with cancer.

1. Introduction

The growing availability of computed tomography pulmonary angiography (CTPA) to diagnose pulmonary embolism (PE) has contributed to an increase in the detection of acute PE, particularly those confined to the subsegmental pulmonary arteries. Despite the rising incidence of PE over recent decades, there have been no changes in the overall mortality rate [1]. However, the case fatality rate has decreased, suggesting a potential issue of overdiagnosis and a reduced severity of the illness [1].

The clinical significance of single or multiple isolated subsegmental pulmonary embolism (SSPE) remains unclear. Although a recent multicenter prospective management cohort study of patients with SSPE who did not receive anticoagulant therapy has reported a higher-than-expected rate of recurrent venous thromboembolism (VTE), the risk of recurrent events in this patient population seems to be similar to the rate observed in patients with more proximal PE (i.e., segmental or greater) receiving anticoagulant therapy [2]. Furthermore, the long-term risk of

Abbreviations: CRNMB, Clinically Relevant Non-Major Bleeding; CTPA, Computed Tomography Pulmonary Angiography; DOAC, Direct Oral Anticoagulant; DVT, Deep Vein Thrombosis; LMWH, Low Molecular Weight Heparin; MB, Major Bleeding; PE, Pulmonary Embolism; SSPE, Subsegmental Pulmonary Embolism; VTE, Venous Thromboembolism.

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recurrent VTE (i.e., beyond the initial three months) is unknown as most observational studies followed patients for relatively short periods of time [3]. Hence, the 2021 clinical practice guidelines from the American College of Chest Physicians (ACCP) suggest considering either clinical surveillance or anticoagulant therapy in patients with SSPE depending on the underlying risks of recurrent VTE and bleeding [4]. These recommendations are considered weak and only supported by a low level of evidence. Current available evidence suggests that further studies with longer follow-up periods are needed to establish the risk benefit ratio of anticoagulant therapy in patients with SSPE. Hence, we sought to assess the risk of recurrent VTE and bleeding in patients with acute SSPE, comparing those who received anticoagulant therapy to those who did not.

2. Methods

This is a single center, retrospective cohort study of consecutive patients with SSPE managed at The Ottawa Hospital, Ontario, Canada between June 01, 2019 and August 31, 2022. The study was approved by the Ottawa Health Science Network Research Ethics Board and was conducted according to the Declaration of Helsinki.

Adult patients (≥ 18 years old) with a confirmed diagnosis of acute (single or multiple) SSPE, not started on anticoagulation for concomitant lower extremity deep vein thrombosis (DVT), were included. Acute SSPE was defined as filling defect isolated to sub-segmental pulmonary arteries on CTPA reports based in routine clinical care. Patients were excluded if they had an ongoing indication for anticoagulation for any other indications (e.g., atrial fibrillation, recurrent VTE). Data collection included patients' characteristics (e.g., age, sex, etc.), common risk factors for VTE, comorbidities (e.g., active cancer, chronic kidney failure, etc.), concomitant medications (e.g., antiplatelet agents), SSPE characteristics (incidental vs. symptomatic, single vs. multiple), and anticoagulant therapy regimen (type, dose, duration).

The primary outcome was objectively confirmed recurrent VTE (symptomatic and asymptomatic), defined as a new diagnosis of DVT (at any site) and/or new diagnosis of PE, involving at least segmental pulmonary arteries' branches (not isolated to subsegmental ones). Secondary outcomes included recurrent SSPE, major bleeding (MB), clinically relevant non-major bleeding (CRNMB), overall mortality, fatal recurrent VTE and bleeding episodes. Death of unknown cause was not considered to be related to PE. Recurrence of isolated SSPE was defined as new diagnosis of SSPE, single or multiple, not extending into more proximal vessels, involving either different sites as compared to the index event, or the same ones, as long as there had been an interim scan showing resolution of the index event. Major bleeding and CRNMB were defined as per the International Society on Thrombosis and Haemostasis (ISTH) criteria [5,6].

Continuous variables were summarized using mean and standard deviations (SD) and categorical variables as frequencies and proportions. Comparisons between groups were done using Student *t*-test for continuous variables, and chi-2 test or Fischer's exact test (when appropriate) for categorical variables. Rates of the primary and secondary outcomes were computed during and following discontinuation of anticoagulant therapy (when appropriate). Kaplan-Meier method was used to estimate the cumulative probability of recurrent VTE among overall population, among patients left untreated and among those who received an anticoagulant therapy (i.e., ≥3 months). The log-rank test was used to compare the groups for statistical differences. Patients were censored at time of recurrent event, time of death, or time of the end of follow-up, whichever came first. Analyses were performed using SPSS version 29.0, IBM Corp. We also conducted competing risk analyses, accounting for the risk of death from any cause. The analysis for competing risk was performed using SAS Analytics software.

3. Results

Of the 222 patients with confirmed SSPE identified, 118 patients were included in the analysis (Figs. 1 and 2). Main reasons for exclusion were the presence of another indication to anticoagulant therapy or a concomitant diagnosis of DVT. Mean (± SD) duration of follow-up was 438 (± 426) days. Baseline patients' characteristics are depicted in Table 1. The mean (± SD) age of the overall population was 59 (± 17) years, 53 % were men and 44 % of them had active cancer. A total of 56 (47 %) and 62 (53 %) patients had single and multiple SSPE, respectively.

Seventy-seven patients (65 %) were initially treated with anticoagulation. The most frequently used anticoagulant therapy (78 %) was a direct oral anticoagulant (DOAC). Of the 77 patients managed with anticoagulant therapy, 23 (30 %) were kept on extended-duration anticoagulation (i.e., beyond 3 months and for indefinite duration) for secondary prevention of VTE (Appendix Table 1). The proportion of treated patients among single and multiple SSPE was 32/56 (57 %) and 45/62 (73 %), respectively. Patients left untreated were more likely to be on an anti-platelet treatment and had lower D-dimer levels (Table 1).

Recurrent VTE occurred in 6 (5 %, 95 % CI 2.4 to 10.7) patients. All recurrent events were more proximal PEs (i.e., segmental pulmonary artery or greater). The majority of recurrent events were symptomatic, only one was an incidental finding. Four events (4/77 = 5.2 %, 95 % CI 2.0 to 12.6) occurred in initially treated patients: recurrent VTE occurred despite anticoagulation ($n = 1$), following early discontinuation of anticoagulation (< 3 months) due to interim complications (i.e., stroke and acute kidney injury requiring dialysis) ($n = 2$) or after discontinuation of anticoagulation (≥ 3 months) (n = 1) (Table 2). Two recurrent VTE occurred in patients initially left untreated (2/41 = 4.9 %, 95 % CI 1.4 to 16.1): one was diagnosed with a segmental PE 18 days following the index SSPE diagnosis in the context of hospitalization for medical illness, and one was found to have an incidental segmental unprovoked PE 2 years after the index SSPE. Three patients who had recurrent VTE (50 %) also had active cancer and 5 of them had multiple SSPEs (1 left untreated and 4 treated). Details on recurrent VTE are reported in Appendix Table 2. Of note, one untreated patient had concomitant distal DVT, and did not develop recurrent VTE during follow-up. Although the presence of concomitant DVT is routinely assessed in patients with SSPE in our center, this information was missing in seven patients (all in the group managed without anticoagulation).

The cumulative incidence of recurrent VTE during follow-up was 4.4/100 person-years (95 % CI 2.0 to 9.2). The incidence of recurrent VTE for patients that received anticoagulant therapy vs. left untreated were 4.2/100 person-years (95 % CI 1.6 to 10.2) vs. 4.7/100 person-years (95 % CI 1.3 to 15.7), respectively. Log-rank tests comparing the groups (anticoagulant therapy vs. left untreated) was non-significant ($p = 0.9$) (Appendix Fig. 1). Out of the 35 patients in whom anticoagulation was discontinued after 3 months, 1 experienced a recurrent event, corresponding to an incidence of 1.7/100 person-years (95 % CI 0.3 to 8.9).

Overall, 20 patients (17 %) had MB or CRNMB complications. A total of 19 (24.7 %, 95 % CI 16.4 % to 35.4 %) patients receiving anticoagulant therapy (11 MB and 8 CRNMB) had bleeding complications, whereas only 1 (2.4 %, 95 % CI 0.4 % to 12.6 %) patient left untreated had a CRNMB. Among patients managed with anticoagulation who developed bleeding complications, only 3/19 (16 %) occurred after treatment discontinuation, whereas the majority of them (16/19 = 84 %) were detected while on anticoagulation. Seven of the latter 16 (44 %) patients experienced bleeding events within the first 3 months of treatment of the index event, while the remaining 9/16 (56 %) developed bleeding beyond 3 months of anticoagulation. Log-rank tests comparing the groups (anticoagulant therapy vs. left untreated) was significant ($p = 0.01$) (Appendix Fig. 2).

Most bleeding events were gastrointestinal leading to a significant drop of hemoglobin levels and/or transfusion requirements (Appendix

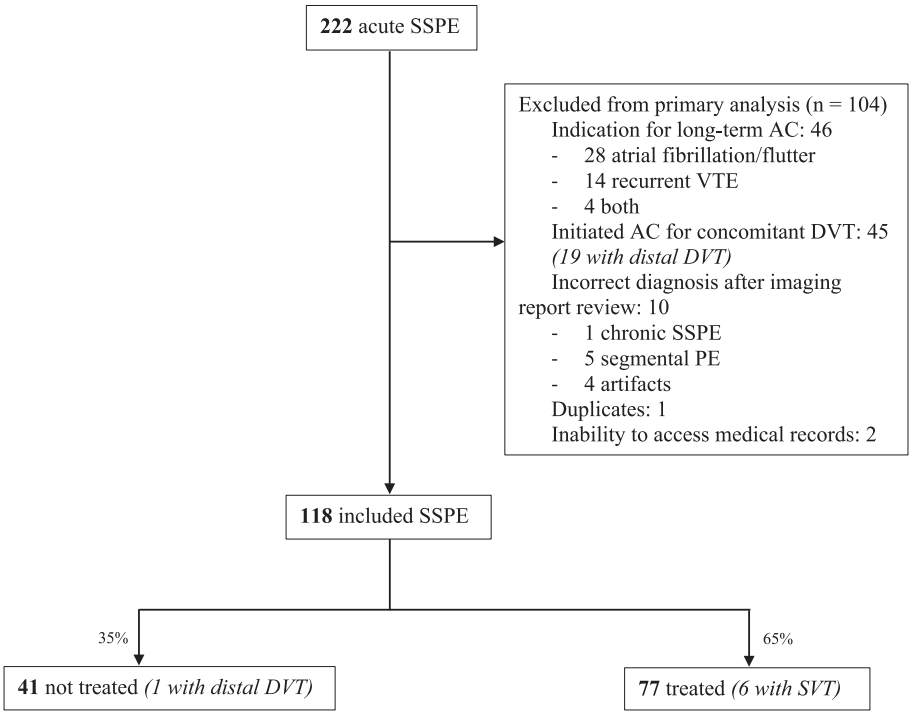

Fig. 1. Study flow diagram. Selection.
AC: anticoagulation. DVT: deep vein thrombosis. SSPE: subsegmental pulmonary embolism. SVT: superficial vein thrombosis. VTE: venous thromboembolism.

Table 3).

Forty-one patients (35 %) died during follow-up, with a similar distribution between treated and untreated patients. Overall, 27/77 (35 %) fatal events occurred among patients treated with anticoagulation, whereas 14/41 (34 %) occurred among those left untreated. The most common cause of death (30/41, 73 %) was cancer. None of the patients died from VTE or bleeding. The majority of patients died within the first few days and up to 3 months after SSPE diagnosis, whereas mortality risk tended to later stabilize (Appendix Fig. 3).

A sensitivity analysis using death from any cause as a competing risk was conducted, and we found similar results when comparing patients managed with anticoagulation to patients who were left untreated (*p* value calculated by Gray test = 0.9).

4. Discussion

In our study, the majority of patients diagnosed with an acute SSPE received anticoagulant therapy. The incidence of recurrent VTE was relatively high and similar between patients receiving anticoagulant therapy and those who did not. Half of the recurrent VTE occurred in patients with active cancer, highlighting that cancer status might be an important underlying risk factor for recurrent events in this patient population.

Most patients with SSPE in our cohort received anticoagulant therapy. Patients included in the study were at high risk of recurrent event. Overall, 44 % of patients had active cancer. Active cancer is a known major risk factor for recurrent VTE [7,8]. A previously published observational study has reported that patients with cancer and SSPE have a high rate of recurrent VTE compared to patients without cancer and patients treated with anticoagulant therapy were at a lower risk of recurrent events (8 % vs. 13 %) compared those who were left untreated [9]. Similarly, another international prospective cohort study reported that patients with cancer and SSPE had a risk of VTE recurrence comparable to patients with more proximal PE, regardless of the type and dose of anticoagulation [10]. Hence, most clinical practice guidelines suggest treatment of any VTE, including SSPE, in patients with cancer [4,11–14]. Furthermore, in our study, patients receiving anticoagulant therapy were more likely to have multiple SSPE and higher D-dimer level (i.e., higher thrombus burden), which are associated with higher risk of recurrent VTE [15]. A recent multicenter prospective management cohort study of patients with SSPE who did not receive anticoagulant therapy has reported a higher rate of recurrent VTE for patients with multiple SSPE compared to those with single SSPE (5.7 % vs. 2.1 %) [2]. Given that the ACCP clinical practice guidelines suggest anticoagulant therapy in patients with SSPE at high risk of recurrent VTE, it is not surprising that clinicians were more likely to initiate anticoagulation for patients with known risk factors for recurrent events (e.g., active cancer, multiple SSPE and high D-dimer) [4,16]. Interestingly, in our study the proportion of cancer patients managed without anticoagulation was not negligible (39 %). In addition to thrombus burden and possible concomitant antiplatelets treatments, other important factors contributing to the decision of starting anticoagulation or not in this subgroup of patients included the overall clinical picture (for example, half of them deceased within 14 days from diagnosis of the index event) and the higher bleeding risk profile (three presented with bleeding complications at the time of SSPE diagnosis and one was on chronic dialysis treatment).

A previous systematic review and meta-analysis assessing the rate of recurrent VTE in patients with SSPE reported incidences of recurrent events of 5.3 % and 3.9 % at 90 days for patients receiving anticoagulant therapy or not, respectively [3]; whereas the frequency of death was 2.1 % for treated versus 3.0 % for untreated patients [3]. Similarly, a multicenter prospective cohort study of patients with SSPE left untreated showed a cumulative incidence of recurrent VTE of 3.1 % (95 % CI 1.6 % to 6.1 %) over a 90-day follow-up period [2]. Hence, our reported rates of recurrent VTE are consistent with previous literature, but also provide cumulative incidence rates over longer follow-up periods. Previous studies mostly reported outcome events over a follow-up period of 90 days or using cumulative incidences up to a maximum 12 months. We also report on the risk of recurrent VTE after completing an at least 3-month course of anticoagulant therapy, which has been understudied thus far. The risk was low but interestingly, a significant

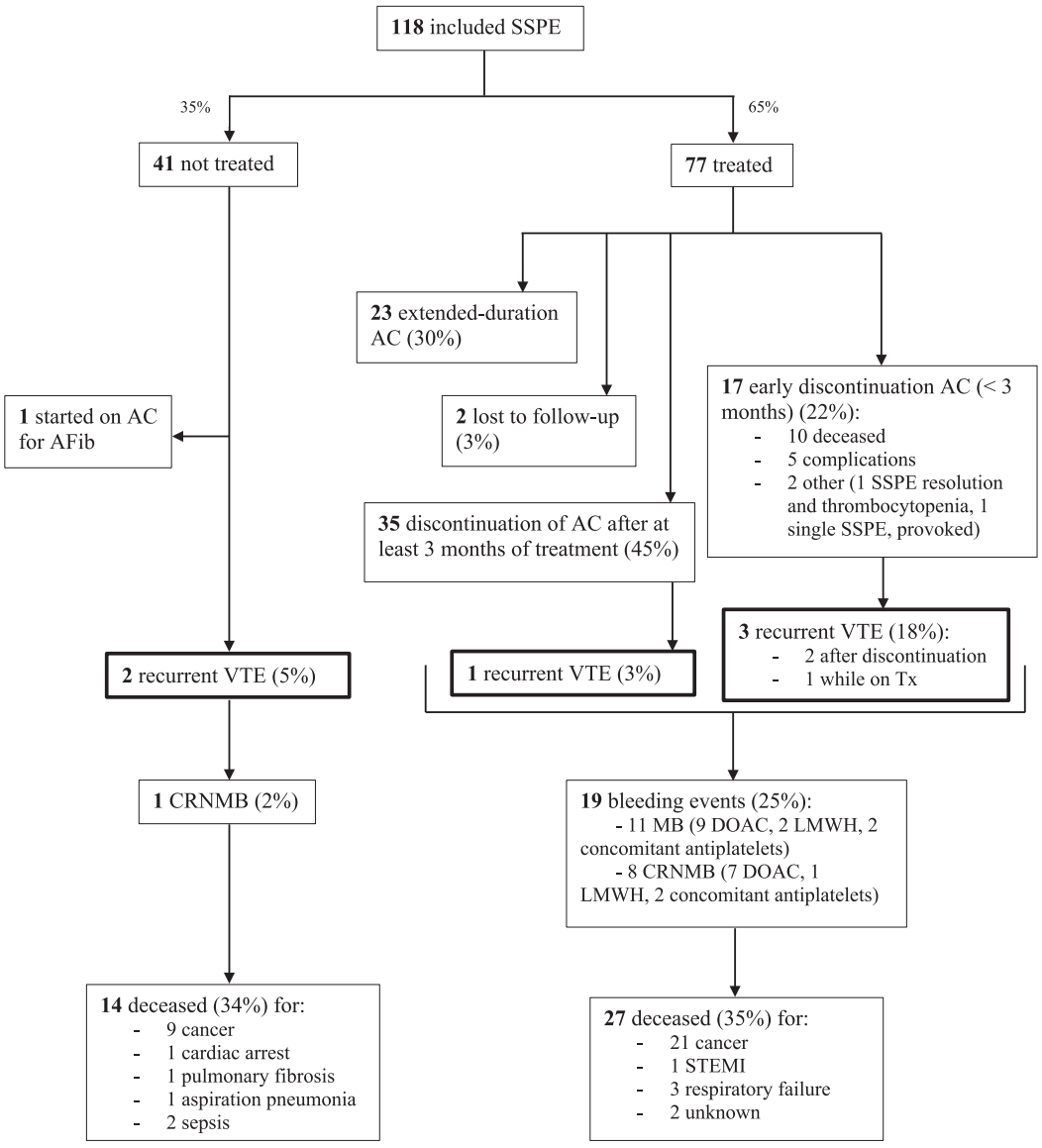

Fig. 2. Study flow diagram. Follow-up.
AC: anticoagulation. AFib: atrial fibrillation. CRNMB: clinically relevant non-major bleeding. DOAC: direct oral anticoagulant. LMWH: low molecular weight heparin. MB: major bleeding. STEMI: ST-elevation myocardial infarction. Tx: treatment. VTE: venous thromboembolism.

proportion (30 %) of SSPE patients were kept on extended anticoagulation, almost half of them were cancer patients (10/23 (43 %)), indicating that physicians often consider extending anticoagulation in patients with isolated SSPE. Two of the six recurrent VTE were diagnosed >2 years after the index SSPE diagnosis. One was an unprovoked segmental PE, occurred in a patient who was left untreated for the index SSPE event, and the other one was a provoked segmental PE, occurred after more than two years after discontinuation of anticoagulation for the index event. These events rates are important for clinicians as they have to be balanced with the potential risk of bleeding complications associated with anticoagulant therapy. In our study, the rates of bleeding complications (MB and CRNMB) were significantly higher in patients receiving anticoagulant therapy compared to patients left untreated (25 % and 2 %, respectively, $p = 0.01$). Patients at high risk of recurrent VTE are also at high risk of bleeding complications, especially in those with cancer [7]. Nine out of 20 patients experiencing bleeding complications had active cancer. The majority of bleeding events were gastrointestinal in origin and occurred in patients receiving anticoagulation beyond 3 months after the index event. Hence, clinicians need to carefully estimate the risks of both recurrent VTE and bleeding complications to decide on initiation of anticoagulant therapy or the use of extended duration of anticoagulation in patients with SSPE. The ongoing SAFE-SSPE trial (NCT04263038) comparing rivaroxaban to placebo for the management of patients with SSPE will provide more insight for clinicians.

It is important to knowledge the limitations of our study. First, the retrospective time horizon may have led to potential selection bias. Second, therapeutic strategies were heterogeneous (anticoagulant type, dose, and duration). The duration of follow-up was also heterogeneous and some patients were lost to follow-up. Third, our sample size was modest with a relatively low number of outcome events leading to wide confidence intervals and imprecision of the event rates. Nonetheless, these event rates provided much-needed evidence to help clinicians make decision about anticoagulant therapy. Furthermore, it provided foundation for researchers to plan future studies to address these important knowledge gaps in the management of patients with SSPE. Fourth, given the low event rates, one cannot adjust for baseline differences, which could lead to confounding. Finally, although the total

Table 1
Comparison of baseline clinical characteristics between patients treated and not treated with anticoagulation.

	Anticoagulation group $n = 77$ (65 %)	No anticoagulation group $n = 41$ (35 %)	*P* values
Demographic			
Mean age (SD), years	59 ± 17	58 ± 16	0.72
Male, n (%)	42 (55 %)	20 (50 %)	0.55
Mean body weight (SD), kg	78 ± 18	73 ± 22	0.32
Comorbidities			
CKD, n (%)	9 (12 %)	3 (7 %)	0.54
CHF, n (%)	8 (10 %)	6 (15 %)	0.56
COPD, n (%)	13 (17 %)	6 (15 %)	0.75
Diabetes, n (%)	9 (12 %)	7 (17 %)	0.42
Previous VTE, n (%)	4 (7 %)	1 (4 %)	1.00
Active cancer, n (%)	36 (47 %)	16 (39 %)	0.42
Disease burden			
Multiple SSPE, n (%)	45 (58 %)	17 (42 %)	0.08
Incidental, n (%)	12 (16 %)	11 (27 %)	0.14
Unprovoked, n (%)	16 (21 %)	14 (34 %)	0.11
Concomitant SVT, n (%)	6 (8 %)	0 (0 %)	0.18
Concomitant DVT not anticoagulated, n (%)	0 (0 %)	1 (2.9 %)[a]	0.31
Other info			
CrCl by CG (SD), mL/min	110 ± 53 mL/min	100 ± 44 mL/min	0.32
D-dimer (SD), μg/L	3553 ± 4378 μg/L	1630 ± 1256 μg/L	0.04
Antiplatelets, n (%)	9 (12 %)	11 (27 %)	0.04
Statin, n (%)	22 (29 %)	16 (39 %)	0.25
Family history of VTE, n (%)	2 (8 %)	1 (11 %)	1.00

CrCl: creatinine clearance. CG: Cockcroft-Gault. CHF: congestive heart failure. CKD: chronic kidney disease. COPD: chronic obstructive pulmonary disease. DVT: deep vein thrombosis. GI: gastrointestinal. GU: genitourinary. SSPE: subsegmental pulmonary embolism. SVT: superficial vein thrombosis. VTE: venous thromboembolism.

[a] Distal lower extremity deep vein thrombosis.

Table 2
Results on outcomes.

	Anticoagulation group n = 77 (65 %)	No anticoagulation group n = 41 (35 %)
Primary outcome		
Recurrent VTE, n (%)	4 (5.2 %)	2 (4.9 %)
Following discontinuation of anticoagulant therapy	1 (1.3 %)	N/A
Despite anticoagulant therapy	1 (1.3 %)	N/A
After early termination of anticoagulant therapy	2 (2.6 %)	N/A
Secondary outcomes		
Recurrent SSPE, n (%)	0	0
MB, n (%)	11 (14.3 %)	0
CRNMB, n (%)	8 (10.4 %)	1 (2.4 %)
Fatal VTE, n (%)	0	0
Fatal bleeding, n (%)	0	0

CRNMB: clinically relevant non-major bleeding. MB: major bleeding. N/A: not applicable. SSPE: subsegmental pulmonary embolism. VTE: venous thromboembolism.

sample population is overall representative of patients with SSPE, subgroup analyses (e.g., patients with cancer, etc.) could not be performed due to the limited sample size.

5. Conclusions

In our study, the majority of patients diagnosed with an acute SSPE received anticoagulant therapy. The incidence of recurrent VTE detected over time was relatively high and similar between patients managed with and without anticoagulant therapy, whereas the rates of bleeding complications were higher among patients receiving anticoagulation, although our study is limited by retrospective design and a modest sample size. Further studies are needed to better understand the risk and benefit of anticoagulant therapy in this patient population.

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CRediT authorship contribution statement

Laura Girardi: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Leonardo Augusto Ciuffini:** Project administration, Conceptualization. **Vicky Mai:** Writing – review & editing, Supervision. **Davide Santagata:** Writing – review & editing, Supervision. **Walter Ageno:** Writing – review & editing, Validation, Supervision. **Tzu-Fei Wang:** Writing – review & editing, Validation, Methodology. **Marc Carrier:** Writing – review & editing, Writing – original draft, Methodology. **Grégoire Le Gal:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

L. Girardi, L. A. Ciuffini, V. Mai, D. Santagata and TF. Wang report no conflicts of interests. W. Ageno reports advisory board honoraria from Bayer, Boehringer Inghelheim, Daiichi Sankyo, BMS/Pfizer, Sanofi, and Portola, and reports research funding and personal fees from Bayer, and personal fees from BMS/Pfizer, Daiichi Sankyo, Sanofi, Aspen, Janssen, and Portola, outside the submitted work. M. Carrier has received research funding from BMS, Pfizer, and Leo Pharma, and honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma. G. Le Gal reports advisory board honoraria from Inari, Pfizer, Sanofi. G. Le Gal holds a Chair on Diagnosis of Venous Thromboembolism at the Faculty of Medicine, University of Ottawa.

Appendix A

Appendix Table 1
Treatments characteristics.

	Tot. patients anticoagulated ($n = 77$)
LMWH, n (%)	17 (22 %)
DOACs, n (%)	60 (78 %)
Prophylactic dose, n (%)	5 (7 %)
Extended-duration AC[a], n (%)	23 (30 %)
IVC filter, n (%)	2 (2 %)

AC: anticoagulation. DOACs: direct oral anticoagulants. IVC: inferior vena cava. LMWH: low molecular weight heparin. Tx: treatment.
[a] Beyond 3 months and for indefinite duration.

Appendix Table 2
Summaries of recurrent venous thromboembolism.

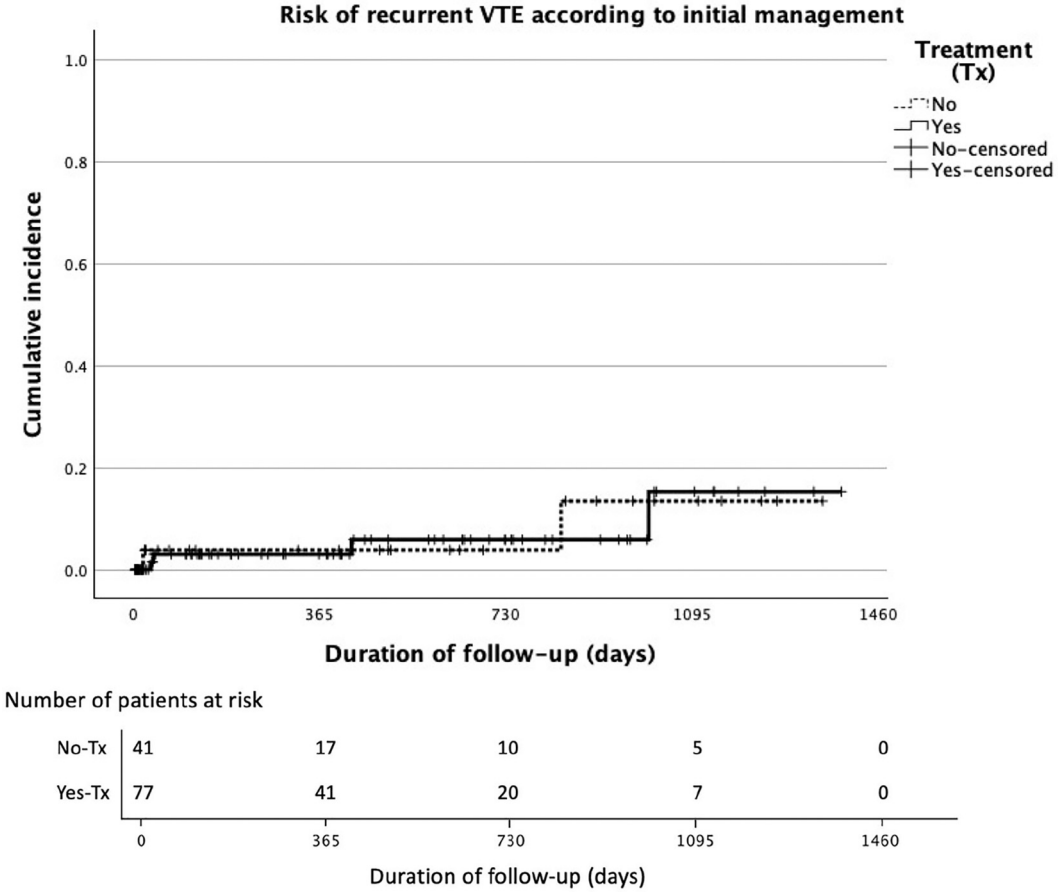
Events among each group	Summary	Time after diagnosis/treatment discontinuation (days)
No anticoagulation group (n = 41)		
Patient 1	Segmental PE, unprovoked, incidental	838
Patient 2	Segmental PE, provoked, symptomatic	18
Anticoagulation group (n = 77)		
Patient 1	Segmental PE, distal DVT, UEDVT, provoked, symptomatic	825 (off treatment)
Patient 2	Segmental PE, provoked, symptomatic	3 (off treatment)
Patient 3	Segmental PE, provoked, symptomatic	406 (off treatment)
Patient 4	Segmental PE, provoked, symptomatic	38 (while **on** treatment)

DVT: deep vein thrombosis. PE: pulmonary embolism. UEDVT: upper extremity deep vein thrombosis.

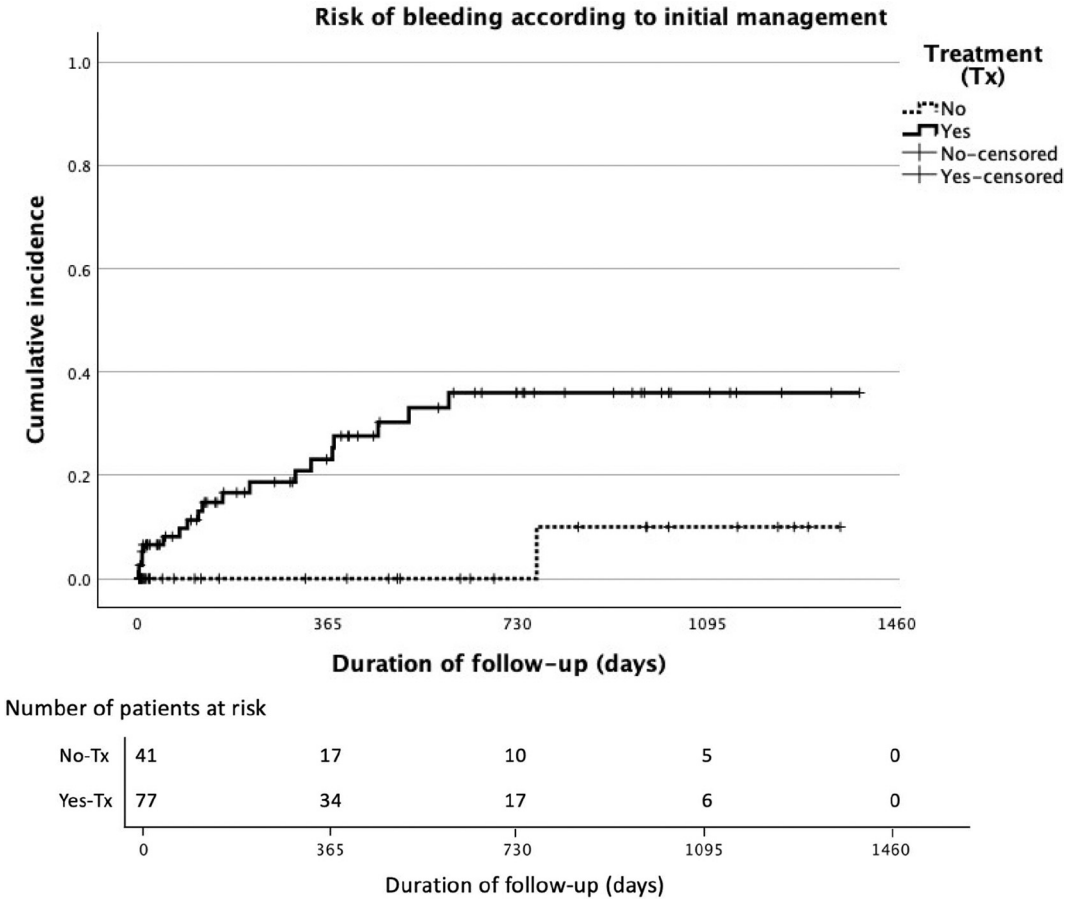
Appendix Table 3
Summaries of bleeding events.

Events among each group	Summary	Time after diagnosis/treatment discontinuation (days)
No anticoagulation group (n = 41)		
Patient 1	CRNMB, premenopausal AUB, after IUD removal	767
Anticoagulation group (n = 77)		
Patient 1[a]	MB, epistaxis leading to drop HGB > 20 g/dL	80 (while **on** treatment)
Patient 2	MB, hemoperitoneum, provoked by surgery	521 (while **on** treatment)
Patient 3	MB, hip hematoma, provoked by surgery	8 (while **on** treatment)
Patient 4	MB, GI + GU, cancer infiltration	163 (while **on** treatment)
Patient 5[a]	MB, GI, melena, transfused 2 units	116 (while **on** treatment)
Patient 6	MB, GI, melena, transfused 2 units	441 (after Tx discontinuation)
Patient 7	MB, GI, melena, transfused 2 units	49 (while **on** treatment)
Patient 8	MB, GI, melena, transfused 2 units	598 (while **on** treatment)
Patient 9	MB, GI, hematemesis and melena, reduction >2 pt. Hgb	377 (while **on** treatment)
Patient 10	MB, GI, hematemesis and melena	333 (while **on** treatment)
Patient 11	MB, GI, chronic angiodysplasia, transfused 2 units	374 (while **on** treatment)
Patient 12	CRNMB, thumb spontaneous hematoma	32 (after Tx discontinuation)
Patient 13	CRNMB, hemoptysis	303 (while **on** treatment)
Patient 14	CRNMB, GU, hematuria	2 (while **on** treatment)
Patient 15	CRNMB, GU, hematuria	1 (while **on** treatment)
Patient 16[a]	CRNMB, GI, chronic angiodysplasia	4 (after Tx discontinuation)
Patient 17	CRNMB, GI, rectal bleeding (rectal tube in place + internal hemorrhoids)	8 (while **on** treatment)
Patient 18[a]	CRNMB, GI, chronic	10 (while **on** treatment)
Patient 19	CRNMB, GI, stoma (Hartmann)	215 (while **on** treatment)

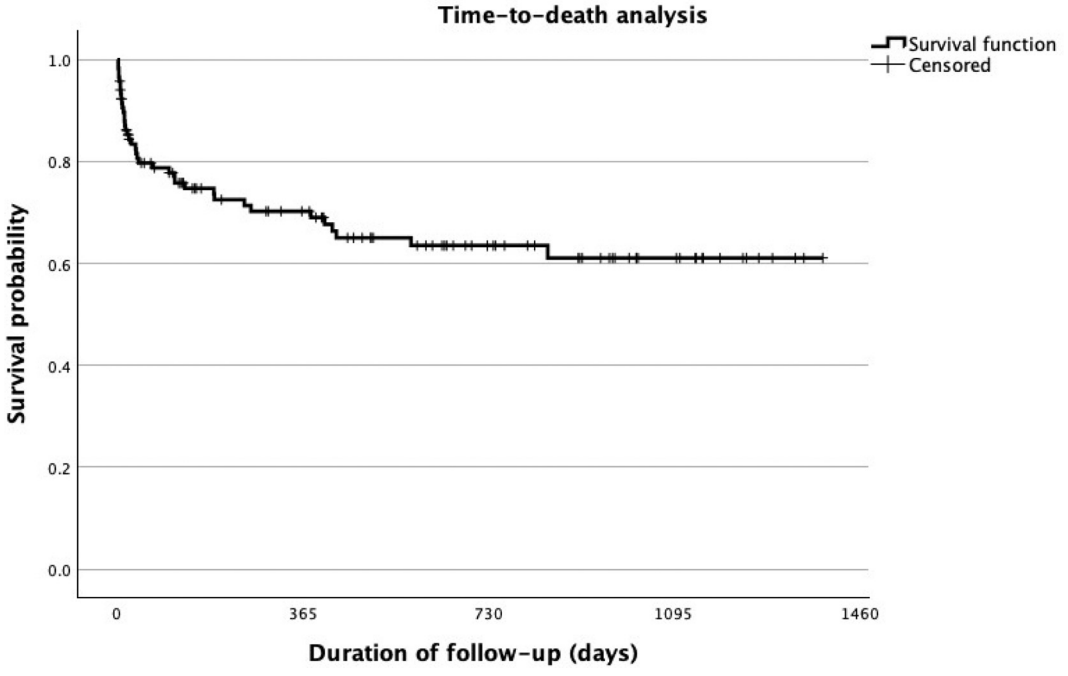
AUB: abnormal uterine bleeding. CRNMB: clinically relevant non-major bleeding. GI: gastrointestinal. GU: genitourinary. HGB: hemoglobin. IUD: intra-uterine device. MB: major bleeding. Tx: treatment.
[a] Patients 1, 5, 16, 18 were using concomitant antiplatelets (patients 1, 5, 16 were on ASA and patient 18 was on ticagrelor).



Appendix Fig. 1. Comparison between patients managed with or without anticoagulation on the risk of recurrent VTE.



Appendix Fig. 2. Comparison between patients managed with or without anticoagulation on the bleeding risk.



Appendix Fig. 3. Mortality analysis.

References

[1] R. C. Auer *et al.*, "Use of helical CT is associated with an increased incidence of postoperative pulmonary emboli in cancer patients with no change in the number of fatal pulmonary emboli," J. Am. Coll. Surg., vol. 208, no. 5, pp. 871–878, May 2009, doi:https://doi.org/10.1016/J.JAMCOLLSURG.2008.12.030.

[2] G. Le Gal *et al.*, "Risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation: a multicenter prospective cohort study," Ann. Intern. Med., vol. 175, no. 1, pp. 29–35, Jan. 2022, doi:https://doi.org/10.7326/M21-2981.

[3] A. Bariteau, L. K. Stewart, T. W. Emmett, and J. A. Kline, "Systematic review and Meta-analysis of outcomes of patients with subsegmental pulmonary embolism with and without anticoagulation treatment," Acad. Emerg. Med., vol. 25, no. 7, pp. 828–835, Jul. 2018, doi:https://doi.org/10.1111/ACEM.13399.

[4] S. M. Stevens *et al.*, "Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report," Chest, vol. 160, no. 6, pp. 2247–2259, Dec. 2021, doi:https://doi.org/10.1016/J.CHEST.2021.07.056.

[5] S. Schulman and C. Kearon, "Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients," J. Thromb. Haemost., vol. 3, no. 4, pp. 692–694, Apr. 2005, doi:https://doi.org/10.1111/J.1538-7836.2005.01204.X.

[6] S. Kaatz, D. Ahmad, A. C. Spyropoulos, and S. Schulman, "Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH," J. Thromb. Haemost., vol. 13, no. 11, pp. 2119–2126, Nov. 2015, doi:https://doi.org/10.1111/JTH.13140.

[7] P. Prandoni *et al.*, "Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis," Blood, vol. 100, no. 10, pp. 3484–3488, Nov. 2002, doi:https://doi.org/10.1182/BLOOD-2002-01-0108.

[8] A. T. Cohen, A. Katholing, S. Rietbrock, L. Bamber, and C. Martinez, "Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study," Thromb. Haemost., vol. 117, no. 1, pp. 57–65, Jan. 2017, doi:https://doi.org/10.1160/TH15-08-0686.

[9] M. Yan, R. Kieser, C. C. Wu, W. Qiao, and C. M. Rojas-Hernandez, "Clinical factors and outcomes of subsegmental pulmonary embolism in cancer patients," Blood Adv., vol. 5, no. 4, pp. 1050–1058, Feb. 2021, doi:https://doi.org/10.1182/BLOODADVANCES.2020003136.

[10] N. Kraaijpoel *et al.*, "Treatment and long-term clinical outcomes of incidental pulmonary embolism in patients with Cancer: an international prospective cohort study," J. Clin. Oncol., vol. 37, no. 20, pp. 1713–1720, Jul. 2019, doi:https://doi.org/10.1200/JCO.18.01977.

[11] H. Robert-Ebadi and M. Righini, "The 2019 ESC guidelines on pulmonary embolism: some further insights," Eur. J. Intern. Med., vol. 77, pp. 6–8, Jul. 2020, doi:https://doi.org/10.1016/J.EJIM.2020.05.007.

[12] N. S. Key *et al.*, "Venous thromboembolism prophylaxis and treatment in patients with Cancer: ASCO clinical practice guideline update," J. Clin. Oncol., vol. 38, no. 5, pp. 496–520, Feb. 2020, doi:https://doi.org/10.1200/JCO.19.01461.

[13] G. H. Lyman *et al.*, "American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer," Blood Adv., vol. 5, no. 4, pp. 927–974, Feb. 2021, doi:https://doi.org/10.1182/BLOODADVANCES.2020003442.

[14] D. Farge *et al.*, "2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19," Lancet Oncol., vol. 23, no. 7, pp. e334–e347, Jul. 2022, doi:https://doi.org/10.1016/S1470-2045(22)00160-7.

[15] P. Wiklund, K. Medson, and J. Elf, "Unreported incidental pulmonary embolism in patients with cancer: radiologic natural history and risk of recurrent venous thromboembolism and death," Thromb. Res., vol. 224, pp. 65–72, Apr. 2023, doi:https://doi.org/10.1016/J.THROMRES.2023.02.010.

[16] C. Kearon *et al.*, "Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report," Chest, vol. 149, no. 2, pp. 315–352, Feb. 2016, doi:https://doi.org/10.1016/J.CHEST.2015.11.026.