Risk factors for recurrent venous thromboembolism after unprovoked pulmonary embolism: the PADIS-PE randomised trial

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ABSTRACT We aimed to identify risk factors for recurrent venous thromboembolism (VTE) after unprovoked pulmonary embolism.

Analyses were based on the double-blind randomised PADIS-PE trial, which included 371 patients with a first unprovoked pulmonary embolism initially treated during 6 months who were randomised to receive an additional 18 months of warfarin or placebo and followed up for 2 years after study treatment discontinuation. All patients had ventilation/perfusion lung scan at inclusion (*i.e.* at 6 months of anticoagulation).

During a median follow-up of 41 months, recurrent VTE occurred in 67 out of 371 patients (6.8 events per 100 person-years). In main multivariate analysis, the hazard ratio for recurrence was 3.65 (95% CI 1.33–9.99) for age 50–65 years, 4.70 (95% CI 1.78–12.40) for age >65 years, 2.06 (95% CI 1.14–3.72) for patients with pulmonary vascular obstruction index (PVOI) ⩾5% at 6 months and 2.38 (95% CI 1.15–4.89) for patients with antiphospholipid antibodies. When considering that PVOI at 6 months would not be available in practice, PVOI ⩾40% at pulmonary embolism diagnosis (present in 40% of patients) was also associated with a 2-fold increased risk of recurrence.

After a first unprovoked pulmonary embolism, age, PVOI at pulmonary embolism diagnosis or after 6 months of anticoagulation and antiphospholipid antibodies were found to be independent predictors for recurrence.

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Introduction

After a first episode of unprovoked venous thromboembolism (VTE), extending anticoagulation beyond 3–6 months is associated with a major reduction in the risk of recurrence as long as treatment is continued, but this benefit is not maintained after treatment discontinuation [1, 2]. These results support international guidelines that recommend indefinite anticoagulation in patients with a first unprovoked VTE and a low or moderate risk of bleeding [3, 4].

However, based on the long-term risk estimates of recurrence after unprovoked VTE, indefinite anticoagulation will benefit approximately one-third of patients and expose the remaining two-thirds to an unjustified risk of bleeding [1–7]. As a consequence, identifying risk factors of recurrent VTE remains a major issue in order to select low-risk groups in whom anticoagulation should not be extended and high-risk patients who require indefinite anticoagulation [8]. Several clinical, biochemical or morphological predictors of recurrence have been identified; however, for most of them, the strength of the association with recurrent VTE and their clinical impact were moderate or uncertain [3, 5, 9–17]. Such an issue is of particular importance when unprovoked VTE initially occurred as unprovoked pulmonary embolism because there is evidence that these patients will more likely develop recurrence as a new pulmonary embolism (*i.e.* in ∼80% of cases of recurrence) rather than deep vein thrombosis (DVT), which is associated with a higher case fatality rate [2, 18].

We previously published the results of the PADIS-PE (Prolonged Anticoagulation During 18 months *versus* placebo after Initial Six-month treatment for a first episode of idiopathic Pulmonary Embolism) study, a randomised, double-blind, trial comparing an additional 18 month of warfarin *versus* placebo in 371 patients initially treated during an uninterrupted 6-month period for a first unprovoked pulmonary embolism [2]. In this planned substudy, we aimed to identify predictors of recurrent VTE in this population.

Methods

Study design and population

The design and the main results of the PADIS-PE study have been previously described [2]. Briefly, consecutive patients aged ⩾18 years having experienced a first episode of a proven symptomatic unprovoked pulmonary embolism and having been treated initially for an uninterrupted 6-month period with a vitamin K antagonist were eligible [2]. Pulmonary embolism was unprovoked when occurring in the absence of any major reversible risk factor for VTE within 3 months before diagnosis (*i.e.* surgery with locoregional or general anaesthesia >30 min, trauma with or without plaster cast of the lower limbs and bed rest >72 h) and in the absence of active cancer or cancer resolved within <2 years prior to diagnosis [2]. All participants were enrolled in 14 French hospital centres from July 13, 2007 to March 15, 2012 [2]. The PADIS-PE study was registered at ClinicalTrials.gov with identifier number NCT00740883.

Randomisation and interventions

After an initial 6 months of anticoagulation, patients were included and randomised to either warfarin or placebo for 18 months [2]. After the end of the study treatment period, all patients were followed up for

an additional median period of 24 months (supplementary figure S1) [2]. At the time of inclusion (*i.e.* after the initial 6 months of anticoagulation), all patients underwent centralised frozen blood samples, leg vein ultrasound, ventilation/perfusion (*V*/*Q*) lung scan and transthoracic echocardiography (TTE) according to a predefined methodology and before randomisation (supplementary figure S1) [2]. Centralised frozen blood plasmas were also taken at 1, 18, 19 and 42 months for all patients. After the last patient was followed up, thrombophilia testing was performed by biologists blinded from study treatment allocation and patients' characteristics [2], and all *V*/*Q* lung scans (at inclusion and at pulmonary embolism diagnosis) and spiral computed tomography pulmonary angiography (CTPA) at pulmonary embolism diagnosis were centrally re-interpreted by two independent readers, blinded from the study treatment allocation, the results of other imaging tests and the patients' characteristics.

Outcome measures

The primary outcome for this subanalysis study was symptomatic recurrent VTE, including objectively confirmed nonfatal symptomatic pulmonary embolism or proximal DVT or fatal VTE during follow-up after inclusion in the study [2, 19, 20]. All outcomes were adjudicated blindly by an independent central Clinical Events Committee [2].

The primary assessment of risk factors of symptomatic recurrent VTE was based on pre-specified and prospectively collected variables, including clinical, biochemical (*i.e.* thrombophilia and D-dimer level at inclusion) and imaging variables (residual DVT on leg ultrasound and pulmonary vascular obstruction index (PVOI) on *V*/*Q* lung scan at inclusion) (supplementary material) [2]. The secondary aim was to assess the impact of PVOI measured at the time of pulmonary embolism diagnosis, which was collected retrospectively.

Imaging parameters

Right ventricular dysfunction (RVD) was assessed using TTE at inclusion and using CTPA or TTE in the absence of CTPA at pulmonary embolism diagnosis. RVD was defined by 1) right ventricular/left ventricular diameter ratio >1.0 if measured on CTPA scan (right ventricular and left ventricular diameters were measured by identifying the maximum distance between ventricular endocardium and the interventricular septum perpendicular to the long axis) or >0.9 if measured on TTE (apical or subcostal four-chamber view), or 2) systolic pulmonary arterial pressure >50 mmHg estimated from tricuspid velocity on TTE [21].

PVOIs at pulmonary embolism diagnosis and at inclusion were calculated using scores that were validated and correlated with the Miller index [22]. For PVOI measured on *V*/*Q* lung scan, each perfusion scan was scored as described by Meyer *et al.* [23]; for PVOI measured on CTPA, each lung was scored as described by Qanadli *et al.* [24] (supplementary material).

Residual DVT was defined by failure to fully compress a proximal vein based on bilateral compression ultrasonography of the lower limbs [25].

Laboratory assays

Thrombophilia testing included Factor V Leiden, G20210A prothrombin gene variant, Factor VIII, antithrombin, anticardiolipin antibody assays and D-dimer levels. Testing was performed for all the patients from centralised 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 month in the placebo group and 19 months in the warfarin group in order to obtain results in the absence of anticoagulation (supplementary material).

Statistical methods

All analyses were performed on all randomised patients. Consistent with the PADIS-PE study design, where baseline characteristics were collected at inclusion, the primary outcome was estimated during the follow-up after inclusion (*i.e.* study treatment period plus follow-up after study treatment discontinuation) [2].

Univariate analyses were performed to select predictive variables for the multivariate model, and to determine the association between each potential predictor and VTE recurrence. In univariate analysis, time-to-event outcome was estimated, for each predefined variable, using a Cox proportional hazard regression model with adjustment on study treatment allocation, which provided hazard ratios and corresponding 95% confidence intervals. In multivariate analysis, variables were selected on the following basis: 1) p-value <0.15 in univariate analysis, 2) prevalence >3% and 3) clinical relevance. Prior to the multivariate analysis, correlations and interactions were systematically searched between variables of interest. For continuous variables that were statistically significant, the discriminant power was determined

by calculating the area under the curve (AUC) on receiver operating characteristic (ROC) curve analysis; the most discriminant cut-off was then determined by calculating the Youden index.

For the primary objective of the study, a multivariate model was performed including all the variables selected on the above criteria. Regarding the second objectives, additional multivariate models were performed: 1) in the case where *V*/*Q* lung scan at inclusion would not be available in current practice and where PVOI at the diagnosis of pulmonary embolism could be properly calculated (model 2), and 2) in the case where both PVOI at inclusion and at pulmonary embolism diagnosis would be available (model 3).

Based on hazard ratio estimates, a score was built from each of these multivariate models. Cut-off values were chosen for each score to discriminate low-, intermediate- and high-risk groups. The predictive accuracy was assessed for each score by calculating sensitivity, specificity, negative and positive predictive values, and their 95% confidence intervals. Regarding internal validation, the Harrell C index, uncorrected and corrected after bootstrapping, was calculated for each score [26]. The bootstrapping procedure was repeated 500 times.

Lastly, predefined sensitivity analyses were performed: 1) using a multiple imputation model and 2) on a modified study population where primary outcome was estimated after anticoagulation was stopped (*i.e.* from inclusion in the placebo group and from anticoagulation discontinuation in the warfarin group). All tests were two sided and a p-value <0.05 was considered to be statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 374 enrolled patients, three withdrew consent and refused inclusion of their data in the analysis, leaving 184 patients randomised to warfarin and 187 to placebo (371 in total) [2]. At inclusion, the median (interquartile range (IQR)) duration of initial anticoagulation in the entire cohort was 6.3 (6.0–6.7) months. After randomisation, the median (IQR) length of follow-up was 40.9 (29.3–41.3) months in the overall cohort (40.9 (29.2–41.3) and 40.9 (29.3–41.3) months in the warfarin and placebo group, respectively).

Characteristics of the study population

Mean±SD age was 58.0±17.7 years and 190 (51.2%) patients were female. 55 females were on the oestrogen-containing pill and none were on substitutive hormonal therapy. Among persistent risk factors for VTE, chronic inflammatory disease was present in 12 (3%) patients (rectocolitis in one patient; polyarthritis or Horton disease in 11 patients) and previous cancer in 14 (3.8%) patients (supplementary table S1).

At the time of pulmonary embolism diagnosis, a proximal DVT was present in 112 out of 357 patients (31.4%); RVD was present in 110 out of 305 patients (36.1%). The mean±SD PVOI measured using CTPA in 284 patients and *V*/*Q* lung scan in 87 patients was 35.0±23.9%.

At inclusion, a nonfully compressible proximal vein was present in 61 out of 365 patients (16.7%); RVD was present in 24 out of 269 patients (8.9%). Mean±SD PVOI measured using *V*/*Q* lung scan in 356 patients was 8.7±13.6%. Mean±SD D-dimer level while on anticoagulant therapy was 352±458 $\mu g \cdot L^{-1}$.

Thrombophilia was present in 120 (34.3%) patients. Elevated Factor VIII level (90th percentile) and Factor V Leiden were the most common minor thrombophilias (10% and 9.4% of patients, respectively). The presence of antiphospholipid antibodies (APLAs) was the most frequent major thrombophilia (9% of patients with either lupus anticoagulant or anticardiolipin antibodies (99th percentile)); protein C, protein S and antithrombin deficiencies were found in six out of 362 patients (1.7%).

Outcome

Symptomatic recurrent VTE occurred during follow-up in 67 patients (20.0%; 6.8 events per 100 person-years). All events occurred in the absence of anticoagulation, 53 events (68.0%) being unprovoked (*i.e.* no major nor minor transient risk factors and no cancer), 48 events (71.0%) being nonfatal pulmonary embolism and four events being fatal pulmonary embolism.

Primary assessment of predictors for recurrent VTE

In univariate analysis, age, previous cancer resolved from >2 years before the inclusion, chronic inflammatory disease, residual DVT (at inclusion), APLAs and elevated Factor VIII were found to be associated with an increased risk of recurrent VTE. There was no impact of sex, abnormal D-dimer and, as previously reported [4], duration of anticoagulation on the risk of recurrence (table 1). RVD measured at the time of pulmonary embolism diagnosis was a significant predictor of recurrence but not RVD at inclusion. PVOI at inclusion as a continuous variable was associated with +2% increased risk of recurrence

for each additional percentage point of PVOI (HR 1.02, 95% CI 1.00–1.03) (table 1). Based on ROC analysis (supplementary figure S2), the most discriminant value of PVOI was 5% (AUC 0.62, 95% CI 0.57–0.68) and patients with PVOI at inclusion ⩾5% had a 2- to 3-fold increased risk of recurrence (tables 1 and 2).

In the primary multivariate analysis (first multivariate model), age, APLAs and PVOI at inclusion ⩾5% remained significant predictors of recurrent VTE; patients with at least one of these factors represented 95.4% (63 patients) of all recurrences (table 3).

Secondary assessments of predictors for recurrent VTE

In univariate analysis, PVOI at pulmonary embolism diagnosis, as a continuous variable, was associated with +2% increased risk of recurrent VTE for each additional percentage point of PVOI (HR 1.02, 95% CI 1.01–1.04) (table 1). Based on ROC analysis (supplementary figure S3), the most discriminant value of PVOI at pulmonary embolism diagnosis was 40% (AUC 0.67, 95% CI 0.61–0.73) and patients with PVOI at diagnosis of pulmonary embolism ⩾40% had a 3-fold increased risk of recurrence (tables 1 and 2).

In the second multivariate model, in which PVOI at inclusion was excluded (table 3), age, APLAs and PVOI at pulmonary embolism diagnosis ⩾40% remained significant predictors of recurrent VTE; patients with at least one of these factors represented 96.7% (64 patients) of all recurrences.

When taking in account both PVOI at inclusion and at pulmonary embolism diagnosis, we found a significant correlation between these two parameters (r=0.28; p<0.0001) as well as a significant interaction (p=0.002 for interaction test). We therefore combined these two parameters into one variable with two categories (table 2) and in the third multivariate model (table 3), age, APLAs and combined PVOI at diagnosis and at inclusion remained associated with a significant risk of recurrent VTE. Patients with at least one of these factors represented 95.4% (63 patients) of all recurrences.

Prediction score for recurrent VTE

A prediction score for recurrent VTE was derived from each multivariate model (table 4 and figure 1). All scores showed similar high sensitivity and negative predictive values; the proportions of patients classified at low risk of recurrent VTE (annual incidence rate <2% per year) were 22.3%, 18.1% and 16.2% for the first, second and third score, respectively. In addition, all scores identified a subgroup at high risk of recurrent VTE (annual incidence rate >12% per year), which represented 38.7%, 37.1% and 51.8% of patients for the first, second and third score, respectively.

Sensitivity analyses

Multiple imputation models or modified multivariate models performed in patients after stopping anticoagulation (*i.e.* after randomisation in the placebo group and at the end of the 18 months of anticoagulation in the warfarin group) confirmed our three major potential predictors of recurrent VTE (supplementary table S2).

Discussion

In this analysis based on 371 patients who experienced a first episode of unprovoked pulmonary embolism, we found that age, PVOI at the time of pulmonary embolism diagnosis and/or after 6 months of anticoagulation and APLAs were independent predictors of recurrent VTE during a median follow-up of 41 months. Depending on local radiological expertise and geographic accessibility to *V*/*Q* lung scan in clinical practice, we derived three predictive scores for recurrence, all showing high and similar sensitivity and negative predictive values, and allowing us to classify one-fifth of patients at low risk of recurrence (annual incidence rate <2% per year).

One of the most striking findings is the observation, in the main and all secondary multivariate analyses (supplementary table S2), of a strong and independent impact of PVOI, either at 6 months of anticoagulation or at diagnosis of pulmonary embolism, on the risk of recurrent VTE. Consistent with previous prospective or retrospective studies where PVOI after the first months of anticoagulation was assessed using *V*/*Q* lung scan, we found that residual pulmonary vascular obstruction was present in about one-third of patients and was associated with an increased risk of recurrent VTE [17, 27–31]. In our study, ROC curve analysis yielded a 5% PVOI threshold, which was lower than in previous studies and whose reproducibility might be questionable [17, 27]; however, a 5% perfusion defect on *V*/*Q* lung scan represents one segmental perfusion defect that is clinically relevant in the setting of suspected pulmonary embolism [32]. In studies that assessed residual pulmonary vascular obstruction using CTPA, no association between this parameter and the risk of recurrent VTE was observed [33, 34]; however, it has been shown that the accuracy of CTPA to detect residual pulmonary vascular obstruction is inferior to that of *V*/*Q* lung scan [34]. At pulmonary embolism diagnosis, consistent with others, mean PVOI was

TABLE 1 Risk factors of recurrent venous thromboembolism (VTE) in univariate analysis

	Recurrent VTE	No recurrent VTE	Hazard ratio (95% CI)	p-value
Age years[#]	66.1±15.0	57.6±17.5	1.03 (1.02–1.05)	<0.0001
<50	8/67 (11.9)	78/246 (31.7)	Reference	0.0003
50–65	20/67 (29.9)	76/246 (30.9)	2.96 (1.30–6.72)	
>65	39/67 (58.2)	92/246 (37.4)	4.65 (2.17–9.95)	
Female	30/67 (44.8)	129/246 (52.4)	0.73 (0.45–1.18)	0.20
BMI kg·m^{-2}	28.0±4.9	27.5±5.6	1.02 (0.98–1.06)	0.32
BMI ⩾30 kg·m^{-2}	18/67 (26.9)	61/246 (24.8)	1.18 (0.69–2.03)	0.54
Creatinine clearance category mL·min^{-1}[#]				
⩽50	8/65 (12.3)	15/240 (6.3)	2.43 (1.15–5.16)	0.02
>50	57/65 (87.7)	225/240 (93.8)	Reference	
Blood group				
O	18/67 (26.9)	58/231 (25.1)	Reference	0.79
Non-O	49/67 (73.1)	173/231 (74.9)	0.93 (0.54–1.60)	
Medical conditions				
Previous cancer	5/67 (7.5)	7/246 (2.8)	2.52 (1.01–6.28)	0.048
Previous distal DVT or superficial vein thrombosis	7/67 (10.4)	21/246 (8.5)	1.36 (0.62–2.97)	0.45
Chronic heart failure	1/67 (1.5)	11/246 (4.5)	0.36 (0.05–2.63)	0.32
Chronic respiratory failure	14/67 (20.9)	50/246 (20.3)	1.06 (0.59–1.91)	0.85
Chronic inflammatory disease	5/67 (7.5)	5/246 (2.0)	3.06 (1.22–7.65)	0.017
Characteristics of pulmonary embolism at diagnosis				
RVD[¶]	28/56 (50.0)	66/203 (32.5)	1.93 (1.14–3.26)	0.014
PVOI %	47.1±24.4	32.2±22.9	1.02 (1.01–1.04)	<0.0001
PVOI ⩾40%[+]	41/62 (66.1)	75/203 (36.9)	2.90 (1.71–4.91)	0.0001
Associated proximal DVT[§]	26/65 (40.0)	73/237 (30.8)	1.53 (0.93–2.51)	0.094
Characteristics of pulmonary embolism at inclusion				
RVD	4/49 (8.2)	16/178 (9.0)	1.01 (0.36–2.82)	0.98
PVOI %	11.6±12.8	8.0±13.8	1.02 (1.00–1.03)	0.029
PVOI ⩾5%[f]	40/64 (62.5)	91/236 (38.6)	2.58 (1.56–4.29)	0.0002
Residual DVT[§]	18/67 (26.9)	40/243 (16.5)	2.01 (1.17–3.45)	0.01
Villalta score				
⩽5	58/66 (87.9)	203/223 (91.0)	Reference	0.26
>5	8/66 (12.1)	20/223 (9.0)	1.53 (0.73–3.21)	
D-dimer concentration ng·mL^{-1}	362.6±310.7	369.7±521.1	1.00 (1.00–1.00)	0.60
D-dimer concentration <250 ng·mL^{-1}	30/67 (44.8)	128/243 (52.7)	0.67 (0.41–1.08)	0.098
Thrombophilia				
Minor thrombophilia	14/64 (21.9)	49/237 (20.7)	1.17 (0.64–2.12)	0.61
Heterozygous Factor V Leiden	4/64 (6.3)	25/241 (10.4)	0.62 (0.23–1.71)	0.36
Heterozygous G20210A prothrombin gene variant	6/64 (9.4)	14/242 (5.8)	1.52 (0.65–3.53)	0.33
Elevated Factor VIII (90th percentile)	12/65 (18.5)	21/241 (8.7)	2.30 (1.23–4.30)	0.009
Major thrombophilia	14/64 (21.9)	25/237 (10.5)	1.83 (1.00–3.34)	0.0497
Antithrombin deficiency	2/64 (3.1)	4/241 (1.7)	2.08 (0.51–8.51)	0.31
Protein C deficiency	0/65 (0.0)	1/240 (0.4)		0.98
Protein S deficiency	0/65 (0.0)	3/240 (1.3)		0.98
Homozygous Factor V Leiden	0/64 (0.00)	0/241 (0.0)		
Heterozygous Factor V Leiden and heterozygous G20210A prothrombin gene variant	1/64 (1.6)	1/241 (0.4)	2.37 (0.32–17.3)	0.40
Antiphospholipid antibodies	12/65 (18.5)	17/235 (7.2)	2.07 (1.09–3.91)	0.025
Anticardiolipin antibodies (99th percentile)	2/65 (3.1)	2/236 (0.8)	2.44 (0.59–9.98)	0.22
Lupus anticoagulant	11/65 (16.9)	15/239 (6.3)	2.21 (1.14–4.27)	0.018
Treatment of pulmonary embolism				
Low-molecular-weight heparin	43/67 (64.2)	155/246 (63.0)	1.07 (0.65–1.76)	0.80
Unfractionated heparin[¶]	16/67 (23.9)	41/246 (16.7)	1.65 (0.94–2.89)	0.083
Pentasaccharides	21/67 (31.3)	73/246 (29.7)	1.09 (0.65–1.83)	0.76
Thrombolytic therapy	2/67 (3.0)	4/246 (1.6)	1.71 (0.42–6.98)	0.46
Vena cava filter (retrievable)	3/67 (4.5)	10/246 (4.1)	1.18 (0.37–3.77)	0.77
Unstable INR before inclusion (TTR <65%)	22/64 (34.4)	95/234 (40.6)	0.83 (0.49–1.38)	0.47
Use of compression stockings	47/66 (71.2)	147/246 (59.8)	1.47 (0.86–2.50)	0.16

Continued

TABLE 1 Continued

	Recurrent VTE	No recurrent VTE	Hazard ratio (95% CI)	p-value
Concomitant treatment at the time of pulmonary embolism diagnosis				
Antiplatelet agents	4/67 (6.0)	22/246 (8.9)	0.77 (0.28–2.12)	0.61
Statins	17/67 (25.4)	50/246 (20.3)	1.50 (0.86–2.60)	0.15
Oestrogen contraceptive pill[##]	0/67 (0.0)	44/246 (17.9)		0.98

Data are presented as mean±SD or n/N (%), unless otherwise stated. BMI: body mass index; DVT: deep vein thrombosis; RVD: right ventricular dysfunction; PVOI: pulmonary vascular obstruction index; INR: international normalised ratio; TTR: time in the therapeutic range; ROC: receiver operating characteristic; AUC: area under the curve. [#]: age was strongly correlated with creatinine clearance (r=−0.70; p<0.0001): only age was selected for multivariate analysis as this variable was available for all the patients and as the p-value was the lowest. [¶]: RVD at diagnosis of pulmonary embolism and unfractionated heparin used at the initial phase of treatment were correlated (r=0.24; p<0.001); however, the two variables were included in the multivariate model as unfractionated heparin was also used for other reasons than severe pulmonary embolism. [+]: based on ROC curve analysis (supplementary figure S1), the most discriminant value of PVOI was 40% (AUC 0.67, 95% CI 0.61–0.73; sensitivity 66.1 and specificity 63.1). [§]: the presence of an associated DVT at the diagnosis of pulmonary embolism was strongly correlated with residual DVT at inclusion (r=0.44; p<0.0001); however, the p-value for residual DVT was the lowest and residual DVT was systematically screened in patients at inclusion, whereas the presence of an associated DVT at the diagnosis of pulmonary embolism has not been systematically documented. [f]: based on ROC curve analysis (supplementary figure S2), the most discriminant value of PVOI was 5% (AUC 0.62, 95% CI 0.57–0.68; sensitivity 62.5 and specificity 63.1). [##]: at the time where the PADIS-PE trial was designed and started, it was still uncertain if oestrogen-containing pill use was associated with a lower risk of recurrence and this population was therefore kept in the analysis when study recruitment ended; for all of these females, oestrogen-containing pill use was stopped after pulmonary embolism diagnosis.

elevated (*i.e.* 35%) [28, 30]. In the only prospective trial that assessed the impact of this parameter on the risk of recurrent VTE after stopping anticoagulation, no association was observed between PVOI ⩾10% at pulmonary embolism diagnosis (cut-off based on clinical relevance) and the risk of recurrent VTE [17]. In our study, ROC curve analysis yielded a 40% threshold PVOI value at diagnosis to predict a high risk of recurrent VTE, which is close to that observed in prospective trials that evaluated PVOI at pulmonary embolism diagnosis on the risk of death [35, 36] or early recurrent VTE during anticoagulation [37]. Consistent with the observation of a significant correlation between PVOI at pulmonary embolism diagnosis and PVOI at 6 months of anticoagulation, these parameters, when evaluated separately, were associated with an independent 2-fold increased risk of recurrence without identifying predictors other than age and APLAs, and subsequent scores showed similar accuracy (tables 3 and 4). The combination of

TABLE 2 Pulmonary vascular obstruction index (PVOI) at inclusion and at pulmonary embolism diagnosis

	Total	Recurrent VTE	No recurrent VTE	Hazard ratio (95% CI)	p-value
PVOI at inclusion (n=300)					
PVOI inclusion <5%	169	24 (14.2)	145	Reference	0.0002
PVOI inclusion ⩾5%	131	40 (30.5)	91	2.58 (1.56–4.29)	
PVOI at diagnosis (n=265)					
PVOI diagnosis <40%	149	21 (14.1)	128	Reference	0.0001
PVOI diagnosis ⩾40%	116	41 (35.3)	75	2.90 (1.71–4.91)	
Combined PVOI at diagnosis and at inclusion in four categories (n=263)[#]					
PVOI diagnosis <40% and PVOI inclusion <5%	96	8 (8.3)	88	Reference	0.0003
PVOI diagnosis <40% and PVOI inclusion ⩾5%	51	13 (25.4)	38	3.85 (1.59–9.30)	
PVOI diagnosis ⩾40% and PVOI inclusion <5%	46	17 (37.0)	29	5.35 (2.31–12.40)	
PVOI diagnosis ⩾40% and PVOI inclusion ⩾5%	70	24 (34.3)	46	5.29 (2.37–11.8)	
Combined PVOI at diagnosis and at inclusion in two categories (n=263)[¶]					
PVOI diagnosis <40% and PVOI inclusion <5%	96	8 (8.3)	88	Reference	<0.0001
PVOI diagnosis ⩾40% and/or PVOI inclusion ⩾5%	167	54 (32.3)	100	4.87 (2.32–10.03)	

Data are presented as n or n (%), unless otherwise stated. VTE: venous thromboembolic disease. [#]: in order to evaluate the concomitant impact of PVOI at inclusion and at the time of pulmonary embolism diagnosis, and taking in account the significant correlation and interaction between these two variables, these latter were combined into one variable and four combinations were considered: 1) initial PVOI <40% and PVOI at inclusion <5%, 2) initial PVOI <40% and PVOI at inclusion ⩾5%, 3) initial PVOI ⩾40% and PVOI at inclusion <5%, and 4) initial PVOI ⩾40% and PVOI at inclusion ⩾5%. [¶]: as the relative risks of recurrent VTE were increased by a similar extent in three categories compared with the reference category (*i.e.* PVOI at diagnosis <40% and PVOI at inclusion <5%), the combined variable coding for the two PVOIs was dichotomised for multivariate analysis (table 3).

TABLE 3 Risk of recurrent venous thromboembolism in multivariate analyses

Variables	Main multivariate model[#]			Second multivariate model[¶]			Third multivariate model[+]		
	Hazard ratio (95% CI)	p-value	Score value	Hazard ratio (95% CI)	p-value	Score value	Hazard ratio (95% CI)	p-value	Score value
Age years									
<50	Reference	0.008		Reference	0.007		Reference	0.02	
50–65	3.65 (1.33–9.99)		+2	2.95 (1.07–8.14)		+2	2.80 (1.01–7.75)		+2
>65	4.70 (1.78–12.4)		+3	4.49 (1.73–11.70)		+3	3.73 (1.43–9.77)		+3
Previous cancer (resolved >2 years)	1.66 (0.56–4.91)	0.36		1.82 (0.61–5.38)	0.28		2.05 (0.70–6.02)	0.19	
Chronic inflammatory disease	2.03 (0.69–5.94)	0.20		1.95 (0.66–5.73)	0.23		2.05 (0.70–5.99)	0.19	
Unfractionated heparin	1.58 (0.84–2.98)	0.15		1.29 (0.65–2.57)	0.47		1.23 (0.63–2.39)	0.54	
RVD at diagnosis	1.08 (0.59–1.96)	0.81		0.86 (0.46–1.62)	0.65		0.87 (0.48–1.59)	0.66	
PVOI									
Model 1: PVOI at inclusion ⩾5% (over PVOI at inclusion <5%)[#]	2.06 (1.14–3.72)	0.016	+2						
Model 2: PVOI at diagnosis ⩾40% (over PVOI at diagnosis <40%)[¶]				2.36 (1.34–4.17)	0.003	+2			
Model 3: PVOI at diagnosis ⩾40% and/or PVOI at inclusion ⩾5% (over PVOI at diagnosis <40% and PVOI at inclusion <5%)[+]							4.73 (1.99–11.2)	0.0004	+3
Residual DVT at inclusion	1.72 (0.92–3.23)	0.09		1.60 (0.85–3.01)	0.14		1.70 (0.90–3.22)	0.10	
D-dimer <250 μg·L^{-1}	1.49 (0.79–2.80)	0.21		1.53 (0.81–2.88)	0.19		1.74 (0.92–3.28)	0.09	
Antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)	2.38 (1.15–4.89)	0.01	+2	2.64 (1.32–5.28)	0.006	+2	2.57 (1.29–5.11)	0.007	+2
Elevated Factor VIII (90th percentile)	1.07 (0.48–2.40)	0.86		1.08 (0.48–2.43)	0.86		0.91 (0.41–2.06)	0.83	

RVD: right ventricular dysfunction; PVOI: pulmonary vascular obstruction index; DVT: deep vein thrombosis. [#]: main model: estimate of PVOI at pulmonary embolism diagnosis was not included (Harrell's C index including three significant variables was 0.66 (observed score) and 0.68 after bootstrapping); [¶]: second model: estimate of PVOI at inclusion was excluded (Harrell's C index including three significant variables was 0.66 (observed score) and 0.68 after bootstrapping); [+]: third model: PVOI at pulmonary embolism diagnosis and at inclusion were combined into one variable with two categories (Harrell's C index including three significant variables was 0.63 (observed score) and 0.65 after bootstrapping).

these two PVOI into one variable added little to discriminate between patients at a low or high risk of recurrence (tables 3 and 4). In practice, if *V/Q* lung scan is not available, scoring PVOI at pulmonary embolism diagnosis based on CTPA requires local expertise and should be performed at distance from the acute episode; if available, *V/Q* lung scan should be performed at ⩾3 months [4].

Consistent with other studies in patients with unprovoked VTE, age and the presence of APLAs were associated with an increased risk of recurrent VTE [5, 8, 15, 16]. Our high frequency of positive lupus anticoagulant might appear surprising and one could argue that such patients should have been excluded from the PADIS-PE trial. However, systematic screening for thrombophilia was not required to be eligible in our study and our high frequency of APLAs is consistent with other studies on unprovoked VTE where systematic detection of APLAs was not required [15]. Even after exclusion of patients with APLAs, the results remained unchanged (supplementary table S2E). Conversely, the risk of recurrent VTE in females was not lower than that in males, despite the inclusion of females who had an initial pulmonary embolism associated with oestrogen-containing pill use (supplementary table S1). If the lack of power is plausible, however, it has been shown that this risk estimate is lower in randomised trials compared with prospective cohorts [9]. Lastly, similarly to others [11], low D-dimer concentration (*i.e.* <250 μg·mL^{-1} while on anticoagulation) was also not associated with a lower risk of recurrence.

TABLE 4 Accuracy of prediction scores

Score values	Recurrent VTE[#]	No recurrent VTE	Hazard ratio (95% CI)	Annual incidence per 100 person-years	Comparisons between classes for accuracy	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	PPV (95% CI)
Model 1[¶]	n=62	n=227							
0	3 (5.7)	50	Reference	1.29 (0.00–2.74)					
2	12 (16.2)	62	3.49 (0.98–12.4)	4.86 (2.12–7.60)					
3	8 (19.0)	34	4.27 (1.13–16.1)	6.21 (1.92–10.50)					
4	10 (25.6)	29	6.27 (1.73–22.8)	9.17 (3.49–14.85)					
5	21 (30.0)	49	7.75 (2.31–26.0)	11.85 (6.77–16.93)					
6	1 (50.0)	1	8.44 (0.88–81.2)	15.28 (0.00–45.23)					
7	7 (77.8)	2	27.9 (7.19–108)	67.85 (17.58–118.1)					
Combination									
Low risk 0	3	50	Reference	1.29 (0.00–2.74)					
Intermediate risk 2–3	20	96	3.77 (1.12–12.7)	5.32 (2.99–7.65)	Score 0 *versus* ⩾2	95.2 (86.5–99.0)	94.3 (84.3–98.8)	22.0 (16.8–28.0)	25.0 (19.6–31.0)
High risk 4–7	39	81	8.34 (2.58–27.0)	12.86 (8.82–16.90)	Score ⩽3 *versus* >3	62.9 (49.7–74.8)	86.4 (80.3–91.2)	64.3 (57.7–70.5)	32.5 (24.2–41.6)
Model 2[+]	n=60	n=197							
0	2 (5.6)	34	Reference	1.23 (0.00–2.94)					
2	13 (18.3)	58	4.32 (0.97–19.1)	5.86 (2.67–9.05)					
3	7 (14.3)	42	3.46 (0.72–16.7)	4.59 (1.20–7.98)					
4	9 (28.1)	23	6.85 (1.48–31.7)	10.17 (3.53–16.81)					
5	21 (36.8)	36	9.78 (2.29–41.7)	15.64 (8.96–22.32)					
6	0	3		0					
7	8 (88.9)	1	52.6 (11.2–248.7)	211.2 (64.85–357.6)					
Combination									
Low risk 0	2	34	Reference	1.23 (0.00–2.94)					
Intermediate risk 2–3	20	100	3.98 (0.93–17.0)	5.34 (3.01–7.67)	Score 0 *versus* ⩾2	96.7 (88.5–99.6)	94.4 (81.3–99.3)	17.3 (12.3–23.3)	26.2 (20.6–32.6)
High risk 4–7	38	63	10.00 (2.42–41.6)	15.85 (10.81–20.89)	Score ⩽3 *versus* > 3	63.3 (49.9–75.4)	85.9 (79.4–90.9)	68.0 (61.0–74.5)	37.6 (28.2–47.8)

Continued

TABLE 4 Continued

Score values	Recurrent VTE[#]	No recurrent VTE	Hazard ratio (95% CI)	Annual incidence per 100 person-years	Comparisons between classes for accuracy	Sensitivity (95% CI)	NPV (95% CI)	Specificity (95% CI)	PPV (95% CI)
Model 3[§]	n=60	n=195							
0	2 (6.4)	29	Reference	1.39 (0.00–3.33)					
2	4 (9.8)	37	2.03 (0.37–11.1)	3.07 (0.05–6.09)					
3	5 (12.2)	36	2.26 (0.44–11.6)	3.38 (0.42–6.34)					
4	0 (0)	2		0					
5	17 (30.4)	39	6.80 (1.57–29.4)	11.57 (6.06–17.08)					
6	22 (31.9)	47	7.38 (1.73–31.4)	12.76 (7.43–18.09)					
7	3 (45.9)	4	10.3 (1.72–61.6)	17.79 (0.00–37.92)					
8	7 (87.5)	1	31.5 (6.53–152.00)	102.2 (26.51–178.00)					
Combination									
Low risk 0	2	31	Reference	1.39 (0.00–3.33)					
Intermediate risk 2–4	12	84	2.11 (0.45–9.75)	3.16 (1.10–5.22)	Score 0 *versus* ⩾2	96.7 (88.5–99.6)	93.5 (78.6–99.2)	14.9 (10.2–20.7)	25.9 (20.3–32.1)
High risk 5–8	46	80	8.17 (1.99–33.6)	14.28 (10.28–18.28)	Score ⩽4 *versus* >4	81.7 (71.9–91.5)	90.4 (83.5–95.1)	53.3 (46.1–60.5)	35.0 (27.1–43.5)

Data are presented as n (%) or n, unless otherwise stated. VTE: venous thromboembolic disease; NPV: negative predictive value; PPV: positive predictive value. [#]: percentages per strata; [¶]: main model: PVOI at diagnosis of pulmonary embolism was not included in the model; [+]: second model: PVOI at inclusion was not included in the model; [§]: third model: given the interaction between PVOI at diagnosis of pulmonary embolism and at inclusion, these variables were combined into one variable with two categories.

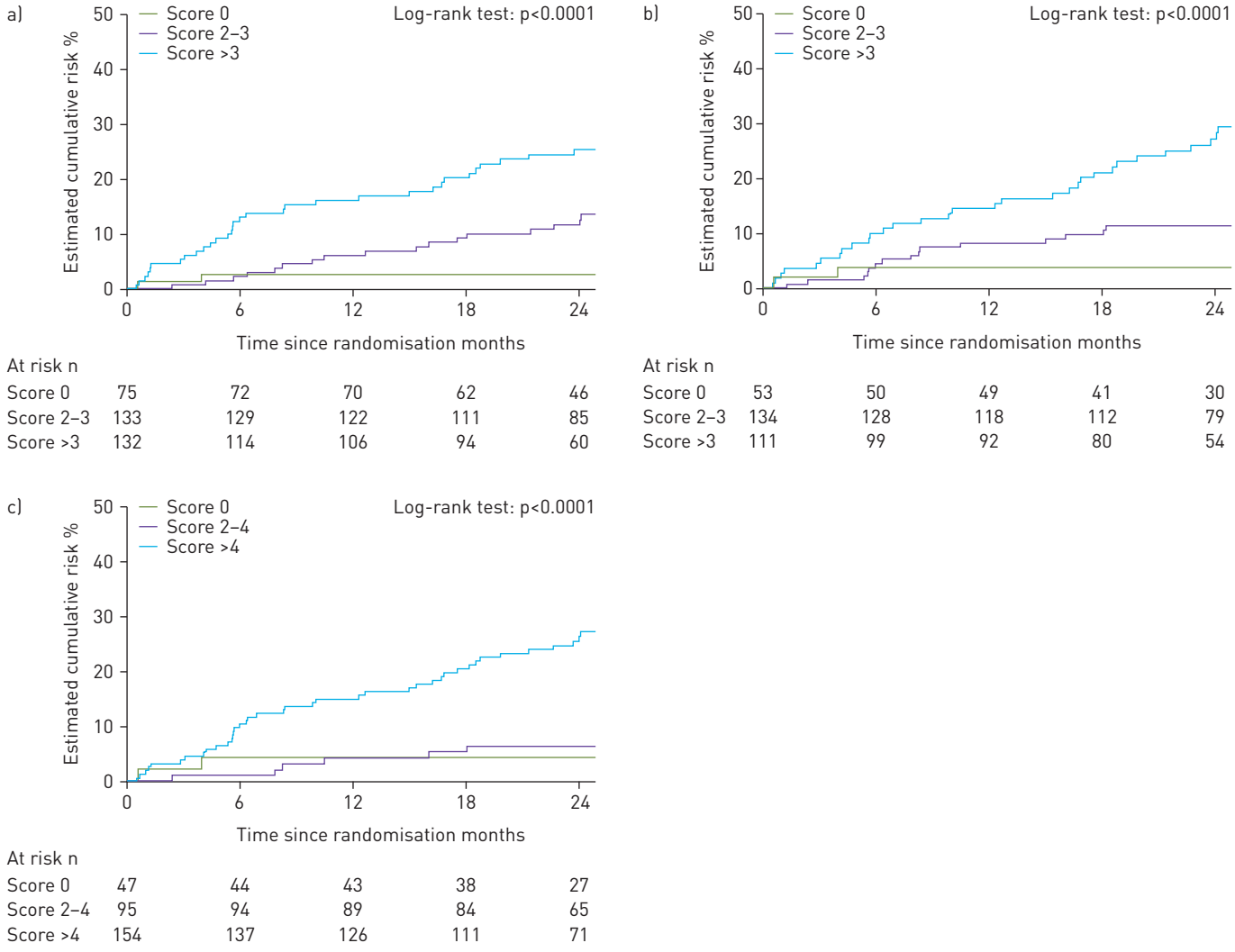

FIGURE 1 Kaplan–Meier estimates of the probability of the outcome of recurrent venous thromboembolism during follow-up after stopping anticoagulation, according to score values: a) when pulmonary vascular obstruction index (PVOI) measured at pulmonary embolism diagnosis was excluded from the model, b) when PVOI measured at inclusion was excluded from the model, and c) when PVOI measured at diagnosis of pulmonary embolism and at inclusion were combined in a single variable.

Similarly to others [8, 38, 39], our three derived scores showed high sensitivity and negative predictive values. The annual incidence rate of recurrent VTE was <5% per year in the low-risk group, suggesting that anticoagulation should be stopped after 6 months; in contrast, the annual incidence rate of recurrence was ⩾10% per year in the high-risk group (which is 4-fold higher than the risk of major bleeding in the PADIS-PE trial and others), suggesting that anticoagulation should be continued, at least in patients with a low or moderate risk of bleeding (table 4) [3, 4]. In previous scores, most of them included at least age, sex and D-dimer, none of them were derived from cohorts with only pulmonary embolism patients, and PVOI for pulmonary embolism patients and APLAs were not available [8, 38, 39]. In our study, all the components of these previous scores were available and evaluated in univariate analysis, and, except for age, none of them was significantly associated with an increased risk of recurrent VTE. Thus, if PVOI and APLAs have the potential to provide additional information to these existing scores, this issue deserves further analyses.

Strengths of our study include: 1) a carefully predefined and characterised population (in terms of clinical, morphological and biochemical data) that was included in a double-blind randomised trial; 2) a minimal loss to follow-up; 3) a long follow-up period of all patients after anticoagulant therapy was discontinued; 4) a blind review and validation of all outcomes by an independent centralised adjudication committee; 5) a central assessment of PVOI and RVD by independent physicians blinded from the study treatment allocation, the results of other imaging tests and the patients' characteristics; and 6) consistency of results across main, secondary and sensitivity analyses.

Our study has the following limitations. First, the sample size was too small to evaluate the impact of potential important predictors, such as sex, chronic inflammatory disease, residual DVT or protein C, protein S and antithrombin deficiencies. Second, unlike the data obtained for PVOI at inclusion, data collection for the measurement of PVOI at pulmonary embolism diagnosis was retrospective and not exhaustive. However, all available CTPAs and *V*/*Q* lung scans were interpreted by independent physicians blinded from study treatment allocation and the impact of PVOIs on the risk of recurrent VTE was consistent across all statistical models.

Conclusions

Among patients with a first episode of unprovoked pulmonary embolism, age, PVOI measured either at diagnosis or at 6 months of anticoagulation and APLAs were found to be independent predictors of recurrent VTE. Scores combining these variables identified patients at low risk of recurrent VTE in one-fifth of cases and patients at a particular high risk in one-third of cases. Validation in independent cohorts and comparison with existing rules are needed.

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