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Risk for Recurrent Venous Thromboembolism in Patients With Subsegmental Pulmonary Embolism Managed Without Anticoagulation

A Multicenter Prospective Cohort Study

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Background: The incidence of pulmonary embolism has been increasing, but its case-fatality rate is decreasing, suggesting a lesser severity of illness. The clinical importance of patients with pulmonary embolism isolated to the subsegmental vessels is unknown.

Objective: To determine the rate of recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation.

Design: Multicenter prospective cohort study. (ClinicalTrials.gov: NCT01455818)

Setting: Eighteen sites between February 2011 and February 2021.

Patients: Patients with isolated subsegmental pulmonary embolism.

Intervention: At diagnosis, patients underwent bilateral lower-extremity venous ultrasonography, which was repeated 1 week later if results were negative. Patients without deep venous thrombosis did not receive anticoagulant therapy.

Measurements: The primary outcome was recurrent venous thromboembolism during the 90-day follow-up period.

Results: Recruitment was stopped prematurely because the predefined stopping rule was met after 292 of a projected 300 patients were enrolled. Of the 266 patients included in the primary analysis, the primary outcome occurred in 8 patients, for a cumulative incidence of 3.1% (95% CI, 1.6% to 6.1%) over the 90-day follow-up. The incidence of recurrent venous thromboembolism was 2.1% (CI, 0.8% to 5.5%) and 5.7% (CI, 2.2% to 14.4%) over the 90-day follow-up in patients with single and multiple isolated subsegmental pulmonary embolism, respectively. No patients had a fatal recurrent pulmonary embolism.

Limitation: The study was restricted to patients with low-risk subsegmental pulmonary embolism.

Conclusion: Overall, patients with subsegmental pulmonary embolism who did not have proximal deep venous thrombosis had a higher-than-expected rate of recurrent venous thromboembolism.

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The increasing availability of computed tomography pulmonary angiography in hospital emergency departments and advances in technology have led to a significant increase in the reporting of acute pulmonary embolism, especially for events isolated to the subsegmental pulmonary arteries (1). Although the incidence of pulmonary embolism has been increasing in recent decades, the overall mortality rate has not changed and the case-fatality rate has been decreasing, suggesting overdiagnosis and a lesser severity of illness (2, 3). Hence, the clinical significance of single or multiple isolated subsegmental pulmonary embolism (that is, no pulmonary embolism in segmental or more proximal vessels) remains unknown (4–7).

Previous observational retrospective studies have reported low rates of recurrent venous thromboembolism in some patients with subsegmental pulmonary embolism managed without anticoagulation (8, 9). The American College of Chest Physicians clinical practice guidelines suggest clinical surveillance over anticoagulation in selected patients with subsegmental pulmonary embolism without lower-extremity deep venous thrombosis who have low risk for recurrent venous thromboembolism (10). However, this is a weak recommendation with a low level of evidence (grade 2C). We conducted a prospective international multicenter management cohort study to assess the rate of recurrent venous thromboembolism in patients with single or multiple isolated subsegmental pulmonary embolism without proximal deep venous thrombosis that was managed without anticoagulation.

See also:

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METHODS

Study Conduct and Oversight

The SubSegmental Pulmonary Embolism (SSPE) study (ClinicalTrials.gov: NCT01455818) was a prospective management cohort study assessing clinical outcomes among patients with single and multiple isolated subsegmental pulmonary embolism managed without anticoagulation. The members of the steering committee had final responsibility for the trial design, clinical protocol, and study oversight. The institutional review boards at each of the 18 participating sites from the Investigation Network on Venous Thromboembolism (INNOVTE), the Dutch Thrombosis Network, and the Canadian Venous Thromboembolism Research Network (CanVECTOR) approved the protocol (see the **Supplement**, available at Annals.org). Data were collected at the sites and entered in an online database managed by the Methods Centre of The Ottawa Hospital Research Institute (Canada and the Netherlands) and by the Direction de la Recherche et de l'Innovation at Brest University Hospital (France and Switzerland). A central adjudication committee reviewed all suspected outcome events. An independent data and safety monitoring board (see the **Appendix**, available at Annals.org) periodically reviewed all suspected outcome events and all deaths. The trial was sponsored by Brest University Hospital (France), the Ottawa Hospital Research Institute (Canada), Leiden University Medical Center (the Netherlands), and Geneva University Hospital (Switzerland).

Study Design and Participants

All patients with newly diagnosed isolated subsegmental pulmonary embolism in the study centers over the study period were potentially eligible to participate in the study. Patients were diagnosed in the emergency department and referred to a thrombosis clinic for management. Isolated subsegmental pulmonary embolism was defined as a computed tomography scan showing 1 or more intraluminal filling defects in a subsegmental artery with no filling defects visualized at more proximal pulmonary artery levels. Patients were excluded if they had active cancer, a history of venous thromboembolism, a requirement for oxygen therapy to maintain an oxygen saturation over 92%, or an indication for long-term oral anticoagulant therapy; if they were pregnant; if they had received more than 48 hours of therapeutic anticoagulation before enrollment; or if they were hospitalized at the time of the subsegmental pulmonary embolism diagnosis. Active cancer was defined as any new or ongoing (not in remission) cancer or receipt of any cancer treatment within 6 months of the subsegmental pulmonary embolism diagnosis. The full list of inclusion and exclusion criteria is provided in the protocol (**Supplement**).

Eligible patients with isolated subsegmental pulmonary embolism underwent bilateral lower-extremity venous ultrasonography. Patients with no evidence of deep venous thrombosis did not start anticoagulant treatment, and repeated ultrasonography was performed on day 5, 6, or 7 (diagnostic algorithm period [**Figure 1**]). Patients who remained without deep venous thrombosis on the second bilateral lower-extremity venous ultrasonography did not receive anticoagulant therapy. All patients with proximal (trifurcation of the popliteal vein or more proximal vessels) deep venous thrombosis on initial or repeated ultrasonography were initiated on anticoagulation, whereas the decision to initiate anticoagulation in patients with distal (distal to the trifurcation of the popliteal vein) deep venous thrombosis was left to the treating physicians. All patients were followed for 90 days (follow-up period [**Figure 1**]). Study participants were carefully instructed on the signs and symptoms of venous thromboembolism and were instructed to contact study personnel if they occurred. They were also provided with a reminder card outlining the signs and symptoms and contact information for research staff. At enrollment and at each follow-up telephone call, participants were elicited for new signs and symptoms of deep venous thrombosis and pulmonary embolism. Four interviews were conducted, at day 10 to 14, day 17 to 21, day 24 to 28, and day 85 to 100. Patients with suspected venous thromboembolic events were evaluated by standard testing.

Outcomes

The primary outcome was recurrent venous thromboembolism during follow-up, which was diagnosed according to the following previously published criteria (11, 12): lower-extremity ultrasonography revealing new noncompressibility at the trifurcation of the popliteal vein or more proximal vessels; venography showing a new constant intraluminal filling defect above the trifurcation of the popliteal vein; pulmonary angiography demonstrating a new constant intraluminal filling defect or cutoff of a vessel; ventilation–perfusion scanning with a high probability of pulmonary embolism; computed tomography pulmonary angiography showing a new intraluminal filling defect in a subsegmental or larger pulmonary artery; or pulmonary embolism shown at autopsy. Follow-up started on the date of the repeated bilateral ultrasonography and continued for up to 90 days.

Secondary outcomes included death due to pulmonary embolism and major and minor bleeding during the overall study period. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis as overt bleeding that was associated with a decrease in hemoglobin level of 2 g/dL or more, led to transfusion of 2 or more units of packed red blood cells, occurred at a critical site, or contributed to death (13). Minor bleeding was defined as a bleeding event not meeting the major bleeding criteria. Recurrent venous thromboembolism during the diagnostic algorithm period was identified as a post hoc outcome measure.

Statistical Analysis

The study hypothesis was that isolated subsegmental pulmonary embolism without deep venous thrombosis on repeated bilateral ultrasonography that is managed without anticoagulation is associated with a low rate of recurrent venous thromboembolism. The rate of recurrent events in this patient population was estimated to be 1% at 90 days (8). Using a significance level of $\alpha = 0.05$ and a power of 80%, the target sample size was 300 patients to ensure that the upper bound of the 95% CI of the rate of recurrent venous thromboembolism during the 90-day follow-up would be no higher than 3.0%. No interim analyses were planned, but a stopping rule was in place to cease the study once the upper bound of the 95% CI of the 90-day rate of recurrent venous thromboembolism

was to exceed 5.0% at the end of the study. The data safety and monitoring board recommended stopping recruitment once the a priori stopping rule was met on 18 February 2021. However, follow-up of study participants was continued without anticoagulation. The final sample size was 292 patients, 97% of the initial target.

The primary analysis was the cumulative incidence of recurrent venous thromboembolism during the 90-day follow-up. The start date for each patient was the baseline visit date. The events that were counted in this analysis were those occurring during the follow-up period after the repeated bilateral lower-extremity ultrasonography (days 5 to 7) in patients managed without anticoagulation until the end of follow-up. Patients initiating anticoagulation were censored at the date of treatment. For participants who did not have a recurrent event, the time to "not having an event" was censored at 90 days, the last day the participant was assessed for study outcomes, or death, whichever came first. The Kaplan–Meier method was used to calculate the survival estimates. These estimates were used to calculate the cumulative incidence rate and the associated 95% CI. A cumulative incidence plot was created for graphical presentation of the time to the primary outcome.

Secondary analyses included the incidence of recurrent venous thromboembolism during the diagnostic algorithm period, death due to pulmonary embolism, and major and minor bleeding during the overall study period. Finally, subgroup analyses assessed whether the rate of recurrent venous thromboembolism varied by age (<65 vs. ≥65 years) and the number of isolated subsegmental pulmonary embolisms (single vs. multiple) given that the literature lacks outcomes in those with single versus multiple subsegmental pulmonary embolism (14). The incidence rate and 95% CI were calculated using Poisson regression, with individual-patient follow-up as the exposure variable. Cox proportional hazards regression was used to calculate hazard ratios and the associated 95% CIs.

All statistical analyses were performed with SAS, version 9.4 (SAS Institute), using PROC LIFETEST and PROC GLIMMIX. The cumulative incidence plots were created using R, version 4.0.5 (R Foundation for Statistical Computing).

Role of the Funding Source

The study was funded by the Heart and Stroke Foundation of Canada and the French Ministry of Health Programme Hospitalier de Recherche Clinique. The investigators performed the statistical analyses and wrote the manuscript independent of the funding sources.

RESULTS

Patient Characteristics

From February 2011 through February 2021, a total of 292 patients were included at 18 centers in Canada (8

Figure 1. Study flow diagram.

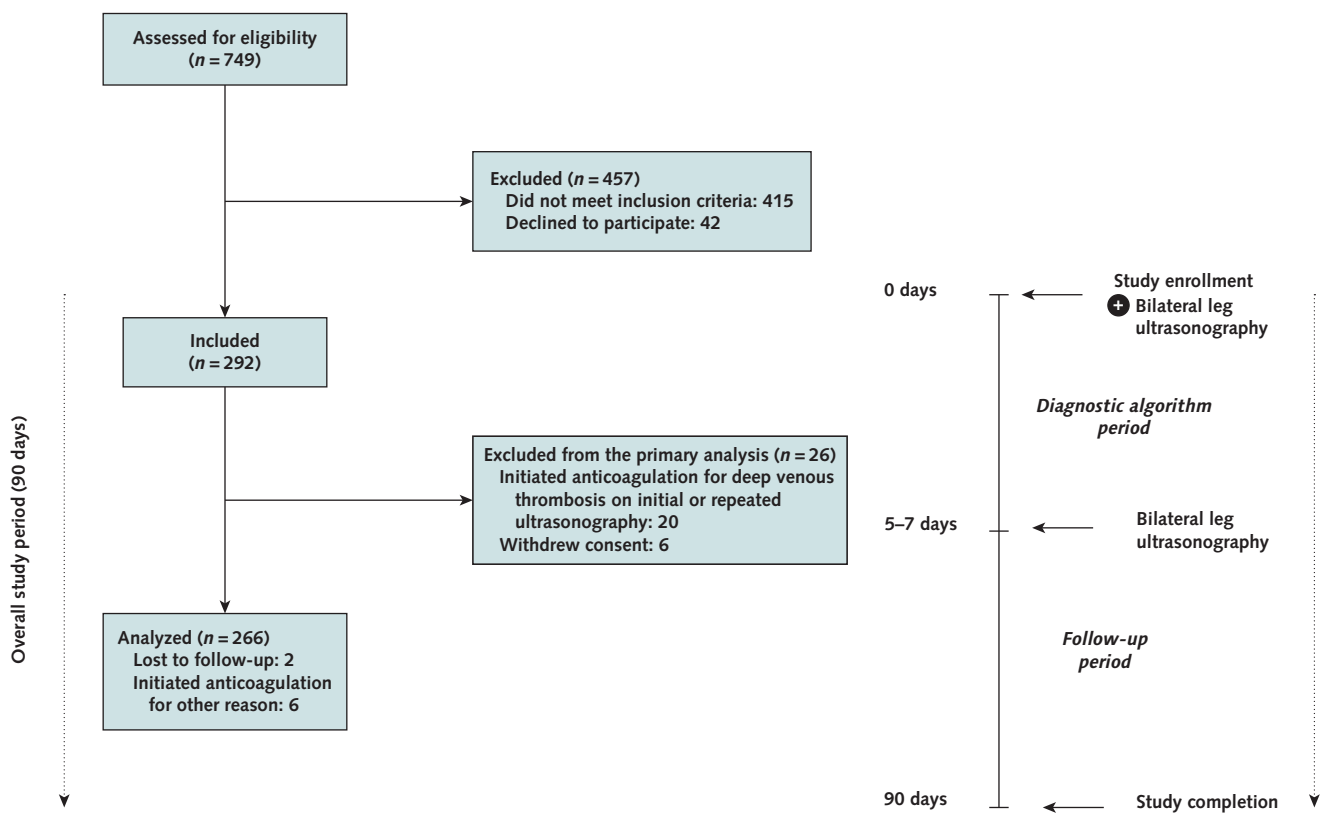


Table. Baseline Clinical Characteristics

Characteristic	Patients With Isolated SSPE (*n* = 292)
Demographic	
Mean age (SD), *y*	55.6 (15.5)
Female, *n (%)*	156 (53.4)
Race/ethnicity, *n (%)*	
White	187 (64.0)
African American	20 (6.9)
Asian	7 (2.4)
Other	4 (1.4)
Unknown*	74 (25.3)
History of cancer, *n (%)*	27 (9.3)
Signs and symptoms of pulmonary embolism, *n (%)*	
Shortness of breath (*n* = 290)	172 (58.9)
Chest pain (*n* = 291)	214 (73.3)
Palpitation (*n* = 274)	78 (26.7)
Hemoptysis (*n* = 281)	18 (6.2)
Syncope (*n* = 277)	42 (14.4)
Number of isolated SSPEs, *n (%)*	
Single	209 (71.6)
Multiple	83 (28.4)
Positive D-dimer result, *n (%)* (*n* = 228)	217 (95.2)
CT scanner, *n (%)*	
Single-detector	1 (0.34)
Multiple-detector (*n* = 218)	
16	2 (0.92)
32	25 (11.5)
64	56 (25.7)
>64	135 (61.9)
Unknown	74 (25.3)
Antiplatelet, *n (%)*	
Acetylsalicylic acid	51 (17.5)
Clopidogrel	4 (1.4)

CT = computed tomography; SSPE = subsegmental pulmonary embolism.
* National regulations prohibit collection of race in France.

centers), France (7 centers), the Netherlands (2 centers), and Switzerland (1 center) (Figure 1; Appendix Tables 1 and 2, available at Annals.org). Baseline characteristics of the patients are shown in the Table. The mean age was 56 years, and a majority were women (53%). The most common presenting symptoms were chest pain (73%) and shortness of breath (59%). Thirteen patients had incidental subsegmental pulmonary embolism. Patients were followed for a total of 793 patient-months.

Of the 292 included patients, 18 (6.2%) and 10 (3.4%) had deep venous thrombosis (6 proximal and 22 distal) on initial or repeated bilateral leg ultrasonography, respectively. Twenty of these patients were initiated on anticoagulation (6 proximal and 14 distal). Eight patients with distal deep venous thrombosis did not receive anticoagulation and were included in the analysis. Six additional patients were initiated on therapeutic dosing of anticoagulation during follow-up for reasons other than recurrent venous thromboembolism (investigator decision [*n* = 4] and atrial fibrillation [*n* = 2]) (Figure 1).

Primary and Secondary Outcomes

Among the 266 patients with isolated subsegmental pulmonary embolism managed without anticoagulation, the primary outcome occurred in 8 patients, for a cumulative incidence of 3.1% (95% CI, 1.6% to 6.1%) over the 90-day follow-up. The incidence of recurrent venous thromboembolism was 1.1% (CI, 0.5% to 2.1%) per month (Figure 2). Four (1.4%) patients had recurrent proximal pulmonary embolism, and 4 (1.5%) had proximal deep venous thrombosis (see Appendix Table 3, available at Annals.org, for details). No patients had a fatal recurrent pulmonary embolism.

During the overall study period, 2 (0.7%) of the 292 included patients had a major bleeding episode, for a rate of 0.7% (CI, 0.2% to 2.9%) over the 90-day follow-up. These patients were not using any antithrombotic therapy, and 1 of the major bleeding events was fatal (massive hemoptysis). Four (1.4%) patients had a minor bleeding event, for a rate of 1.5% (CI, 0.6% to 4.0%) over follow-up (see Appendix Table 4, available at Annals.org, for details). Four (1.4%) patients died; the causes were cancer (*n* = 2), sepsis (*n* = 1), and major bleeding (*n* = 1).

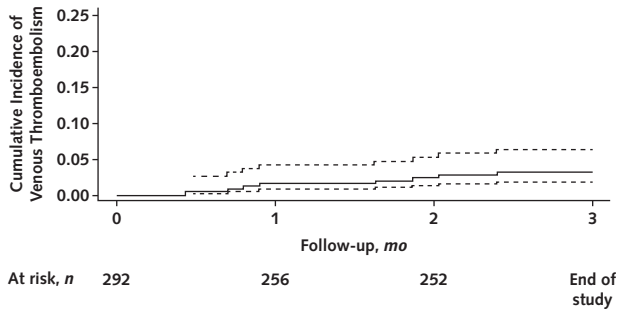
The cumulative incidence of recurrent venous thromboembolism was 2.1% (CI, 0.8% to 5.5%) and 5.7% (CI, 2.2% to 14.4%) over the 90-day follow-up in patients with single and multiple isolated subsegmental pulmonary embolism, respectively (hazard ratio, 2.7 [CI, 0.7 to 11.0]). One of the 8 patients with distal deep venous thrombosis managed without anticoagulation had a recurrent venous thromboembolism (extension to proximal vessels), for an incidence of 12.5% (CI, 1.9% to 61.3%) over the 90-day follow-up. Finally, the cumulative incidence of recurrent venous thromboembolism in the 191 patients with isolated subsegmental pulmonary embolism who were aged 65 years or younger was 1.8% (CI, 0.6% to 5.4%), whereas those older than 65 years (*n* = 101) had a rate of recurrent venous thromboembolism of 5.5% (CI, 2.3% to 12.7%) over the 90-day follow-up (hazard ratio, 3.2 [CI, 0.8 to 13.5]).

DISCUSSION

The SSPE study showed that, among patients who had isolated subsegmental pulmonary embolism without proximal deep venous thrombosis on repeated bilateral ultrasonography and were managed without anticoagulation, the cumulative incidence of recurrent venous thromboembolism was 3.1% (CI, 1.6% to 6.1%) over the 90-day follow-up. No patient had a fatal recurrent pulmonary embolism.

To our knowledge, this is the first prospective study assessing patients with single or multiple subsegmental pulmonary embolism. Recruitment was stopped prematurely because the a priori–predefined stopping rule was met after 292 patients of a projected 300 (97%) were enrolled. During the study planning phase, there was uncertainty in the expected rate of recurrent venous thromboembolism and concerns about potential harms in managing these patients without anticoagulation; therefore, we adopted a conservative stopping rule. The rate of recurrent venous thromboembolism in patients with isolated subsegmental pulmonary embolism was

Figure 2. Time-to-event analysis of recurrent venous thromboembolism.



Dashed lines indicate the 95% CI.

higher than initially expected but seems similar to those with more proximal pulmonary embolism receiving anticoagulation: In a systematic review, the rate of recurrent venous thromboembolism during the first 90 days of anticoagulant therapy in patients with pulmonary embolism was 3.0% (CI, 2.5% to 3.7%) (15). Nevertheless, these event rates need to be considered when deciding on anticoagulation management for this patient population.

Our study can inform patients and clinicians about the risks of managing isolated subsegmental pulmonary embolism without anticoagulation. Our subgroup analyses suggest that the rate of recurrent venous thromboembolism may differ in younger versus older patients or those with single versus multiple isolated subsegmental pulmonary embolism. A subgroup of patients with lower risk for recurrent events might be identifiable in future studies; however, our results support the use of anticoagulation in this patient population. The risk for recurrent venous thromboembolism was identified by the American College of Chest Physicians clinical practice guideline as the most important factor in the decision-making process, in addition to other parameters such as the presence of deep venous thrombosis, cardiopulmonary comorbidities, underlying risk for bleeding, and the patient's values and preferences (10).

A total of 9.6% (CI, 6.5% to 13.6%) of patients with isolated subsegmental pulmonary embolism had deep venous thrombosis on initial or repeated bilateral ultrasonography of the lower extremities. Although this rate is lower than previously reported in patients with more proximal pulmonary embolism (16), it highlights the importance of performing ultrasonography when considering managing patients without anticoagulation because proximal deep venous thrombosis is a definite indication for anticoagulation (10).

All participating centers provide comprehensive venous thrombosis care in their respective regions, and all patients with pulmonary embolism were assessed for eligibility and enrollment, so we believe our results are generalizable to patients with isolated subsegmental pulmonary embolism not requiring oxygen supplementation. However, we did not include patients with high-risk features (such as cancer or previous venous thromboembolism), in whom the risk for recurrent events is likely to be even higher (17, 18). Interobserver reliability of subsegmental filling defect detection in patients with suspected pulmonary embolism has been reported to be low (19). Central adjudication of patients' subsegmental pulmonary embolism diagnoses could not be performed at enrollment. However, our study was pragmatic and representative of current clinical practice, so we believe that our results will be helpful for clinical decision making by practicing clinicians. Finally, as in all trials assessing the initial diagnostic and therapeutic management of patients with acute pulmonary embolism, we followed patients for only 90 days (20). Therefore, we have limited ability to draw definitive conclusions about the long-term rate of recurrent venous thromboembolism. Also, we could not assess the effect of leaving patients untreated on resolution of presenting symptoms, health care use, or the future occurrence of chronic thromboembolic pulmonary hypertension.

In conclusion, patients with isolated single or multiple subsegmental pulmonary embolism who do not have proximal deep venous thrombosis have higher-than-expected rates of recurrent venous thromboembolism. This has implications for management of these patients with anticoagulation in clinical practice.

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Note: Dr. Le Gal holds a Clinical Chair on Diagnosis of Venous Thromboembolism from the Department of Medicine, University of Ottawa, and a Clinician-Scientist Award from the Heart and Stroke Foundation of Canada. Dr. Carrier holds a Clinical Chair on Cancer and Thrombosis, University of Ottawa.

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Data Sharing Statement: Deidentified participant data and the statistical/analytic code will be made available at publication, with no restrictions and for any purpose, to researchers after approval of a proposal and a signed data sharing agreement (e-mail, mcarrier@toh.ca).

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Appendix Table 1. Exclusion Criteria

Exclusion Criteria	Patients Excluded, *n*			
	Canada	The Netherlands	France and Switzerland	Total
Proximal lower- or upper-extremity DVT	11	0	9	20
Need for long-term oral anticoagulation	31	4	24	59
Required oxygen therapy	3	16	9	28
History of DVT or PE	19	0	10	29
Geographic inaccessibility for ultrasonography follow-up	8	0	8	16
Active cancer	86	13	41	140
Pregnancy	4	0	0	4
Hospitalized at time of SSPE	11	0	30	41
Received anticoagulants for >48 h	34	0	12	46
Unable or declined to sign informed consent	24	1	17	42
Other	13	2	17	32
Total	244	36	177	457

DVT = deep venous thrombosis; PE = pulmonary embolism; SSPE = subsegmental pulmonary embolism.

Appendix Table 2. Recruitment Numbers, by Site

City (Site)	Activation Date	Total Recruitment, *n*
Canada		
Ottawa	November 2010	138
London	June 2013	19
Montreal (Jewish General Hospital)	September 2012	12
Halifax	September 2012	11
Hamilton	December 2012	4
Toronto	September 2013	11
Montreal (St. Mary's Hospital)	February 2013	6
Edmonton	February 2015	1
France		
Brest (Centre Universitaire)	August 2011	9
Angers	September 2011	5
Paris	June 2011	29
Brest (Hôpital des Armées)	January 2012	5
Saint-Étienne	October 2012	1
Argenteuil	January 2012	0
Clermont-Ferrand	December 2012	1
Agen	March 2015	3
Lyon	November 2016	0
Switzerland		
Geneva	August 2011	20
The Netherlands		
Amsterdam	May 2016	4
Leiden	May 2016	13

Appendix Table 3. Summaries of Recurrent Venous Thromboembolism

Event	Summary
Pulmonary embolism	
Patient 1	Unprovoked bilateral pulmonary embolism (lobar and segmental arteries) on day 73
Patient 2	Unprovoked bilateral pulmonary embolism (segmental arteries) on day 49
Patient 3	Unprovoked interval progression of subsegmental pulmonary emboli into segmental branches on day 25
Patient 4	Bilateral pulmonary embolism (lobar and segmental arteries) on day 15 after hospitalization
Deep venous thrombosis	
Patient 1	Unprovoked proximal deep venous thrombosis (mid-femoral vein) on day 49
Patient 2	Unprovoked proximal deep venous thrombosis (popliteal vein) on day 27
Patient 3	Unprovoked proximal deep venous thrombosis (popliteal vein) on day 14
Patient 4	Unprovoked proximal bilateral deep venous thrombosis (popliteal veins) on day 62

Appendix Table 4. Summaries of Bleeding Events

Event	Summary
Major bleeding	
Patient 1	Fatal massive hemoptysis from aspergillosis
Patient 2	Upper gastrointestinal bleeding from gastric ulcer
Minor bleeding	
Patient 1*	Mechanical fall; lacerated scalp requiring sutures (no intracranial hemorrhage on CT scan of head)
Patient 2	Gross hematuria secondary to radiation cystitis from prostate cancer diagnosed during follow-up
Patient 3	Limited hemorrhoidal bleeding
Patient 4	Limited intraocular bleeding; patient woke with blood stain on pillow

CT = computed tomography.
* Patient 1 was using acetylsalicylic acid. None of the other patients were using an antiplatelet or anticoagulation.