

Risk Factors for Recurrent Venous Thromboembolism after Unprovoked Pulmonary Embolism.

Results from the PADIS-PE randomized clinical trial.*

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Online supplemental content

List of elements

Title Page.....	1
Pulmonary Vascular Obstruction Index.....	2
Laboratory assays.....	2
eFigure 1. PADIS-PE design	3
eTable 1. Baseline characteristics of study participants according to randomized assignment*4	
eFigure 2. Pulmonary vascular obstruction index ROC curve at inclusion for the prediction of recurrent venous thromboembolism.....	6
eFigure 3. Pulmonary vascular obstruction index ROC curve at diagnosis for the prediction of recurrent venous thromboembolism.....	7
eTable 2. Sensitivity analyses.....	8
References	13

Pulmonary Vascular Obstruction Index

PVOI at the diagnosis of PE and at inclusion (i.e.; at 6 months of anticoagulation) were calculated using scores having been validated and correlated with the Miller index.¹

For PVOI measured on V/Q lung scan, each perfusion scan was scored as described by Meyer *et al.*: (i) each lobe was assigned a weight based on the regional distribution of pulmonary blood flow in the supine position (right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12% and left upper lobe 13%); (ii) for each lobe, a semi-quantitative perfusion score (0, 0.25, 0.5, 0.75 or 1) was estimated from the film density in the anterior, posterior and oblique views by comparison with the photodensity of an apparently normally perfused area; (iii) each lobar perfusion score was then calculated by multiplying the weight by perfusion score; and (iiii) the overall perfusion score was determined by summing the six separate lobar perfusion scores and the percentage of vascular obstruction was then calculated.²

For PVOI measured on CTPA, each lung was divided in 10 segmental arteries (3 to the upper lobes, 2 to the middle lobe and to the lingula and 5 to the lower lobes) as previously described by Qanadli *et al.*: (i) the presence of an embolus in a segmental artery was scored 1 point and emboli in the most proximal arterial level were scored a value equal to the number of segmental arteries arising distally; (ii) to evaluate the residual perfusion distal to the embolus, a weighting factor was assigned to each value, depending on the degree of vascular obstruction (factor equal to zero when no embolus was observed or 1 with partially occlusive embolus or 2 with complete occlusion); and (iii) the maximal pulmonary vascular obstruction score was 40 per patient and results were expressed as percentage of vascular obstruction.³

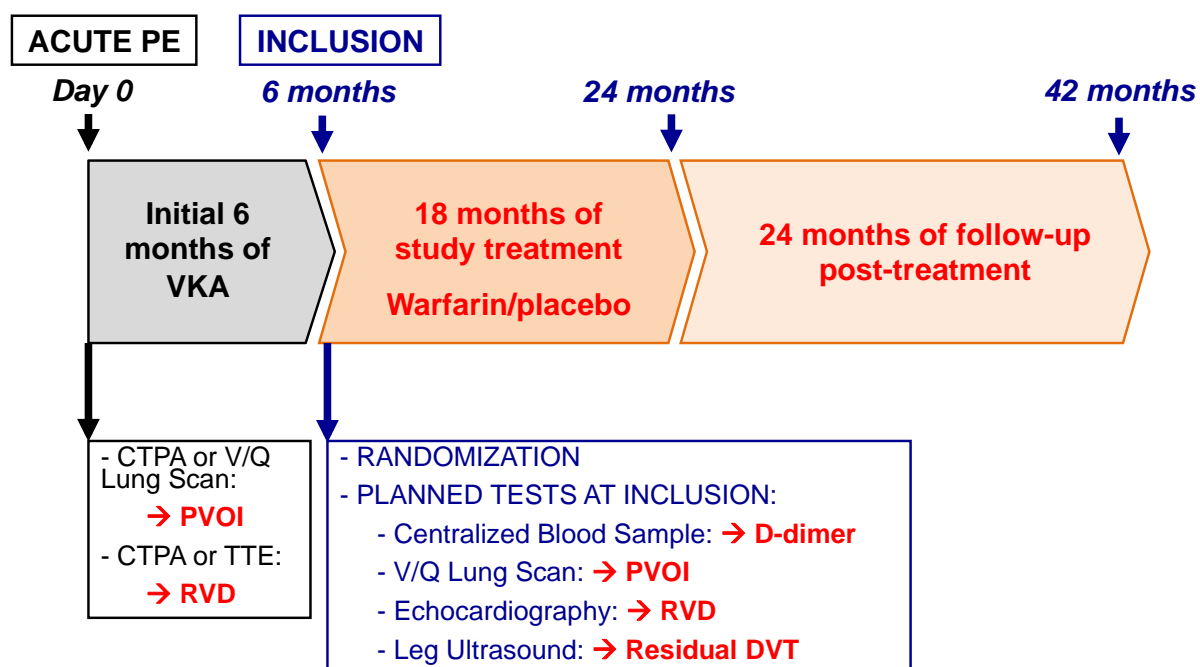
Laboratory assays

Thrombophilia testing was performed for all the patients from centralized frozen blood samples taken at day 0, excepted protein C, protein S and lupus anticoagulant which were measured from frozen plasmas taken at 1 and 19 months in order to obtain results in the absence of anticoagulation (at 1 month in the placebo group and 19 months in the warfarin group). The following assays were performed:

- *Factor V Leiden* was identified as described by Bertina *et al.* and the *G20210A prothrombin gene variant* as described by Poort *et al.*; positive results were classified as heterozygous or homozygous for the mutation.^{4,5}
- *Factor VIII* assay was achieved with a one stage functional clotting assay using specific factor VIII depleted plasma and STA CK Prest (STAGO, Asnières, France). A level above the 90th percentile was considered elevated.
- *Antithrombin* assay (Normal range: 66%-124%) was carried out with a colorimetric anti IIa assay using STA Stachrom AT III kit (STAGO, Asnières, France).
- *Protein C* (Normal range: 54%-166%) and *Protein S* (Normal range: 54%-103%) assays were performed with chromometric methods using respectively STA Staclot Protein C and Protein S kits (STAGO, Asnières, France).
- The presence of *Lupus anticoagulant (LA)* was identified using with at least two LA assays: a dilute Russell viper venom test (dRVVT) (Staclot dRVV Screen and Confirm (STAGO, Asnières, France)), dRVVT being considered positive when the dRVVT screen/dRVVT confirm ratio was >1.2, and a mixing study using LA-sensitive activated partial thromboplastin time reagent PTT (PTT-LA, STAGO, Asnières, France). If either of the assays was abnormal and the confirmatory test provided confirmatory evidence of the test results, patients were considered to have a lupus anticoagulant.⁶
- The presence of an *anticardiolipin antibody*, either IgG or IgM, was determined using a ELISA (Diagnostica Stago, Asnières, France). An anticardiolipin antibody was considered present if either the IgG or IgM antibody titer was more the 99th percentile.⁶
- *D-dimer* levels were measured using quantitative high sensitivity VIDAS D-dimer test (bioMérieux).

eFigure 1. PADIS-PE design

eFigure 1: PADIS-PE design



PE, pulmonary embolism; VKA, vitamin K antagonist; CTPA, spiral computerized tomography pulmonary angiography; V/Q lung scan, ventilation perfusion lung scan; TTE, transthoracic echography; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis

eTable 1. Baseline characteristics of study participants according to randomized assignment*

	Warfarin (N=184)	Placebo (N=187)
Age, mean (SD), yr	58.7 (17.9)	57.3 (17.4)
>65 yr, no. (%)	74 (40.2)	70 (37.4)
<50		
50-65		
>65		
Female, no. (%)	106 (57.6)	84 (44.9)
Body-mass index, mean (SD), kg/m²	27.8 (5.9)	27.1 (5.1)
≥30 kg/m ² , no. (%)	53 (28.8)	39 (20.9)
Blood Group, no. (%)		
A	89/175 (50.9)	98/177 (55.4)
B	15/175 (8.6)	18/177 (10.2)
AB	10/175 (5.7)	6/177 (3.4)
O	47/175 (26.9)	45/177 (25.4)
Not available		
Creatinine clearance category, no. (%)†		
≤50 mL/min	0 (0.0)	0 (0.0)
>50 mL/min	16 (8.9)	7 (3.9)
Medical conditions, no. (%)		
Previous cancer‡	8 (4.3)	6 (3.2)
Previous distal deep-vein thrombosis or superficial-vein thrombosis	17 (9.2)	14 (7.5)
Chronic heart failure	4 (2.2)	9 (4.8)
Chronic respiratory failure	40 (21.7)	35 (18.7)
Chronic inflammatory disease		
Method used to diagnose the incident pulmonary embolism		
High-probability V/Q lung scanning	47 (25.5)	39 (20.9)
CTPA scan	137 (74.5)	148 (79.1)
Characteristics of pulmonary embolism at diagnosis		
RVD at diagnosis, no. (%)§	54/153 (35.3)	56/152 (36.8)
PVOI at diagnosis, mean (SD), %	34.6 (23.4)	35.5 (24.4)
Associated proximal deep-vein thrombosis at diagnosis, no. (%)	56 (31.1)	56 (31.6)
Characteristics of pulmonary embolism at inclusion		
RVD at inclusion, no. (%)¶	13/136 (9.6)	11/133 (8.3)
PVOI at inclusion, mean (SD), %	9.0 (12.7)	8.4 (14.5)
Residual deep-vein thrombosis, no. (%)	25 (13.7)	36 (19.7)
Villalta score		
0 – 4	149 (85.6)	153 (89.0)
5 – 9	16 (9.2)	14 (8.1)
10 – 14	7 (4.0)	4 (2.3)
≥15	2 (1.1)	1 (0.6)
D-dimer level, mean (SD), ng/mL**	382.3 (555.9)	322 (336.4)
D-dimer concentration <250 ng/ml, no. (%)**	92/182 (50.5)	104/185 (56.2)
Treatment of pulmonary embolism prior to randomization		
Warfarin, no. (%)	135 (73.4)	115 (61.5)
Fluindione, no. (%)	49 (26.6)	74 (39.6)
Acecoumarol, no. (%)	2 (1.1)	4 (2.1)
Duration of initial anticoagulation, mean (SD), months	6.3 (0.5)	6.4 (0.5)
Mean (SD) percentage time in therapeutic INR range	69.1 (23.3)	67.8 (22.7)
Use of compression stockings, no. (%)	113 (61.7)	120 (64.2)
Main concomitant treatments, no. (%)		
Antiplatelet agent	16 (8.7)	11 (5.9)

Statins	35 (19.0)	34 (18.2)
Estrogen-containing pill††	28 (15.2)	27 (14.4)
Thrombophilia , no. (%)		
Heterozygous Factor V Leiden	18 (10.1)	16 (8.8)
Homozygous Factor V Leiden	0 (0.0)	1 (0.6)
Heterozygous G20210A prothrombin gene variant	15 (8.5)	9 (5.0)
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	0 (0.0)	2 (1.1)
Elevated factor VIII (90 th percentile)	16 (8.9)	20 (11.1)
Antithrombin deficiency	4 (2.2)	2 (1.1)
Protein C deficiency	0 (0.0)	1 (0.6)
Protein S deficiency	2 (1.1)	2 (1.1)
Anticardiolipin antibodies (99 th percentile)	2 (1.1)	4 (2.3)
Lupus anticoagulant	9 (5.1)	23 (12.7)
Minor thrombophilia – no. (%)‡	46 (26.0)	35 (20.1)
Major thrombophilia – no. (%)‡	6 (3.4)	8 (4.6)

RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; LMWH, low-molecular weight heparin; UFH, unfractionated heparin; INR, international normalized ratio

* Denominators may be lower than 184 and 187 due to missing data for some variables. Baseline characteristics of the two groups were compared using Student's t-test for quantitative variables and Fisher's exact test for qualitative variables. Except for female gender (P=0.02), none of the resulting P values was <0.05.

† Creatinine clearance was estimated by the Cockcroft-Gault method.

‡ Cancer resolved more than two years before patient inclusion.

§ RVD at pulmonary embolism diagnosis was assessed in 305 of 371 patients and was present in 110 of 305 patients: 100 of 305 patients with right ventricular/left ventricular ratio >1 on CTPA or right ventricular/left ventricular ratio >0.9 on trans-thoracic echocardiography and/or 21 of 305 with systolic pulmonary artery pressure >50 mmHg).

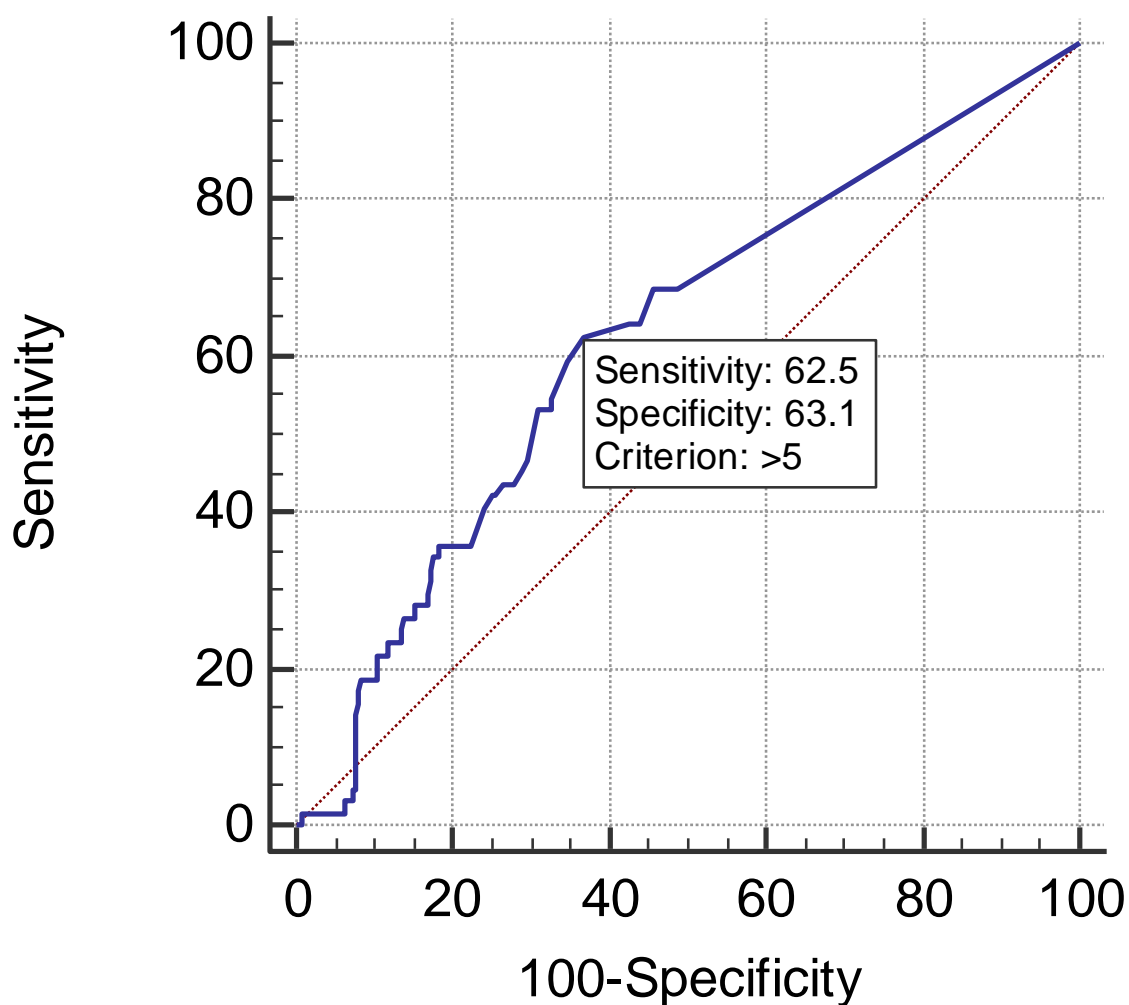
¶ RVD at inclusion was assessed in 269 of 371 patients and was present in 24 of 269 patients (8.9%; 19 patients with right ventricular/left ventricular ratio >0.9 on trans-thoracic echocardiography and/or 7 with systolic pulmonary artery pressure >50 mmHg).

** D-dimer level was measured before randomization while patients were receiving vitamin K antagonist therapy.

†† Fifty five women had an initial pulmonary embolism associated with estrogen-containing pill and stopped this treatment after pulmonary embolism diagnosis; at the time where the PADIS PE trial was designed and started, it was still uncertain if estrogen-containing pill use was associated with a lower risk of recurrence and this population was therefore kept in the analysis when study recruitment ended.

‡‡ Thrombophilia testing was performed for all the patients from centralized frozen blood samples taken at day 0, except for protein C, protein S and lupus anticoagulant which were measured from frozen plasmas taken at 1 and 19 months in order to obtain results in the absence of anticoagulation (at 1 month in the placebo group and 19 months in the warfarin group). Thrombophilia was defined as major if patients had either antithrombin, protein C or protein S deficiency or anticardiolipin antibodies (99th percentile) or positive lupus anticoagulant or homozygous factor V Leiden or combined thrombophilia.

eFigure 2. Pulmonary vascular obstruction index ROC curve at inclusion for the prediction of recurrent venous thromboembolism.



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.623
Standard Error ^a	0.0381
95% Confidence interval ^b	0.565 to 0.678
z statistic	3.225
Significance level P (Area=0.5)	0.0013

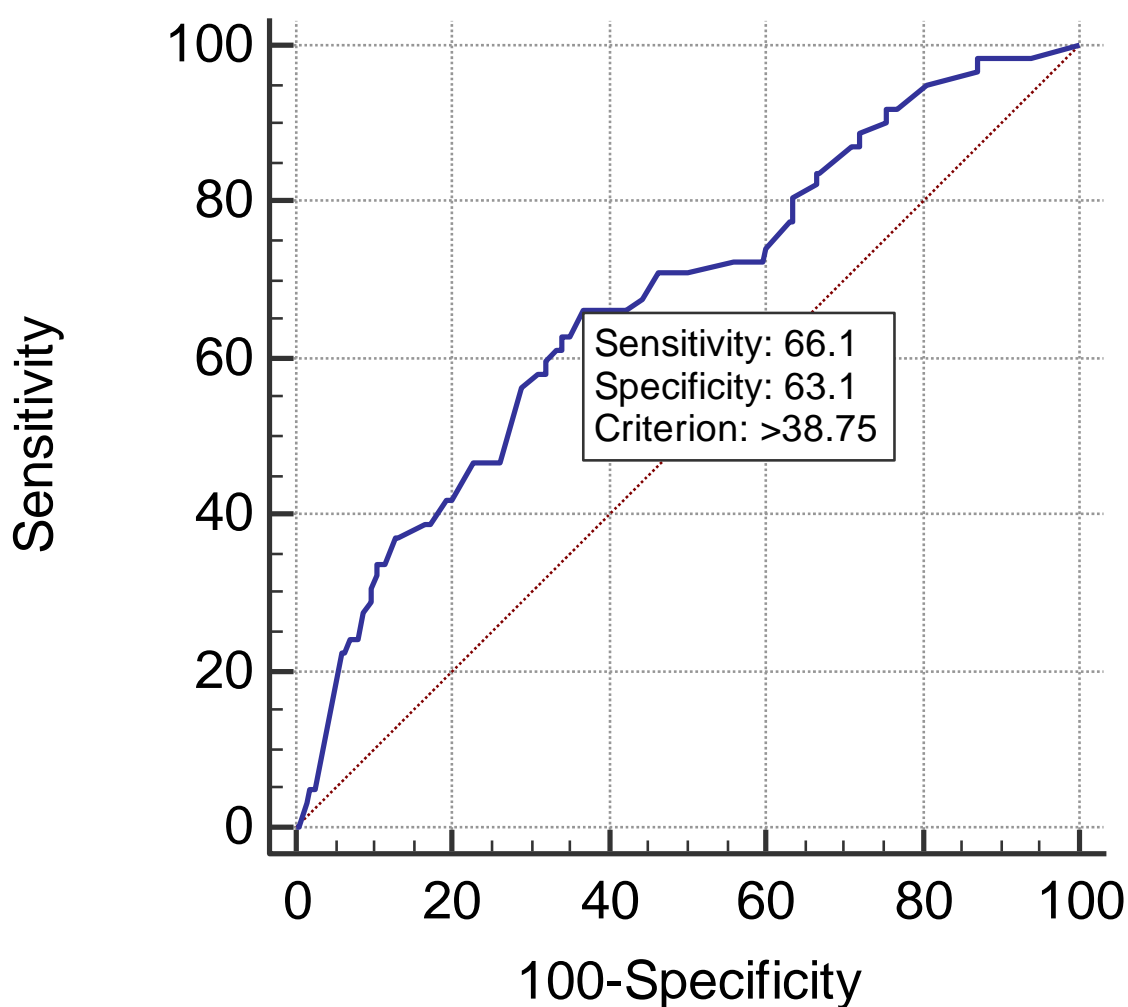
^a DeLong et al., 1988

^b Binomial exact

Youden index

Youden index J	0.2564
Associated criterion	>5
Sensitivity	62.50
Specificity	63.14

eFigure 3. Pulmonary vascular obstruction index ROC curve at diagnosis for the prediction of recurrent venous thromboembolism.



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.672
Standard Error ^a	0.0397
95% Confidence interval ^b	0.612 to 0.728
z statistic	4.342
Significance level P (Area=0.5)	<0.0001

^a DeLong et al., 1988

^b Binomial exact

Youden index

Youden index J	0.2918
Associated criterion	>38.75
Sensitivity	66.13
Specificity	63.05

eTable 2. Sensitivity analyses.

A- Multiple imputation for the three multivariate models

Variables	First Multivariate Model *			Second Multivariate Model†			Third Multivariate Model‡		
	Hazard Ratio (95% CI)	P- value	Estimate (SD)	Hazard Ratio (95% CI)	P- value	Estimate (SD)	Hazard Ratio (95% CI)	P- value	Estimate (SD)
Age <50 y.	Ref.			Ref.			Ref.		
50-65 y.	2.31 (1.00-5.37)	0.051	0.84 (±0.18)	2.31 (0.99-5.38)	0.053	0.84 (±0.19)	2.58 (1.08-6.19)	0.03	0.95 (±0.20)
>65 y.	3.68 (1.69-8.01)	0.001	1.30 (±0.16)	4.07 (1.88-8.81)	0.0004	1.40 (±0.16)	3.56 (1.55-8.15)	0.003	1.27 (±0.18)
Previous Cancer (resolved >2 y.)	2.33 (0.90-6.05)	0.08	0.85 (±0.24)	2.01 (0.76-5.31)	0.16	0.70 (±0.24)	2.24 (0.89-5.67)	0.09	0.81 (±0.22)
Chronic Inflammatory Disease	2.41 (0.93-6.23)	0.07	0.88 (±0.23)	2.02 (0.77-5.33)	0.16	0.71 (±0.24)	2.51 (0.97-6.49)	0.06	0.92 (±0.23)
UFH	1.23 (0.67-2.26)	0.51	0.21 (±0.10)	1.22 (0.66-2.29)	0.53	0.20 (±0.10)	1.40 (0.76-2.60)	0.28	0.34 (±0.10)
RVD at diagnosis	1.07 (0.62-1.87)	0.80	0.07 (±0.08)	0.96 (0.53-1.75)	0.89	-0.04 (±0.09)	1.19 (0.66-2.13)	0.57	0.17 (±0.09)
PVOI									
- <i>First model</i> : PVOI at diagnosis ≥40% and/or PVOI at inclusion ≥5% (over PVOI at diagnosis <40% and PVOI at inclusion <5%)*	2.93 (1.44-5.97)	0.003	1.08 (±0.13)	-	-		-	-	
- <i>Second Model</i> : PVOI at diagnosis ≥40% (over PVOI at diagnosis <40%)†	-	-		2.04 (1.20-3.47)	0.008	0.71 (±0.07)	-	-	
- <i>Third model</i> : PVOI at inclusion ≥5% (over PVOI at inclusion <5%)‡	-	-		-	-		2.23 (1.29-3.85)	0.004	0.80 (±0.08)
Residual DVT at inclusion	2.04 (1.14-3.65)	0.017	0.71 (±0.09)	1.96 (1.10-3.48)	0.02	0.67 (±0.09)	2.05 (1.16-3.62)	0.014	0.72 (±0.08)
D-Dimer <250 µgr/L	1.67 (0.92-3.01)	0.09	0.51 (±0.09)	1.61 (0.89-2.91)	0.12	0.47 (±0.09)	1.75 (0.94-3.26)	0.08	0.56 (±0.10)
APLA (LA and/or CLAs)	1.95 (1.01-3.76)	0.047	0.67 (±0.11)	2.08 (1.08-4.01)	0.03	0.73 (±0.11)	1.76 (0.88-3.51)	0.11	0.56 (±0.12)
Elevated FVIII (90 th percentile)	1.53 (0.78-3.00)	0.21	0.43 (±0.12)	1.79 (0.92-3.47)	0.09	0.58 (±0.11)	1.39 (0.69-2.80)	0.35	0.33 (±0.13)

CI, confidence interval; SD, standart deviation; UFH, unfractionated heparin; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis; APLA, antiphospholipid antibodies; LA, lupus anticoagulant; ACLA, anticardiolipin antibodies; FVIII, factor VIII.

* First model: estimate of PVOI at diagnosis was excluded.

† Second model: estimate of PVOI at inclusion was excluded.

‡ Third model: PVOI at diagnosis and at inclusion were combined into one variable with two categories.

B- Multivariate model that evaluated the impact of predictors for recurrence after stopping anticoagulation (after inclusion in the placebo group and after stopping anticoagulation in the warfarin group)

Variables	First Multivariate Model *		Second Multivariate Model†		Third Multivariate Model‡	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age						
<50 y.	Ref.	0.06	Ref.	0.017	Ref.	0.013
50-65 y.	2.26 (0.72-7.16)		2.56 (1.81-8.05)		3.08 (0.99-9.59)	
>65 y.	3.47 (1.18-10.20)		4.36 (1.49-12.80)		4.98 (1.67-14.8)	
Previous Cancer (resolved >2 y.)	1.93 (0.67-5.60)	0.22	1.95 (0.66-5.71)	0.23	1.73 (0.60-5.01)	0.31
Chronic Inflammatory Disease	2.40 (0.82-7.01)	0.11	2.25 (0.76-6.72)	0.145	2.48 (0.84-7.31)	0.10
UFH	1.20 (0.57-2.52)	0.64	1.24 (0.57-2.69)	0.59	1.62 (0.79-3.30)	0.19
RVD at diagnosis	1.00 (0.51-1.97)	0.99	0.98 (0.47-2.04)	0.97	1.21 (0.62-2.39)	0.57
PVOI						
- <i>First model</i> : PVOI at diagnosis ≥40% and/or PVOI at inclusion ≥5% (over PVOI at diagnosis <40% and PVOI at inclusion <5%)*	6.92 (2.47-19.4)	0.002	-	-	-	-
- <i>Second Model</i> : PVOI at diagnosis ≥40% (over PVOI at diagnosis <40%)†	-	-	2.26 (1.19-3.75)	0.013	-	-
- <i>Third model</i> : PVOI at inclusion ≥5% (over PVOI at inclusion <5%)‡	-	-	-	-	1.95 (1.10-3.73)	0.047
Residual DVT at Inclusion	1.91 (0.97-3.76)	0.06	1.91 (0.97-3.75)	0.06	2.12 (1.09-4.14)	0.027
D-Dimer <250 µgr/L	1.54 (0.73-3.26)	0.26	1.30 (0.61-2.73)	0.49	1.23 (0.59-2.56)	0.59
APLA (LA and/or CLAs)	2.53 (1.20-5.35)	0.015	3.15 (1.45-6.85)	0.004	2.67 (1.17-6.09)	0.019
Elevated FVIII (90 th percentile)	0.98 (0.41-2.34)	0.96	1.12 (0.46-2.71)	0.80	1.12 (0.46-2.69)	0.81

CI, confidence interval; UFH, unfractionated heparin; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis; APLA, antiphospholipid antibodies; LA, lupus anticoagulant; ACLA, anticardiolipin antibodies; FVIII, factor VIII.

* First model: estimate of PVOI at diagnosis was excluded.

† Second model: estimate of PVOI at inclusion was excluded.

‡ Third model: PVOI at diagnosis and at inclusion were combined into one variable with two categories.

C- Multivariate model when excluding antiphospholipid results

Variables	First Multivariate Model *		Second Multivariate Model†		Third Multivariate Model‡	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age						
<50 y.	Ref.	0.01	Ref.	0.009	Ref.	0.03
50-65 y.	3.42 (1.25-9.31)		2.91 (1.06-8.02)		2.69 (0.98-7.44)	
>65 y.	4.24 (1.61-11.2)		4.32 (1.66-11.2)		3.45 (1.32-9.03)	
Previous Cancer (resolved >2 y.)	2.12 (0.73-6.17)	0.16	2.09 (0.72-6.09)	0.17	2.29 (0.78-6.69)	0.13
Chronic Inflammatory Disease	2.01 (0.69-5.82)	0.19	2.01 (0.68-5.92)	0.20	2.25 (0.77-6.54)	0.13
UFH	1.42 (0.76-2.66)	0.27	1.14 (0.57-2.26)	0.71	1.13 (0.58-2.21)	0.72
RVD at diagnosis	1.09 (0.60-1.97)	0.77	0.91 (0.50-1.66)	0.75	0.91 (0.51-1.62)	0.75
PVOI						
- <i>First model</i> : PVOI at inclusion ≥5% (over PVOI at inclusion <5%)*	2.17 (1.21-3.92)	0.0096	-	-	-	-
- <i>Second Model</i> : PVOI at PE diagnosis ≥40% (over PVOI at PE diagnosis <40%)†	-	-	2.46 (1.39-4.34)	0.0019	-	-
- <i>Third model</i> : PVOI at PE diagnosis ≥40% and/or PVOI at inclusion ≥5% (over PVOI at PE diagnosis <40% and PVOI at inclusion <5%)‡	-	-	-	-	4.81 (2.02-11.4)	0.0004
Residual DVT at Inclusion	1.84 (0.98-3.43)	0.05	1.74 (0.93-3.25)	0.08	1.77 (0.95-3.31)	0.07
D-Dimer <250 µgr/L	1.50 (0.79-2.85)	0.21	1.57 (0.82-2.98)	0.17	1.87 (0.97-3.61)	0.06
Elevated FVIII (90 th percentile)	0.98 (0.43-2.20)	0.95	0.99 (0.43-2.28)	0.99	0.84 (0.37-1.90)	0.68

CI, confidence interval; UFH, unfractionated heparin; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis; APLA, antiphospholipid antibodies; LA, lupus anticoagulant; ACLA, anticardiolipin antibodies; FVIII, factor VIII.

* First model: estimate of PVOI at diagnosis was excluded.

† Second model: estimate of PVOI at inclusion was excluded.

‡ Third model: PVOI at diagnosis and at inclusion were combined into one variable with two categories.

D- Multivariate model when excluding the 55 women on estrogen-containing pill at time of pulmonary embolism

Variables	First Multivariate Model *		Second Multivariate Model†		Third Multivariate Model‡	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age						
<50 y.	Ref.	0.03	Ref.	0.02	Ref.	0.07
50-65 y.	2.80 (1.02-7.65)		2.41 (0.87-6.64)		2.29 (0.83-6.35)	
>65 y.	3.54 (1.34-9.36)		3.64 (1.40-9.46)		3.00 (1.14-7.87)	
Previous Cancer (resolved >2 y.)	1.65 (0.56-4.85)	0.36	1.81 (0.61-5.36)	0.28	2.04 (0.69-5.99)	0.19
Chronic Inflammatory Disease	2.04 (0.70-5.98)	0.19	1.98 (0.67-5.84)	0.21	2.08 (0.71-6.07)	0.18
UFH	1.56 (0.83-2.94)	0.16	1.28 (0.64-2.54)	0.48	1.20 (0.62-2.34)	0.58
RVD at diagnosis	1.07 (0.59-1.93)	0.83	0.86 (0.46-1.62)	0.64	0.87 (0.48-1.58)	0.64
PVOI						
- <i>First model</i> : PVOI at inclusion ≥5% (over PVOI at inclusion <5%)*	2.08 (1.15-3.76)	0.01	-	-	-	-
- <i>Second Model</i> : PVOI at PE diagnosis ≥40% (over PVOI at PE diagnosis <40%)†	-	-	2.33 (1.32-4.11)	0.003	-	-
- <i>Third model</i> : PVOI at PE diagnosis ≥40% and/or PVOI at inclusion ≥5% (over PVOI at PE diagnosis <40% and PVOI at inclusion <5%)‡	-	-	-	-	5.83 (2.48-13.7)	<0.0001
Residual DVT at Inclusion	1.66 (0.88-3.11)	0.11	1.57 (0.84-2.95)	0.16	1.64 (0.87-3.10)	0.12
D-Dimer <250 µgr/L	1.46 (0.77-2.76)	0.24	1.52 (0.81-2.86)	0.19	1.73 (0.92-3.26)	0.09
APLA (LA and/or CLAs)	2.38 (1.16-4.92)	0.01	2.58 (1.29-5.16)	0.007	2.07 (1.05-4.08)	0.03
Elevated FVIII (90 th percentile)	1.05 (0.47-2.34)	0.90	1.06 (0.47-2.39)	0.88	0.89 (0.40-2.01)	0.78

CI, confidence interval; UFH, unfractionated heparin; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis; APLA, antiphospholipid antibodies; LA, lupus anticoagulant; ACLA, anticardiolipin antibodies; FVIII, factor VIII.

* First model: estimate of PVOI at diagnosis was excluded.

† Second model: estimate of PVOI at inclusion was excluded.

‡ Third model: PVOI at diagnosis and at inclusion were combined into one variable with two categories.

E- Multivariate model when excluding the 34 patients with APLA

Variables	First Multivariate Model *		Second Multivariate Model†		Third Multivariate Model‡	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age						
<50 y.	Ref.	0.03	Ref.	0.032	Ref.	0.04
50-65 y.	4.83 (1.40-16.7)		4.31 (1.24-15.0)		3.84 (1.09-13.4)	
>65 y.	5.04 (1.47-17.30)		5.09 (1.51-17.20)		3.93 (1.15-13.4)	
Previous Cancer (resolved >2 y.)	1.70 (0.51-5.63)	0.39	1.78 (0.54-5.87)	0.34	1.91 (0.57-6.46)	0.3
Chronic Inflammatory Disease	1.36 (0.31-6.01)	0.69	1.23 (0.27-5.53)	0.79	1.46 (0.33-6.41)	0.62
UFH	1.60 (0.83-3.10)	0.16	1.17 (0.57-2.41)	0.67	1.19 (0.59-2.39)	0.62
RVD at diagnosis	1.19 (0.63-2.26)	0.59	0.95 (0.48-1.86)	0.87	0.96 (0.50-1.86)	0.90
PVOI						
- First model: PVOI at inclusion ≥5% (over PVOI at inclusion <5%)*	1.98 (1.04-3.77)	0.038	-	-	-	-
- Second Model: PVOI at PE diagnosis ≥40% (over PVOI at PE diagnosis <40%)†	-	-	2.51 (1.33-4.75)	0.0046	-	-
- Third model: PVOI at PE diagnosis ≥40% and/or PVOI at inclusion ≥5% (over PVOI at PE diagnosis <40% and PVOI at inclusion <5%)‡	-	-	-	-	5.98 (2.35-15.2)	0.0002
Residual DVT at Inclusion	1.56 (0.75-3.21)	0.23	1.37 (0.64-2.91)	0.42	1.41 (0.66-3.02)	0.37
D-Dimer <250 µgr/L	1.29 (0.62-2.66)	0.50	1.50 (0.70-3.17)	0.29	1.66 (0.78-3.52)	0.19
Elevated FVIII (90 th percentile)	0.90 (0.35-2.31)	0.83	0.90 (0.34-2.40)	0.83	0.81 (0.31-2.09)	0.65

CI, confidence interval; UFH, unfractionated heparin; RVD, right ventricular dysfunction; PVOI, pulmonary vascular obstruction index; DVT, deep vein thrombosis; APLA, antiphospholipid antibodies; LA, lupus anticoagulant; ACLA, anticardiolipin antibodies; FVIII, factor VIII.

* First model: estimate of PVOI at diagnosis was excluded.

† Second model: estimate of PVOI at inclusion was excluded.

‡ Third model: PVOI at diagnosis and at inclusion were combined into one variable with two categories.

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