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Higher risk of pulmonary embolism recurrence when the first event is severe. A cohort study.

Short title: PE severity and recurrence risk

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Conflicts of Interest: None

No previous presentation / abstract/ publication

Key words: pulmonary embolism. Epidemiology. Echocardiography. Biomarkers.

Word count: 1589

Abstract.

Objectives: Severity of a first pulmonary embolism (PE) is sometime proposed as a criterion for prolonging anticoagulant treatment. However, little evidence supports this idea. We attempted to determine the connection between severity of first PE and the risk of recurrence.

Method: Patients admitted with PE between 2012 and 2018 and for which anticoagulant treatment had been discontinued were followed. PEs were classified according to severity into 2 groups: 1) those with associated cardiac involvement if the biomarkers were positive and in the presence of right ventricular dysfunction, and 2) those with no cardiac involvement. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log Rank test.

Results: 417 PEs (186 with cardiac involvement, 231 without) were followed for a least one year after discontinuation of anticoagulant treatment with a mean follow-up of: 3.5 ± 1.9 years. 72 patients (17.3%) experienced venous thromboembolism recurrence (5.8%, 12 %, 28.3 %, respectively, at 1, 2 and 5 years). In 63 patients (88%), recurrence was a PE. Mean time to onset of recurrence was 24.9 ±19.9 months. At 5 years, the recurrence rate was higher when the first PE was severe: p=0.043. When the first PE was unprovoked, no difference was found between recurrence rates according to the degree of initial PE severity: p=0.27. In contrast, in patients with provoked PE, the recurrence rate was higher when the first PE event was severe: p=0.032.

Conclusion: We report, for the first time, a higher recurrence rate when the first PE was severe with a recurrence rate of 9% vs 3% and of 35.5% vs 26% at 1 and 5 years respectively: p=0.043. The correlation between PE severity and risk of recurrence was stronger in cases of provoked PE: p=0.032.

Contributorship statement:

EF and **EF** wrote the protocol and the designed the study.

EF, NR, NB, MB, SB, PM followed up patients who were all reviewed with a long follow-up.

EF, FA, NH collected the data

JP B and **FS** did the statistics

Article summary

Strengths of our study:

We describe for the first time a link between the severity of the first PE and the recurrence risk with a higher rate of recurrence when the first PE is severe.

This relation is even stronger when the first PE is provoked.

The clinical impact could be significant as it may indicate that the severity of a first PE should be taken into account in the choice of the duration of treatment.

Limitations:

Our study is not randomized.

In our cohort, some patients were long-term anticoagulated and were therefore excluded. This exclusion may have skewed the result of the non-provoked PEs sub-group for which the relationship between initial severity and risk of recurrence is paradoxically less strong than in the group of the provoked PEs.

Background

After the acute event, the choice of the duration of treatment is one of the main problems in the management of a first PE. Currently, provoked versus non-provoked circumstance is the main criterion used to determine treatment duration. Alongside this main criterion, other factors can also be taken into account such as bleeding risk, sex, blood group, persistence of a venous clot or the end-of-treatment D-dimers level [1–6]. Some practitioners consider first PE severity as a criterion likely to extend treatment duration. However, very few findings in the literature corroborate this idea.

Objective and methods

Drawing on our regional database [7], we made a prospective assessment of the connection between first PE severity and the risk of recurrence of VTE events. All patients hospitalized for PE from 2012 to 2018 were followed prospectively. Only patients whose treatment had been discontinued and for which we had a minimum 12-month follow-up were included. Consequently, patients requiring long-term anticoagulant treatment were excluded, along with patients with active cancer.

Patients were divided into two groups:

1) PE with cardiac involvement: in the presence of hemodynamic instability, increased cardiac biomarkers: Troponin I (Tp) > 70 ng/l and/or BNP > 100 pg/ml and/or right ventricular (RV) dysfunction corresponding to intermediate or high-risk PE in the European Society of Cardiology (ESC) classification. High-sensitivity Tp and BNP were measured with Siemens Centaur® and the Alere Triage BNP kit (Beckman Coulter®), respectively. The positivity threshold was 70 ng/l for Tp and 100 pg/ml for BNP. RV dysfunction was defined by echocardiography when a right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view or > 0.7 in the parasternal long-axis view, a tricuspid annular plane systolic excursion (TAPSE) < 16 mm or a tricuspid annular peak systolic velocity (S'-DTI) < 10 cm/s were observed.

2) PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding to low-risk PE according to the ESC classification.

All chest CT-scans were reread by one radiology expert blinded to the first reading. Special emphasis was placed on eliminating patients with pre-existing pulmonary hypertension as revealed by the patient's medical history or a search for specific signs on the initial scan such as the presence of arterial webs, mural thrombi or a mosaic parenchymal perfusion. Recurrences were determined by a new venous thrombotic event or by a symptomatic PE confirmed by diagnostic imaging and combined with non-negative D-dimers. If patients presented several recurrences during follow-up, only the first was taken into account. A minimum 12-month follow-up was required although a recurrence within this 12-month period was considered as an event. Mean follow-up was 3.5 ±1.9 years.

Patient and public involvement: This case control study was not suitable for a partnering with patients, their carers, support networks, and the public. Patients were not involved in this study.

Statistical analysis:

All statistical analyses were performed using SPSS software (Statistical Package for Social Science software, version 20, Chicago, Illinois, USA). Quantitative variables were expressed as means ± standard deviation and qualitative variables as count as percentages. Quantitative variables were compared using the Student t test and qualitative variables were compared using the Chi2 test. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log-Rank test. IRB approval was obtained.

Results

Between 2012 and 2018, 1080 patients were hospitalized for PE confirmed by CT-scan. One hundred sixty-four (164) patients had a history of VTE and had received long-term treatment; 113 had active

neoplasia, 104 supraventricular arrhythmia requiring anticoagulant treatment and 91 a cause making follow-up impossible (Figure 1: Flow chart). In all, 417 patients with a follow-up exceeding 12 months after discontinuation of their anticoagulation treatment were included. Among these, 231 had presented PE without cardiac involvement and 186 PE with cardiac involvement (165 intermediate risk PE and 21 high-risk PE). The cohort's initial characteristics are summarized in Table 1.

A factor explaining the first PE event was found in 50.8% of cases. Associated deep vein thrombosis (DVT) was observed in 44.6% of patients. All provoked PE were treated for 3 months. All unprovoked PE were treated for at least 6 months. Mean treatment duration was 5.18 ±2.3 months. Twenty-one patients (5%) received thrombolysis. Patient characteristics according to the severity of the initial clinical presentation are shown in Table 2. Patients in the PE group with cardiac involvement were more often diabetic (18% v 9%), more often presented blood clots in the lower limbs (51% vs 39%) and averaged longer hospital stays (7.3 ±4 days vs 3.7 ±3 days) than patients without cardiac involvement.

Among the entire cohort, 72 patients (17.3%) presented VTE recurrence. The VTE recurrence rate after discontinuation of anticoagulation was 5.8% the first year, 12% at 2 years and 28.3% at 5 years. In patients experiencing recurrence, 88% (n=63) suffered PE and 12% (n=9) suffered proximal DVT. Mean time to onset of recurrence was 24.9 ± 19.9 months. Kaplan Meier analysis of the entire cohort shows the survival rate of recurrence-free patients according to initial severity over a 5-year follow-up (Fig. 2). The recurrence-free survival rate was significantly higher when the first PE was non-severe p=0.043. Twelve months after completion of the anticoagulant treatment, the recurrence rate was 7/231 (3%), in the non-cardiac involvement group versus 17/186 (9.1%), in the cardiac involvement group: p=0.007.

Figure 3 compares the survival rates with no VTE recurrence according to the provoked or unprovoked nature of the first PE. In the sub-group of patients presenting an unprovoked PE, Kaplan Meier analysis revealed no difference in recurrence rate according to first PE severity: p=0.27. On the other hand, (Fig. 4), a higher recurrence rate was noted in the sub-group of patients with a severe provoked PE:

p=0.032. At 12 months, recurrence rates were, respectively, 2/112 (1.8%) when there was no initial cardiac involvement versus 9/100 (9%) when cardiac involvement was observed; p=0.018. Regarding other recurrence risk factors: the unprovoked nature of the initial PE was associated with an over-risk of recurrence (HR 1.99 (CI 95%: 1.12-3.33)), as was the presence of associated DVT (HR 1.82 (CI 95%: 1.13-3.1)).

Discussion

After the acute phase, the duration of anticoagulation treatment raises one of the major problems in PE management. Some features have been correlated with an added risk of recurrence and are taken into account when choosing a longer treatment. Other criteria are considered although their connection with increased risk of recurrence has not been formally proven[9–11]. However, to our knowledge, no study has assessed the benefits of pursuing anticoagulant treatment relative to first PE severity. We thought it would be useful, in a prospective cohort study, to look for a relationship between the severity of the initial PE and the recurrence rate. In the present study including 417 patients followed for a mean of 42 months, the incidence of recurrence was similar to findings described in the literature. In 88% of cases, recurrence occurred at the same site as the first event. We also observed a well-known added risk of recurrence in cases with unprovoked first PE. We confirm a statistical correlation between the risk of recurrence and the presence of DVT at the time of the first PE [12–15].

We describe for the first time a higher recurrence rate when the initial PE was severe with a recurrence rate of 9% vs 3% and 35.5% vs 26%, respectively, at 1 and 5 years: p=0.043. Unexpectedly, the correlation between PE severity and the risk of recurrence was stronger when PE was provoked (p=0.032). The lack of a relationship in our study between severity and recurrence among unprovoked PE could be explained by the fact that we maintained anticoagulation treatment in patients at higher risk of recurrence and consequently these patients were not included in our analysis. It is also possible

that the high rate of spontaneous unprovoked PE recurrences conceals the impact of the severity factor. In the literature, the only data that can come close to our result is that of Grifoni et al[16] who reported a higher rate of recurrence when, after hospitalisation for PE, a RV dysfunction was still present at discharge from hospital.

The human physiological coagulation system is believed to protect us against the risk of thrombosis. The formation of venous clots in risky situations is not the rule. When a venous clot occurs, our coagulation-fibrinolysis system is supposed to control the situation by limiting its spread. The formation of a large amount of clots, and hence the occurrence of severe PE, could mean that control by the physiological coagulation system is even more failing. It could also provide additional, hitherto unknown, information on a greater propensity for recurrence.

In the literature, the recurrence risk of a provoked PE is deemed to be sufficiently low not to require long-term treatment. Nevertheless, the risk is still much higher than in a control population. The survey of the literature by Iorio et al[17] covering 2268 provoked PE with transitory risk shows a mean 0.7% annual recurrence rate after surgery but a 3.3% rate for patients as a whole and a 4.2% annual recurrence rate for non-surgical transitory risk factors. These two latter rates are close to the findings for unprovoked thromboembolic events. Our results indicate that in these provoked PE, an over-risk of recurrence could be associated with the severity of the initial event [2,18-20].

Conclusion: In this cohort study, we demonstrate a connection between the severity of a first PE and the risk of a subsequent recurrence. The provoked status of PE does not shield against a high recurrence rate when the first event was severe. These findings justify a prospective study designed to confirm this relationship which could change the way we determine the duration of anticoagulation treatment after a first PE.

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Table 1: Initial cohort characteristics

Overall population	**N = 417**	**(%)**
Sex F/M, n (%)	221	(53%)
Age, years (mean ± SD)	63.1 (±17.1)	
Arterial hypertension, n (%)	179	(43%)
Obesity, n (%)	74	(18%)
Dyslipidemia, n (%)	109	(26%)
Diabetes, n (%)	55	(13%)
Smoking, n (%)	110	(26%)
History of stroke, n (%)	26	(6%)
Inflammatory disease, n (%)	33	(8%)
Psychiatric pathology, n (%)	83	(20%)
Provoked, n (%)	212	(51%)
Associated DVT, n (%)	186	(45%)
Thrombolysis, n (%)	21	(5%)
Duration of hospital stay, days (mean ±SD)	5.8 (± 3.8)	
Initial anticoagulation duration, months (mean ±SD)	5.18 (± 2.3)	
Follow-up period, months (mean ± SD)	42.1 (± 22.8)	
VTE recurrence, n (%)	72	(18%)
- PE, n (% of recurrence)	*63*	*(88%)*
- DVT, n (% of recurrence)	*9*	*(12%)*
Time to recurrence, in months, (mean ± SD)	24.9 (± 19.9)	

Table 2: Initial characteristics of PE groups without and with cardiac involvement

	PE without cardiac involvement N =231	**PE with cardiac involvement N =186**	*P-value*
Sex F/M, n (%)	113 (48.9)	108 (58.1)	0.074
Age, years (mean ± SD)	61 ± 17.2	63 ± 15.5	0.12
Arterial hypertension, n (%)	90 (39)	89 (48)	0. 068
Obesity, n (%)	43 (19)	31 (17)	0.622
Dyslipidemia, n (%)	53 (23)	56 (30)	0.09
Diabetes, n (%)	21 (9)	34 (18)	0.006
Smoking, n (%)	72 (31)	38 (20)	0.012
History of stroke, n (%)	10 (4)	16 (8.6)	0.073
Inflammatory disease, n (%)	17 (7)	16 (8.6)	0.187
Psychiatric pathology, n (%)	45 (20)	38 (20)	0.809
Provoked, n (%)	112 (49)	100 (54)	0.284
Associated DVT, n (%)	90 (39)	96 (52)	0.01
Length of hospital stay, days (mean ± SD)	*4.7 ± 3*	*7.3 ± 4*	0.004
Tp (ng/l)	29.1 ± 16	240 ± 237	0.0001
BNP (pg/l)	45 ± 21	243.2 ± 106	0.0001
RV/LV	0.62 ± 0.07	0.96 ± 0.05	0.01
Duration in months of initial anticoagulation	5.18 ± 2.4	5.2 ± 2.3	0.417

RV/LV =right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view

Figures legends

Figure 1: Study flow-chart

Figure 2: Recurrence-free survival for VTE according to severity of first PE

Figure 3: Recurrence-free survival following provoked PE according to severity of first PE

Figure 4: Recurrence-free survival following unprovoked PE according to severity of first PE

Figure 1

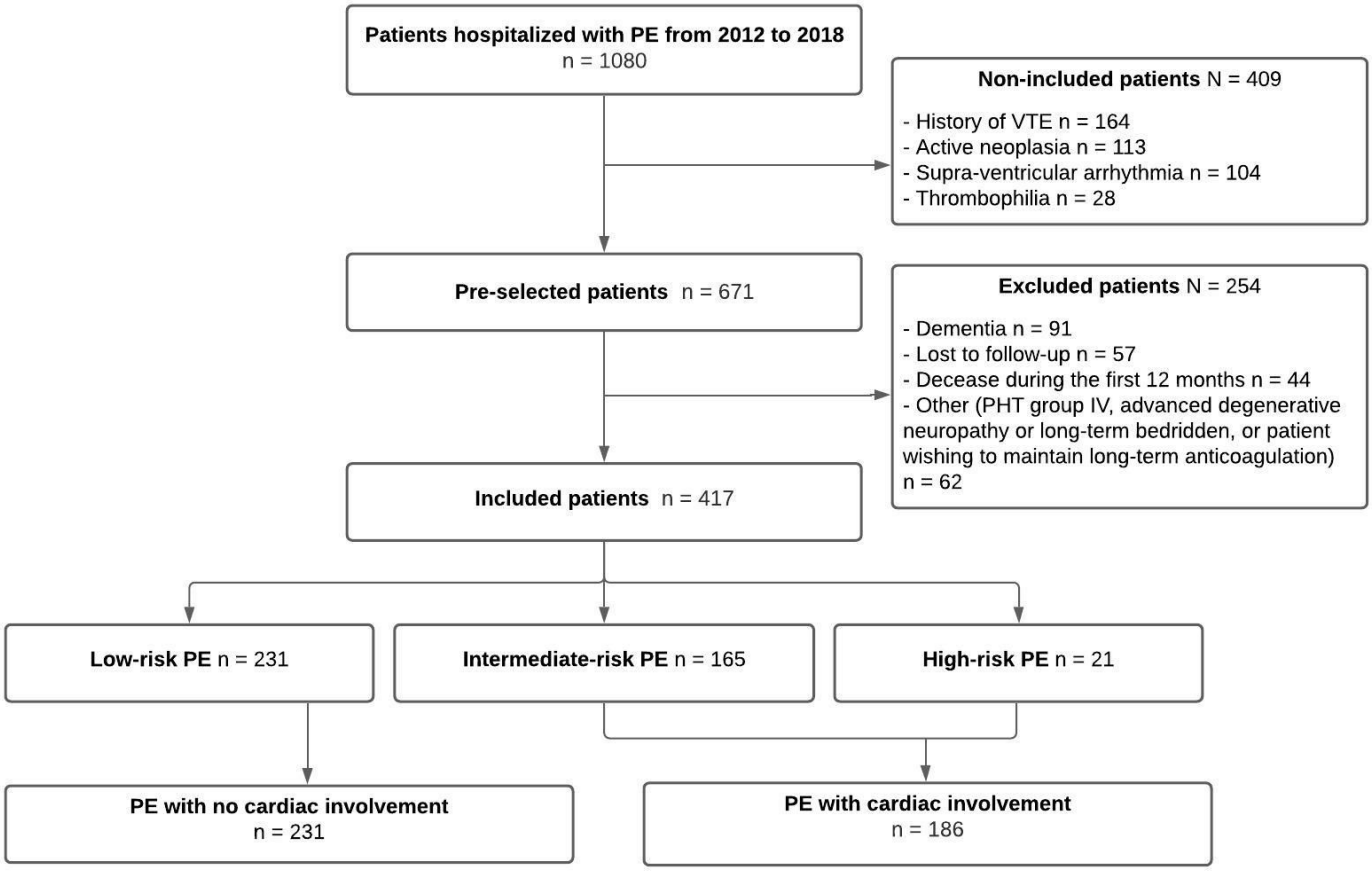
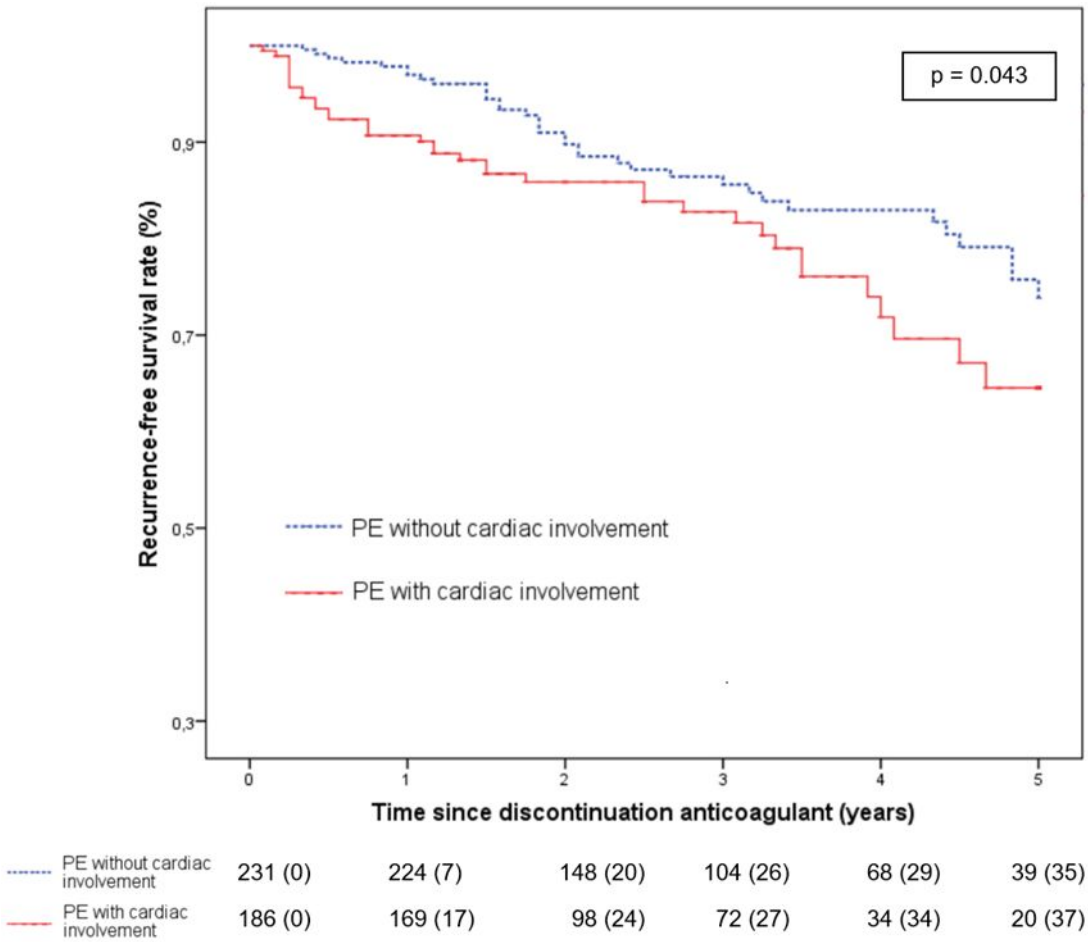
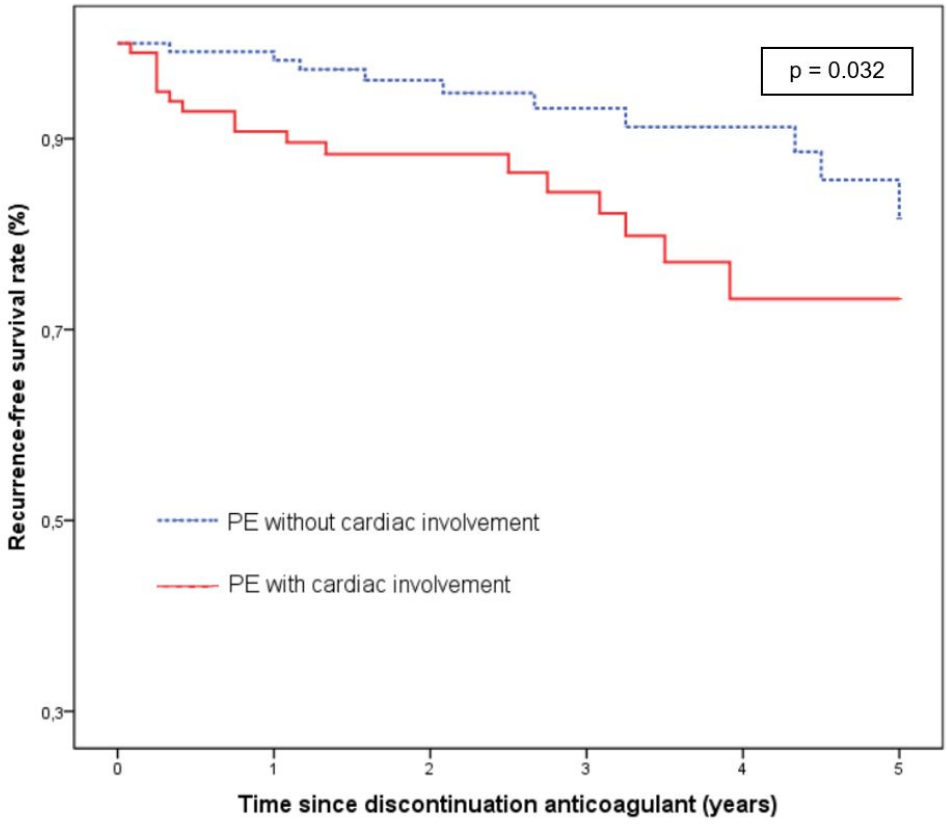


Figure 2



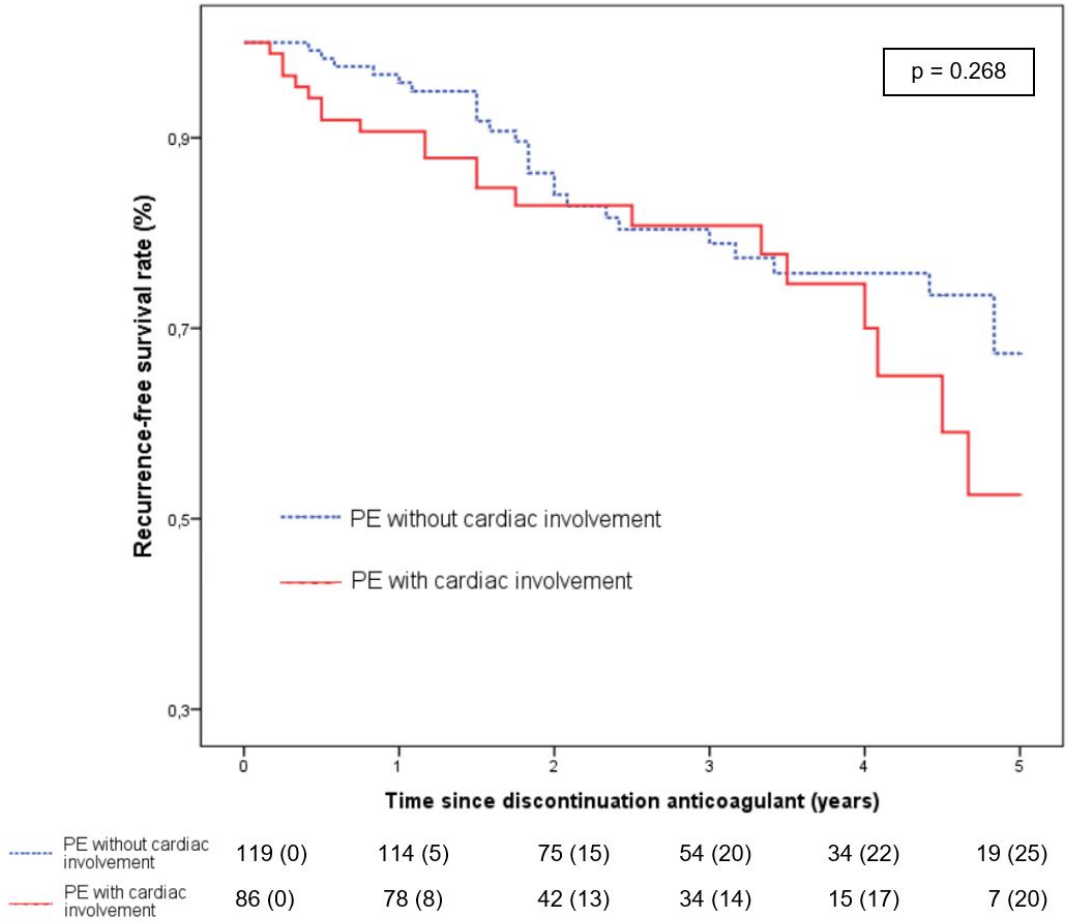
PE without cardiac involvement	231 (0)	224 (7)	148 (20)	104 (26)	68 (29)	39 (35)
PE with cardiac involvement	186 (0)	169 (17)	98 (24)	72 (27)	34 (34)	20 (37)

Figure 3



PE without cardiac involvement	112 (0)	110 (2)	74 (14)	49 (6)	34 (8)	19 (10)
PE with cardiac involvement	100 (0)	91 (9)	56 (11)	37 (14)	18 (17)	13 (17)

Figure 4



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	DONE Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	DONE page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	DONE page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	DONE page 5
Methods			
Study design	4	Present key elements of study design early in the paper	DONE page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	DONE page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	DONE page 5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	DONE page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	DONE page 6
Bias	9	Describe any efforts to address potential sources of bias	DONE page 8
Study size	10	Explain how the study size was arrived at	DONE page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	DONE page 6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	DONE page 8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	DONE page 5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	DONE FIG1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	DONE page 5/6
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	DONE page 5/6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	DONE FIG 2 AND 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	DONE page 5/6
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	DONE p6/7/8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	DONE p 8/9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	DONE p8/9 and article summary
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	DONE p8/9
Generalisability	21	Discuss the generalisability (external validity) of the study results	DONE p8/9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is pulmonary embolism recurrence linked with the severity of the first event ? A French retrospective cohort study.

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Is pulmonary embolism recurrence linked with the severity of the first event ? A French retrospective cohort study.

Short title: PE severity and recurrence risk

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Abstract.

Objectives: Severity of a first pulmonary embolism (PE) is sometimes proposed as a criterion for prolonging anticoagulant treatment. However, little evidence supports this idea. We attempted to determine the connection between severity of first PE and the risk of recurrence.

Participants: Patients admitted with PE between 2012 and 2018 and for whom anticoagulant treatment had been discontinued were followed. PEs were classified according to severity into 2 groups: those with associated cardiac involvement (biomarkers and right ventricular dysfunction) and those with no cardiac involvement. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log Rank test.

Results: 417 PEs (186 with cardiac involvement) were followed for a least one year after discontinuation of treatment with a mean follow-up of: 3.5 ±1.9 years. 72 patients (17.3%) experienced venous thromboembolism recurrence: 24 (5.8%), 44 (12 %) and 72 (28.3 %) respectively, at 1, 2 and 5 years. In 63 patients (88%), recurrence was a PE. Mean time to onset of recurrence was 24.9 ±19.9 months. At 5 years, the recurrence rate was higher when the first PE was severe: p=0.043. When the first PE was unprovoked, no difference is found (p=0.27). In contrast, in patients with provoked PE, the recurrence rate is higher when the first PE event was severe: p=0.032. Multivariate analysis demonstrate that PE severity is an independent factor of recurrence (HR 1.634 [1.015-2.632], p=0.043).

Conclusion: We report for the first time a possible link between a higher recurrence rate and the severity of the first PE, with a recurrence rate of 9% vs 3% and of 35.5% vs 26% at 1 and 5 years respectively. This result which must be confirmed in a dedicated prospective trial could become an important criterion for the duration of anticoagulant therapy after a PE.

Trial registration: NCT04980924

Contributor ship statement:

EF and **EF** wrote the protocol and the designed the study.

EF, NR, NB, ML, SB, PM followed up patients who were all reviewed with a long follow-up.

EF, FA, NH collected the data

JP B and **FS** did the statistics

Strengths and limitations:

- Little is known about the severity of PE and the risk of recurrence.
- This is the first time such a link is investigated.
- This study is a retrospective analysis of prospectively collected data.
- Our study is not randomized.
- The exclusion of patients who were long-term anticoagulated may have skewed the results of the non-provoked PEs sub-group.

Background

After the acute event, the choice of the duration of treatment is one of the main problems in the management of a first PE. Currently, provoked versus non-provoked circumstance is the main criterion used to determine treatment duration. Alongside this main criterion, other factors can also be taken into account such as bleeding risk, sex, blood group, persistence of a venous clot or the end-of-treatment D-dimers level [1–6]. Some practitioners consider first PE severity as a criterion likely to extend treatment duration. However, very few findings in the literature corroborate this idea.

Objective and methods

Drawing on our regional database [7], we made an assessment of the connection between first PE severity and the risk of recurrence of VTE events. All patients hospitalized for PE from 2012 to 2018 were followed. Only patients whose treatment had been discontinued and for which we had a minimum 12-month follow-up were included. Consequently, patients requiring long-term anticoagulant treatment were excluded, along with patients with active cancer.

In accordance with the literature [8], provoked PE was defined as PE which happened within three months of a surgery, a trauma, a significant immobility, pregnancy, a severe thrombophilia, the use of the combined contraceptive pill, hormone replacement therapy or know thrombogenic treatment. Unprovoked PE was defined as PE for which no transient risk factor or medication was involved. This classification was systematically verified at the one month follow-up visit, because new elements, often provided by the family, can highlight unreported aetiologies during the hospitalization of patients.

In our patients care, a first echocardiography is done upon admission, as well as a venous echo-doppler and biomarkers measurement. Biomarkers are repeated at H12, H24 and H48. In this cohort, 99 % of

patients were treated with direct oral anticoagulation treatment, namely rivaroxaban or apixaban with a 21 or 7 days loading dose respectively, then with adapted dosages.

Patients were divided into two groups:

1) PE with cardiac involvement: in the presence of hemodynamic instability, increased cardiac biomarkers: Troponin I (Tp) > 70 ng/l and/or BNP > 100 pg/ml and/or right ventricular (RV) dysfunction corresponding to intermediate or high-risk PE in the European Society of Cardiology (ESC) classification [9]. High-sensitivity Tp and BNP were measured with Siemens Centaur® and the Alere Triage BNP kit (Beckman Coulter®), respectively. The positivity threshold was 70 ng/l for Tp and 100 pg/ml for BNP. RV dysfunction was defined by echocardiography when a right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view or > 0.7 in the parasternal long-axis view, a tricuspid annular plane systolic excursion (TAPSE) < 16 mm or a tricuspid annular peak systolic velocity (S'-DTI) < 10 cm/s were observed. It should be noted that these PEs with cardiac involvement combined the high-risk and intermediate-risk classifications of the ESC guidelines [9].
2) PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding to low-risk PE according to the ESC classification [9].

All chest CT-scans were reread by one radiology expert blinded to the first reading. Special emphasis was placed on eliminating patients with pre-existing pulmonary hypertension as revealed by the patient's medical history or a search for specific signs on the initial scan such as the presence of arterial webs, mural thrombi or a mosaic parenchymal perfusion.

All patients who have had a PE are systematically followed in our department and seen after 1, 3 or 6 months then once a year. Recurrences were determined by a new symptomatic venous thrombotic event or by a symptomatic PE confirmed by diagnostic imaging which had to show a new clot along with positive D-Dimer values. We took into account the age of the patients to construe the D-Dimer values.

If patients presented several recurrences during follow-up, only the first was taken into account. A minimum 12-month follow-up was required although a recurrence within this 12-month period was considered as an event. Mean follow-up was 3.5 ±1.9 years. The causes of deaths which happened during follow–up could not be specified. Our study is in accordance with law n78-17 « Information, technology and freedom » of 6th January 1978 (modified by the new act dated 6th August 2004) and with the EU 2016/679 European Parliament and the 27 April 2016 Council regulation, applicable from May 25th of 2018 (GDRP). Our data base, has been registered as NCT04980924.

Patient and public involvement: This study being a retrospective analysis of prospectively collected data it was not suitable for a partnering with patients, their careers, support networks, and the public. Patients were not involved in this study.

Statistical analysis:

All statistical analyses were performed using SPSS software (Statistical Package for Social Science software, version 20, Chicago, Illinois, USA). Quantitative variables were expressed as medians and confidence intervals and qualitative variables as counts and percentages. Quantitative variables were compared using the Mann Whitney U test and qualitative variables were compared using the Chi2 test. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log-Rank test. Cox proportional hazards regression models were fitted to estimate HRs and 95% CIs to assess the relationship between baseline clinical characteristics and recurrences.

Results

Between 2012 and 2018, 1080 patients were hospitalized for PE confirmed by CT-scan. One hundred sixty-four (164) patients had a history of VTE and had received long-term treatment; 113 had active

neoplasia, 104 supraventricular arrhythmia requiring anticoagulant treatment and 91 a cause making follow-up impossible (Figure 1: Flow chart). In all, 417 patients with a follow-up exceeding 12 months after discontinuation of their anticoagulation treatment were included. Among these, 231 had presented PE without cardiac involvement and 186 PE with cardiac involvement (165 intermediate risk PE and 21 high-risk PE). The cohort's initial characteristics are summarized in Table 1.

A factor explaining the first PE event was found in 212 (50.8%) patients. Associated deep vein thrombosis (DVT) was observed in 186(44.6%) patients. All provoked PE were treated for 3 months. All unprovoked PE were treated for at least 6 months. Mean treatment duration was 5.18 ±2.3 months. Twenty-one patients (5%) received thrombolysis. Patient characteristics according to the severity of the initial clinical presentation are shown in Table 2. Patients in the PE group with cardiac involvement were more often diabetic: 34/186 (18%) vs 21/231 (9%), more often presented blood clots in the lower limbs: 96/186 (51%) vs 90/231 (39%) and averaged longer hospital stays (7.3 ±4 days vs 3.7 ±3 days) than patients without cardiac involvement.

Among the entire cohort, 72 patients (17.3%) presented VTE recurrence. The VTE recurrence rate after discontinuation of anticoagulation was 5.8% (n=24) the first year, 12% (n=44) at 2 years and 28.3% (n=72) at 5 years. In patients experiencing recurrence, 88% (n=63) suffered PE and 12% (n=9) suffered proximal DVT. Mean time to onset of recurrence was 24.9 ± 19.9 months. Kaplan Meier analysis of the entire cohort shows the survival rate of recurrence-free patients according to initial severity over a 5-year follow-up (Fig. 2). The recurrence-free survival rate was significantly higher when the first PE was non-severe p=0.043. Twelve months after completion of the anticoagulant treatment, the recurrence rate was 7/231 (3%), in the non-cardiac involvement group versus 17/186 (9.1%), in the cardiac involvement group: p=0.007.

Multivariate analysis using Cox regression (Table 3) demonstrate that PE with cardiac involvement is an independent factor of recurrence (HR 1.634 [1.015-2.632], p=0.043) as well as family history of PE

(HR 2.851 [1.422-5.716], p=0.003), whereas provoked PE is associated with less recurrence (HR 0.506 [0.308-0.831], p=0.007).

Figure 3 compares the survival rates with no VTE recurrence according to the provoked or unprovoked nature of the first PE. In the sub-group of patients presenting an unprovoked PE, Kaplan Meier analysis revealed no difference in recurrence rate according to first PE severity: p=0.27. On the other hand, (Fig. 4), a higher recurrence rate was noted in the sub-group of patients with a severe provoked PE: p=0.032. At 12 months, recurrence rates were, respectively, 2/112 (1.8%) when there was no initial cardiac involvement versus 9/100 (9%) when cardiac involvement was observed; p=0.018.

Discussion

After the acute phase, the duration of anticoagulation treatment raises one of the major problems in PE management. Some features have been correlated with an added risk of recurrence and are taken into account when choosing a longer treatment. Other criteria are considered although their connection with increased risk of recurrence has not been formally proven [10-12]. However, to our knowledge, no study has assessed the benefits of pursuing anticoagulant treatment relative to first PE severity. We thought it would be useful to look for a relationship between the severity of the initial PE and the recurrence rate. In the present study including 417 patients followed for a mean of 42 months, the incidence of recurrence was similar to findings described in the literature. In 88% of cases, recurrence occurred at the same site as the first event. We also observed a well-known added risk of recurrence in cases with unprovoked first PE. We confirm a statistical correlation between the risk of recurrence and the presence of DVT at the time of the first PE [13-16].

We describe for the first time a higher recurrence rate when the initial PE was severe with a recurrence rate of 9% vs 3% and 35.5% vs 26%, respectively, at 1 and 5 years: p=0.043. Unexpectedly, the correlation between PE severity and the risk of recurrence was stronger when PE was provoked: p=0.032. The lack of a relationship in our study between severity and recurrence among unprovoked

PE could be explained by the fact that we maintained anticoagulation treatment in patients at higher risk of recurrence and consequently these patients were not included in our analysis. It is also possible that the high rate of spontaneous unprovoked PE recurrences conceals the impact of the severity factor. In the literature, the only data that can come close to our result is that of Grifoni et al [17] who reported a higher rate of recurrence when, after hospitalisation for PE, a RV dysfunction was still present at discharge from hospital.

The human physiological coagulation system is believed to protect us against the risk of thrombosis. The formation of venous clots in risky situations is not the rule. When a venous clot occurs, our coagulation-fibrinolysis system is supposed to control the situation by limiting its spread. The formation of a large amount of clots, and hence the occurrence of severe PE, could mean that control by the physiological coagulation system is even more failing. It could also provide additional, hitherto unknown, information on a greater propensity for recurrence.

In the literature, the recurrence risk of a provoked PE is deemed to be sufficiently low not to require long-term treatment. Nevertheless, the risk is still much higher than in a control population. The survey of the literature by Iorio et al [18] covering 2268 provoked PE with transitory risk shows a mean 0.7% annual recurrence rate after surgery but a 3.3% rate for patients as a whole and a 4.2% annual recurrence rate for non-surgical transitory risk factors. These two latter rates are close to the findings for unprovoked thromboembolic events. Our results indicate that in these provoked PE, an over-risk of recurrence could be associated with the severity of the initial event [2,19-21].

Our study was a retrospective analysis of prospectively collected data. It deserves to be confirmed in a dedicated prospective study.

Conclusion: In this cohort study, we highlight a possible link between the severity of a first PE and the risk of a subsequent recurrence. The provoked status of PE may not shield against a high recurrence rate when the first event was severe. These findings justify a prospective study designed to confirm

this relationship which could change the way we determine the duration of anticoagulation treatment after a first PE.

Funding statement: None

Ethics statement: Our study is in accordance with law n78-17 « Information, technology and freedom » of 6th January 1978 (modified by the new act dated 6th August 2004) and with the EU 2016/679 European Parliament and the 27 April 2016 Council regulation, applicable from May 25th of 2018 (GDRP). Our data base, has been registered as NCT04980924. This is a non-interventional retrospective cohort study.

Data Availability: All data relevant to the study are included in the article.

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Table 1: Initial cohort characteristics

Overall population	**N = 417**	**%**
Sex F/M, n (%)	221	53%
Age, years (median, [IC])	65 , [63-67]	
Arterial hypertension, n (%)	179	43%
Obesity, n (%)	74	18%
Dyslipidemia, n (%)	109	26%
Diabetes, n (%)	55	13%
Smoking, n (%)	110	26%
History of stroke, n (%)	26	6%
Inflammatory disease, n (%)	33	8%
Psychiatric pathology, n (%)	83	20%
Provoked, n (%)	212	51%
Associated DVT, n (%)	186	45%
Proximal DVT	92	22%
Distal DVT	94	23%
Thrombolysis, n (%)	21	5%
Aspirin treatment	68	16.3%
Statin treatment	42	10%
Psychotropic medication	76	18.2%
Duration of hospital stay, days (median, [IC])	5 [4-5]	
Initial anticoagulation duration, months (median, [IC])	6 [6-6]	
Follow-up period, months (median, [IC])	36 [33 – 40]	
VTE recurrence, n (%)	72	18%
- PE, n (% of recurrence)	*63*	*88%*
- DVT, n (% of recurrence)	*9*	*12%*
Time to recurrence, in months, (median, [IC])	18.5 [14-24]	

SD = Standard Deviation, DVT = Deep Vein Thrombosis, VTE = Venous Thromboembolism,

PE = Pulmonary Embolism

Table 2: Initial characteristics of PE groups without and with cardiac involvement

	PE without cardiac involvement N =231	**PE with cardiac involvement N =186**	*P-value*
Sex F/M, n (%)	113 (48.9)	108 (58.1)	0.074
Age, years (mean ± SD)	61 ± 17.2	63 ± 15.5	0.12
Arterial hypertension, n (%)	90 (39)	89 (48)	0. 068
Obesity, n (%)	43 (19)	31 (17)	0.622
Dyslipidemia, n (%)	53 (23)	56 (30)	0.09
Diabetes, n (%)	21 (9)	34 (18)	0.006
Smoking, n (%)	72 (31)	38 (20)	0.012
History of stroke, n (%)	10 (4)	16 (8.6)	0.073
Inflammatory disease, n (%)	17 (7)	16 (8.6)	0.187
Psychiatric pathology, n (%)	45 (20)	38 (20)	0.809
Provoked, n (%)	112 (49)	100 (54)	0.284
Associated DVT, n (%)	90 (39)	96 (52)	0.01
Length of hospital stay, days (mean ± SD)	*4.7 ± 3*	*7.3 ± 4*	0.004
Tp (ng/l)	29.1 ± 16	240 ± 237	0.0001
BNP (pg/l)	45 ± 21	243.2 ± 106	0.0001
RV/LV	0.62 ± 0.07	0.96 ± 0.05	0.01
Duration in months of initial anticoagulation	5.18 ± 2.4	5.2 ± 2.3	0.417

SD = Standard Deviation, DVT = Deep Vein Thrombosis, Tp = Troponin, BNP = Brain Natriuretic Peptide, RV/LV = right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view

Table 3. Multivariate analysis using Cox regression for the risk of recurrence.

Clinical factor	Hazard Ratio	P value	95% CI
Female gender	1.022	0.927	[0.636 - 1.644]
Family history of PE	2.851	0.003	[1.422 - 5.716]
Psychotropic medication	1.252	0.471	[0.679 - 2.309]
Provoked PE	0.506	0.007	[0.308 - 0.831]
PE with cardiac involvement	1.634	0.043	[1.015 - 2.632]
Associated DVT	1.216	0.471	[0.679 - 2.309]
Anticoagulation duration after PE	1.023857	0.196	[0.988 - 1.061]

DVT = Deep Vein Thrombosis, VTE = Venous Thromboembolism, PE = Pulmonary Embolism

Figure legend:

Figure 1: Study flow-chart

Figure 2: Recurrence-free survival for VTE according to severity of first PE

Figure 3: Recurrence-free survival following provoked PE according to severity of first PE

Figure 4: Recurrence-free survival following unprovoked PE according to severity of first PE

Figure 1

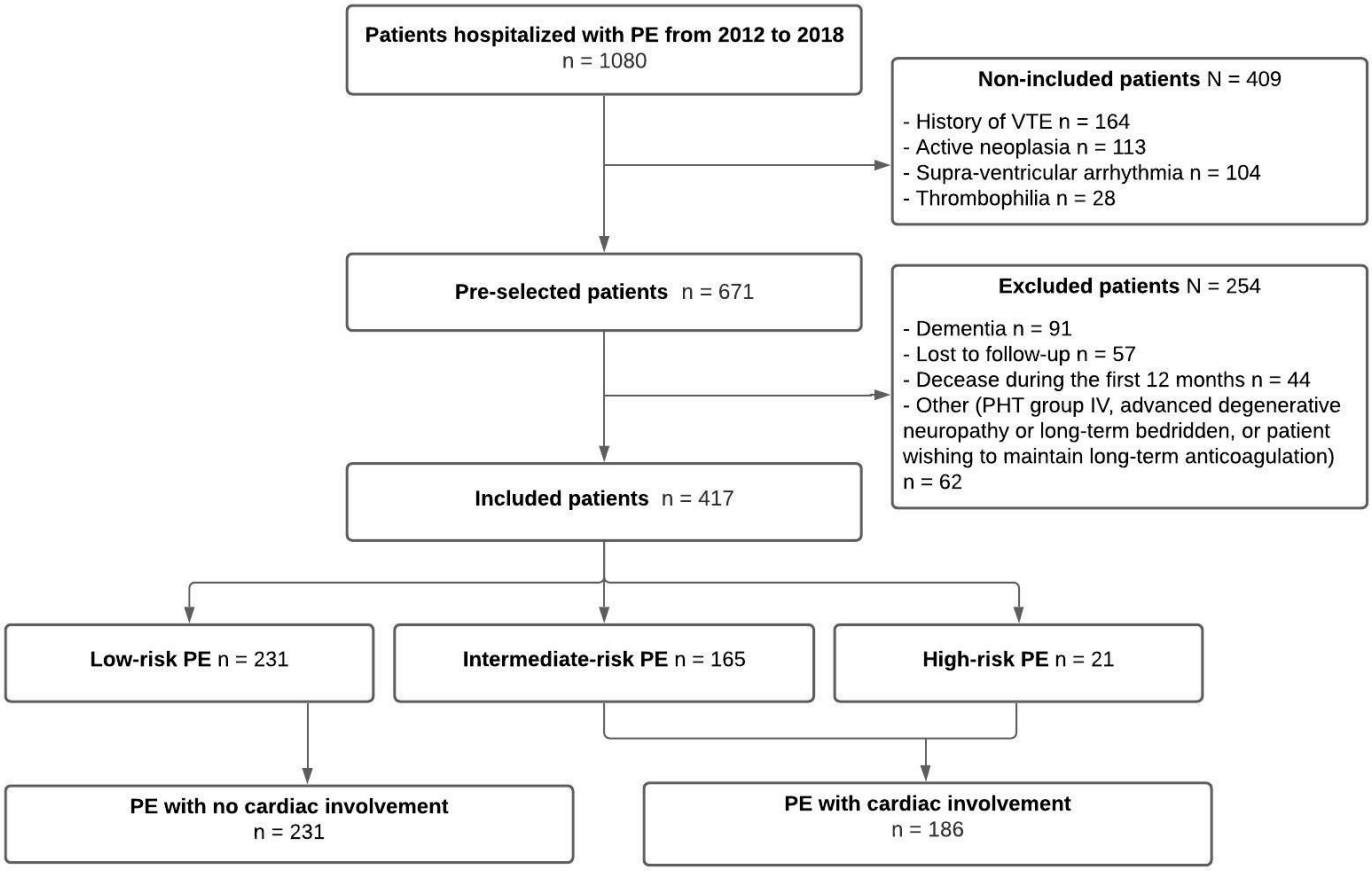
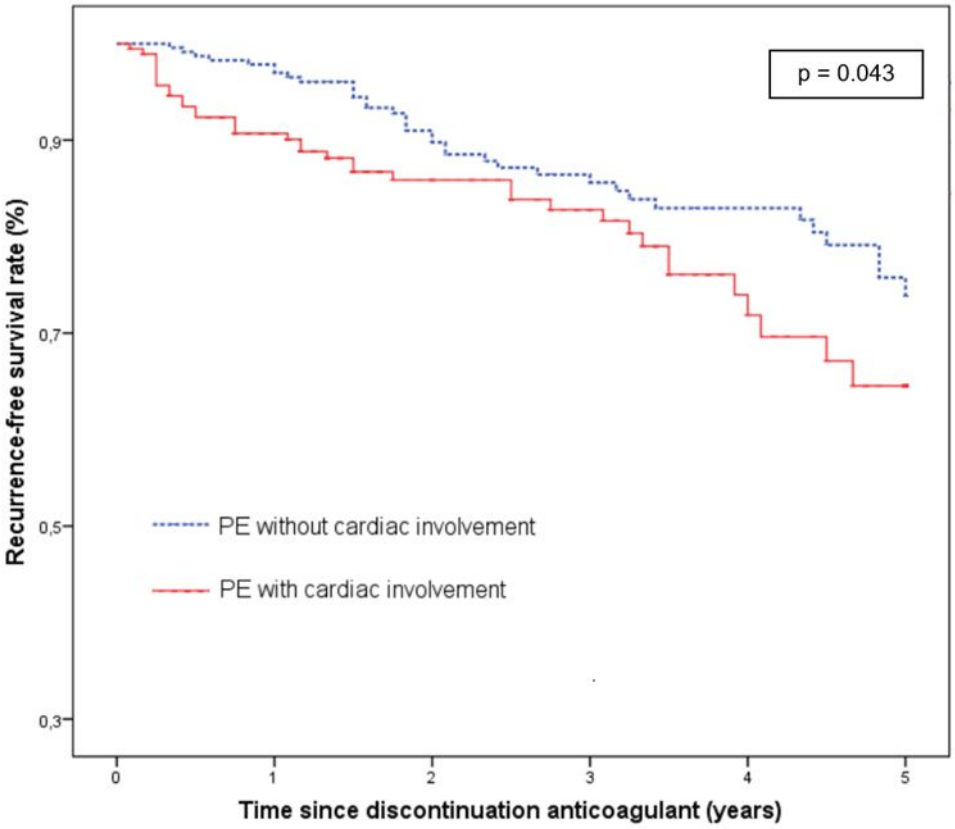
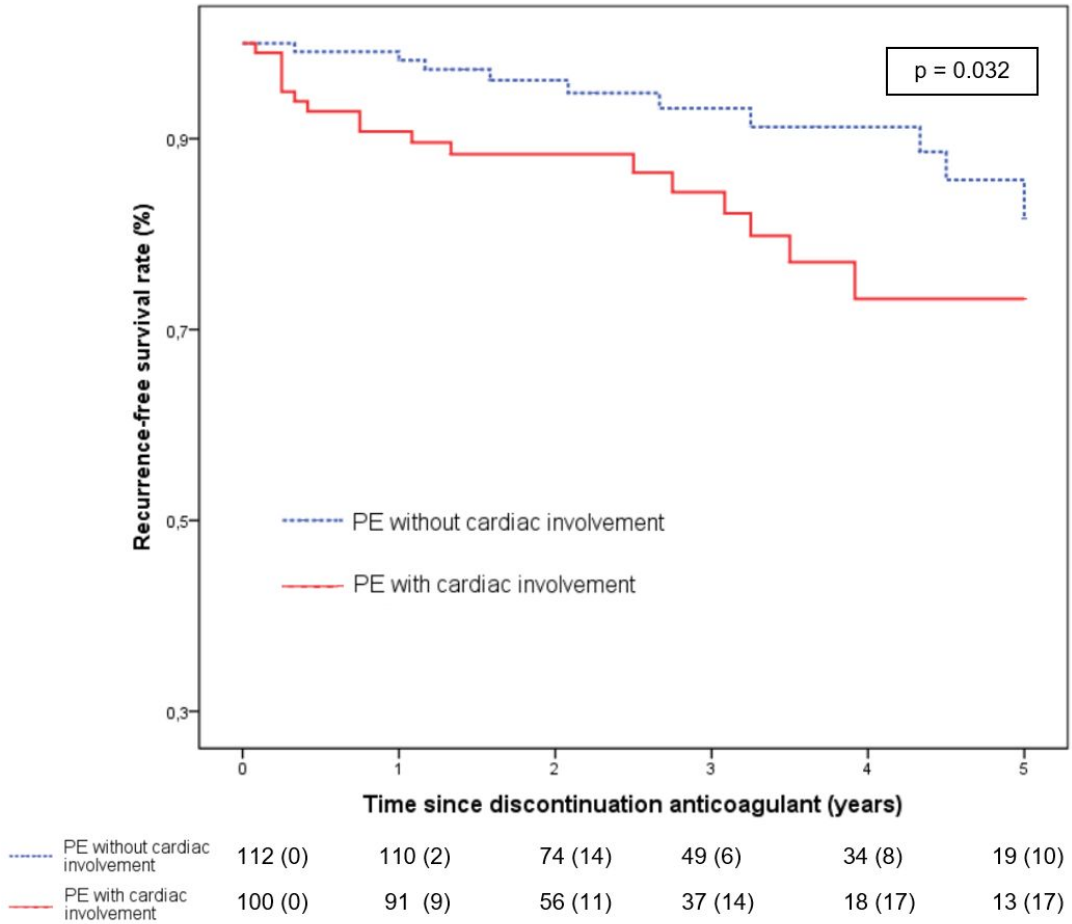


Figure 2



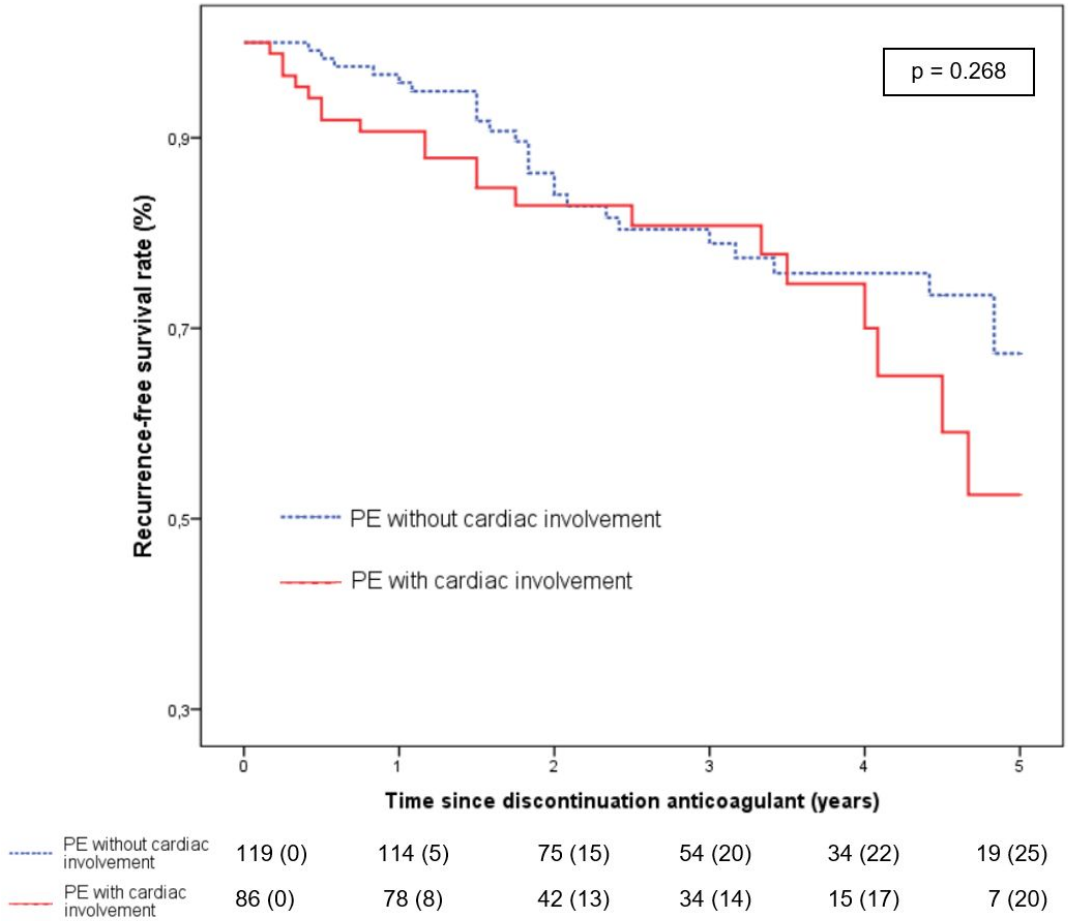
PE without cardiac involvement	231 (0)	224 (7)	148 (20)	104 (26)	68 (29)	39 (35)
PE with cardiac involvement	186 (0)	169 (17)	98 (24)	72 (27)	34 (34)	20 (37)

Figure 3



PE without cardiac involvement	112 (0)	110 (2)	74 (14)	49 (6)	34 (8)	19 (10)
PE with cardiac involvement	100 (0)	91 (9)	56 (11)	37 (14)	18 (17)	13 (17)

Figure 4



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Is pulmonary embolism recurrence linked with the severity of the first event ? A French retrospective cohort study.

Short title: PE severity and recurrence risk

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Abstract.

Objectives: Severity of a first pulmonary embolism (PE) is sometimes proposed as a criterion for prolonging anticoagulant treatment. However, little evidence supports this idea. We attempted to determine the connection between severity of first PE and the risk of recurrence.

Participants: Patients admitted with PE between 2012 and 2018 and for whom anticoagulant treatment had been discontinued were followed. PEs were classified according to severity into 2 groups: those with associated cardiac involvement (increased cardiac biomarker(s) and/or echocardiographic right ventricular dysfunction) and those with no cardiac involvement which were classified as non-severe. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log Rank test.

Results: 417 PEs (186 with cardiac involvement) were followed for a least one year after discontinuation of treatment with a mean follow-up of: 3.5 ±1.9 years. 72 patients (17.3%) experienced venous thromboembolism recurrence: 24 (5.8%), 44 (12 %) and 72 (28.3 %) respectively, at 1, 2 and 5 years. In 63 patients (88%), recurrence was a PE. Mean time to onset of recurrence was 24.9 ±19.9 months. At 5 years, the recurrence rate was higher when the first PE was associated with cardiac involvement p=0.043. In contrast, in patients with provoked PE, the recurrence rate is higher when the first PE event was associated with cardiac involvement: p=0.032. Multivariate analysis demonstrate that PE severity is an independent factor of recurrence (HR 1.634 [1.015-2.632], p=0.043).

Conclusion: We report for the first time a possible link between a higher recurrence rate and the severity of the first PE. This result which must be confirmed in a dedicated prospective trial could become an important criterion for the duration of anticoagulant therapy after a PE.

Trial registration: NCT04980924

Strengths and limitations:

- Little is known about the severity of PE and the risk of recurrence.
- This is the first time such a link is investigated.
- This study is a retrospective analysis of prospectively collected data.
- Only symptomatic references were taken into account
- The exclusion of patients who were long-term anticoagulated may have skewed the results of the non-provoked PEs sub-group.

Background

After the acute event, the choice of the duration of treatment is one of the main problems in the management of a first PE. Currently, provoked versus non-provoked circumstance is the main criterion used to determine treatment duration. Alongside this main criterion, other factors can also be taken into account such as bleeding risk, sex, blood group, persistence of a venous clot or the end-of-treatment D-dimers level [1–6]. Some practitioners consider first PE severity as a criterion likely to extend treatment duration. However, very few findings in the literature corroborate this idea.

Objective and methods

Drawing on our regional database [7], we made an assessment of the connection between first PE severity and the risk of recurrence of VTE events. All patients hospitalized for PE from 2012 to 2018 were followed. Only patients whose treatment had been discontinued and for which we had a minimum 12-month follow-up were included. Consequently, patients requiring long-term anticoagulant treatment were excluded, along with patients with active cancer.

In accordance with the literature [8], provoked PE was defined as PE which happened within three months of a surgery, a trauma, a significant immobility, pregnancy, a severe thrombophilia, the use of the combined contraceptive pill, hormone replacement therapy or know thrombogenic treatment. Unprovoked PE was defined as PE for which no transient risk factor or medication was involved. This classification was systematically verified at the one month follow-up visit, because new elements, often provided by the family, can highlight unreported aetiologies during the hospitalization of patients.

In our patients care, a first echocardiography is done upon admission, as well as a venous echo-doppler and biomarkers measurement. Biomarkers are repeated at H12, H24 and H48. In this cohort, 99 % of

patients were treated with direct oral anticoagulation treatment, namely rivaroxaban or apixaban with a 21 or 7 days loading dose respectively, then with adapted dosages.

Patients were divided into two groups:

1) PE with cardiac involvement: in the presence of hemodynamic instability, increased cardiac biomarkers: Troponin I (Tp) > 70 ng/l and/or BNP > 100 pg/ml and/or right ventricular (RV) dysfunction corresponding to intermediate or high-risk PE in the European Society of Cardiology (ESC) classification [9]. High-sensitivity Tp and BNP were measured with Siemens Centaur® and the Alere Triage BNP kit (Beckman Coulter®), respectively. The positivity threshold was 70 ng/l for Tp and 100 pg/ml for BNP. RV dysfunction was defined by echocardiography when a right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view or > 0.7 in the parasternal long-axis view, a tricuspid annular plane systolic excursion (TAPSE) < 16 mm or a tricuspid annular peak systolic velocity (S'-DTI) < 10 cm/s were observed. It should be noted that these PEs with cardiac involvement combined the high-risk and intermediate-risk classifications of the ESC guidelines [9].
2) PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding mainly to low-risk PE according to the ESC classification [9]. These PE were classified as non-severe in our study.

All chest CT-scans were reread by one radiology expert blinded to the first reading. Special emphasis was placed on eliminating patients with pre-existing pulmonary hypertension as revealed by the patient's medical history or a search for specific signs on the initial scan such as the presence of arterial webs, mural thrombi or a mosaic parenchymal perfusion.

All patients who have had a PE are systematically followed in our department and seen after 1, 3 or 6 months then once a year. Recurrences were determined by a new symptomatic venous thrombotic event or by a symptomatic PE confirmed by diagnostic imaging which had to show a new clot along

with positive D-Dimer values. We took into account the age of the patients to construe the D-Dimer values.

If patients presented several recurrences during follow-up, only the first was taken into account. A minimum 12-month follow-up was required although a recurrence within this 12-month period was considered as an event. Mean follow-up was 3.5 ±1.9 years. The causes of deaths which happened during follow–up could not be specified. Our study is in accordance with law n78-17 « Information, technology and freedom » of 6th January 1978 (modified by the new act dated 6th August 2004) and with the EU 2016/679 European Parliament and the 27 April 2016 Council regulation, applicable from May 25th of 2018 (GDRP). Our data base, has been registered as NCT04980924.

Patient and public involvement: This study being a retrospective analysis of prospectively collected data it was not suitable for a partnering with patients, their careers, support networks, and the public. Patients were not involved in this study.

Statistical analysis:

All statistical analyses were performed using SPSS software (Statistical Package for Social Science software, version 20, Chicago, Illinois, USA). Quantitative variables were expressed as mean and standard deviation when the distribution was normal, or median and confidence interval when the distribution was not normal. The normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Qualitative variables were expressed as counts and percentages. Quantitative variables were compared using the Mann Whitney U test, and qualitative variables were compared using the Chi2 test. Recurrence-free survivals were estimated using the Kaplan Meier method and compared using the Log-Rank test. Cox proportional hazards regression models were fitted to estimate HRs and 95% CIs to assess the relationship between baseline clinical characteristics and recurrences. A $P \leq 0.05$ was considered significant.

Results

Between 2012 and 2018, 1080 patients were hospitalized for PE confirmed by CT-scan. One hundred sixty-four (164) patients had a history of VTE and had received long-term treatment; 113 had active neoplasia, 104 supraventricular arrhythmia requiring anticoagulant treatment and 91 a cause making follow-up impossible (Figure 1: Flow chart). In all, 417 patients with a follow-up exceeding 12 months after discontinuation of their anticoagulation treatment were included. Among these, 231 had presented PE without cardiac involvement and 186 PE with cardiac involvement (165 intermediate risk PE and 21 high-risk PE). The cohort's initial characteristics are summarized in Table 1.

A factor explaining the first PE event was found in 212 (50.8%) patients. Associated deep vein thrombosis (DVT) was observed in 186(44.6%) patients. All provoked PE were treated for 3 months. All unprovoked PE were treated for at least 6 months. Mean treatment duration was 5.18 ±2.3 months. Twenty-one patients (5%) received thrombolysis. Patient characteristics according to the severity of the initial clinical presentation are shown in Table 2. Patients in the PE group with cardiac involvement were more often diabetic: 34/186 (18%) vs 21/231 (9%), more often presented blood clots in the lower limbs: 96/186 (51%) vs 90/231 (39%) and averaged longer hospital stays (7.3 ±4 days vs 3.7 ±3 days) than patients without cardiac involvement.

Among the entire cohort, 72 patients (17.3%) presented VTE recurrence. The VTE recurrence rate after discontinuation of anticoagulation was 5.8% (n=24) the first year, 12% (n=44) at 2 years and 28.3% (n=72) at 5 years. In patients experiencing recurrence, 88% (n=63) suffered PE and 12% (n=9) suffered proximal DVT. Mean time to onset of recurrence was 24.9 ± 19.9 months. Kaplan Meier analysis of the entire cohort shows the survival rate of recurrence-free patients according to initial severity over a 5-year follow-up (Fig. 2). The recurrence-free survival rate was significantly higher when the first PE was non-severe p=0.043. Twelve months after completion of the anticoagulant treatment, the recurrence

rate was 7/231 (3%), in the non-cardiac involvement group versus 17/186 (9.1%), in the cardiac involvement group: p=0.007.

In the multivariate analysis using Cox regression (Table 3) including cardiac involvement, gender, family history of VTE, psychotropic medication, unprovoked PE, associated DVT and duration of anticoagulation; cardiac involvement (HR 1.634 [1.015-2.632], p=0.043)) and family history of VTE ((HR 2.851 [1.422-5.716], p=0.003) were independent risk factors, where as provoked PE is associated with less recurrence (HR 0.506 [0.308-0.831], p=0.007).

Figure 3 compares the survival rates with no VTE recurrence according to the provoked or unprovoked nature of the first PE. In the sub-group of patients presenting an unprovoked PE, Kaplan Meier analysis revealed no difference in recurrence rate according to first PE severity: p=0.27. On the other hand, (Fig. 4), a higher recurrence rate was noted in the sub-group of patients with a severe provoked PE: p=0.032. At 12 months, recurrence rates were, respectively, 2/112 (1.8%) when there was no initial cardiac involvement versus 9/100 (9%) when cardiac involvement was observed; p=0.018.

Discussion

After the acute phase, the duration of anticoagulation treatment raises one of the major problems in PE management. Some features have been correlated with an added risk of recurrence and are taken into account when choosing a longer treatment. Other criteria are considered although their connection with increased risk of recurrence has not been formally proven [10-12]. However, to our knowledge, no study has assessed the benefits of pursuing anticoagulant treatment relative to first PE severity. We thought it would be useful to look for a relationship between the severity of the initial PE and the recurrence rate. In the present study including 417 patients followed for a mean of 42 months, the incidence of recurrence was similar to findings described in the literature. In 88% of cases, recurrence occurred at the same site as the first event. We also observed a well-known added risk of

recurrence in cases with unprovoked first PE. We confirm a statistical correlation between the risk of recurrence and the presence of DVT at the time of the first PE [13-16].

We describe for the first time a higher recurrence rate when the initial PE was severe with a recurrence rate of 9% vs 3% and 35.5% vs 26%, respectively, at 1 and 5 years: p=0.043. Unexpectedly, the correlation between PE severity and the risk of recurrence was stronger when PE was provoked: p=0.032. The lack of a relationship in our study between severity and recurrence among unprovoked PE could be explained by the fact that we maintained anticoagulation treatment in patients at higher risk of recurrence and consequently these patients were not included in our analysis. It is also possible that the high rate of spontaneous unprovoked PE recurrences conceals the impact of the severity factor. In the literature, the only data that can come close to our result is that of Grifoni et al [17] who reported a higher rate of recurrence when, after hospitalisation for PE, a RV dysfunction was still present at discharge from hospital.

The human physiological coagulation system is believed to protect us against the risk of thrombosis. The formation of venous clots in risky situations is not the rule. When a venous clot occurs, our coagulation-fibrinolysis system is supposed to control the situation by limiting its spread. The formation of a large amount of clots, and hence the occurrence of PE with cardiac involvement, could mean that control by the physiological coagulation system is even more failing. It could also provide additional, hitherto unknown, information on a greater propensity for recurrence.

In the literature, the recurrence risk of a provoked PE is deemed to be sufficiently low not to require long-term treatment. Nevertheless, the risk is still much higher than in a control population. The survey of the literature by Iorio et al [18] covering 2268 provoked PE with transitory risk shows a mean 0.7% annual recurrence rate after surgery but a 3.3% rate for patients as a whole and a 4.2% annual recurrence rate for non-surgical transitory risk factors. These two latter rates are close to the findings for unprovoked thromboembolic events. Our results indicate that in these provoked PE, an over-risk of recurrence could be associated with the severity of the initial event [2,19-21].

Our study was a retrospective analysis of prospectively collected data. There are possible limitations; we report only symptomatic episodes, potential changes in risk factors over time (e.g. obesity, smoking…) could not be taken into account. Some known risk factors of recurrence were not considered in the multivariate analysis as high body mass index or high D-dimer level. Our conclusions cannot be applied to cancer patients or those needing long-term treatment since these patients were excluded from the study. Our results deserves to be confirmed in a dedicated prospective study.

Conclusion: In this cohort study, we highlight a possible link between the severity of a first PE and the risk of a subsequent recurrence. The provoked status of PE may not shield against a high recurrence rate when the first event was severe. These findings justify a prospective study designed to confirm this relationship which could change the way we determine the duration of anticoagulation treatment after a first PE.

Contributor ship statement:

EF and **EF** wrote the protocol and the designed the study.

EF, NR, NB, ML, SB, PM followed up patients who were all reviewed with a long follow-up.

EF, FA, NH collected the data

JP B and **FS** did the statistics

Competing interests: None

Funding statement: None

Ethics statement: Our study is in accordance with law n78-17 « Information, technology and freedom » of 6th January 1978 (modified by the new act dated 6th August 2004) and with the EU 2016/679 European Parliament and the 27 April 2016 Council regulation, applicable from May 25th of 2018 (GDRP). Our data base, has been registered as NCT04980924. This is a non-interventional retrospective cohort study.

Data Availability: All data relevant to the study are included in the article.

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Table 1: Initial cohort characteristics

Overall population	**N = 417**	**%**
Sex F/M, n (%)	221	53%
Age, years (median, [IC])	65 , [63-67]	
Arterial hypertension, n (%)	179	43%
Obesity, n (%)	74	18%
Dyslipidemia, n (%)	109	26%
Diabetes, n (%)	55	13%
Smoking, n (%)	110	26%
History of stroke, n (%)	26	6%
Inflammatory disease, n (%)	33	8%
Psychiatric pathology, n (%)	83	20%
Provoked, n (%)	212	51%
Associated DVT, n (%)	186	45%
Proximal DVT	92	22%
Distal DVT	94	23%
Thrombolysis, n (%)	21	5%
Aspirin treatment	68	16.3%
Statin treatment	42	10%
Psychotropic medication	76	18.2%
Duration of hospital stay, days (median, [IC])	5 [4-5]	
Initial anticoagulation duration, months (median, [IC])	6 [6-6]	
Follow-up period, months (median, [IC])	36 [33 – 40]	
VTE recurrence, n (%)	72	18%
- PE, n (% of recurrence)	*63*	*88%*
- DVT, n (% of recurrence)	*9*	*12%*
Time to recurrence, in months, (median, [IC])	18.5 [14-24]	

SD = Standard Deviation, DVT = Deep Vein Thrombosis, VTE = Venous Thromboembolism,

PE = Pulmonary Embolism

Table 2: Initial characteristics of PE groups without and with cardiac involvement

	PE without cardiac involvement N =231	**PE with cardiac involvement N =186**	*P-value*
Sex F/M, n (%)	113 (48.9)	108 (58.1)	0.074
Age, years (mean ± SD)	61 ± 17.2	63 ± 15.5	0.12
Arterial hypertension, n (%)	90 (39)	89 (48)	0. 068
Obesity, n (%)	43 (19)	31 (17)	0.622
Dyslipidemia, n (%)	53 (23)	56 (30)	0.09
Diabetes, n (%)	21 (9)	34 (18)	0.006
Smoking, n (%)	72 (31)	38 (20)	0.012
History of stroke, n (%)	10 (4)	16 (8.6)	0.073
Inflammatory disease, n (%)	17 (7)	16 (8.6)	0.187
Psychiatric pathology, n (%)	45 (20)	38 (20)	0.809
Family history of VTE	15 (6.5)	12 (6.5)	0.986
Provoked, n (%)	112 (49)	100 (54)	0.284
Associated DVT, n (%)	90 (39)	96 (52)	0.01
Length of hospital stay, days (mean ± SD)	*4.7 ± 3*	*7.3 ± 4*	0.004
Tp (ng/l)	17 [17-17]	298 [206-376]	0.0001
BNP (pg/l)	30 [25-34]	293 [241-327]	0.0001
RV/LV	0.62 ± 0.07	0.96 ± 0.05	0.01
Duration in months of initial anticoagulation	5.18 ± 2.4	5.2 ± 2.3	0.417

SD = Standard Deviation, VTE: venous thromboembolic disease, DVT = Deep Vein Thrombosis, Tp = Troponin, BNP = Brain Natriuretic Peptide, RV/LV = right-to-left ventricular end-diastolic diameter ratio > 0.9 in the apical four-chamber view.

Table 3. Multivariate analysis using Cox regression for the risk of recurrence.

Clinical factor	Hazard Ratio	P value	95% CI
Female gender	1.022	0.927	[0.636 - 1.644]
Family history of PE	2.851	0.003	[1.422 - 5.716]
Psychotropic medication	1.252	0.471	[0.679 - 2.309]
Provoked PE	0.506	0.007	[0.308 - 0.831]
PE with cardiac involvement	1.634	0.043	[1.015 - 2.632]
Associated DVT	1.216	0.471	[0.679 - 2.309]
Anticoagulation duration after PE	1.023857	0.196	[0.988 - 1.061]

DVT = Deep Vein Thrombosis, VTE = Venous Thromboembolism, PE = Pulmonary Embolism

Figure legend:

Figure 1: Study flow-chart

Figure 2: Recurrence-free survival for VTE according to severity of first PE

Figure 3: Recurrence-free survival following provoked PE according to severity of first PE

Figure 4: Recurrence-free survival following unprovoked PE according to severity of first PE

Figure 1: Study flow-chart

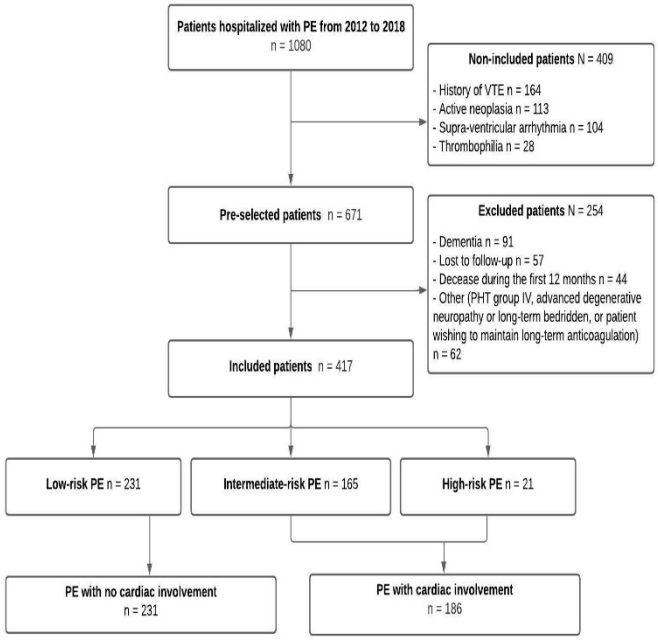

Figure 2: Recurrence-free survival for VTE according to severity of first PE

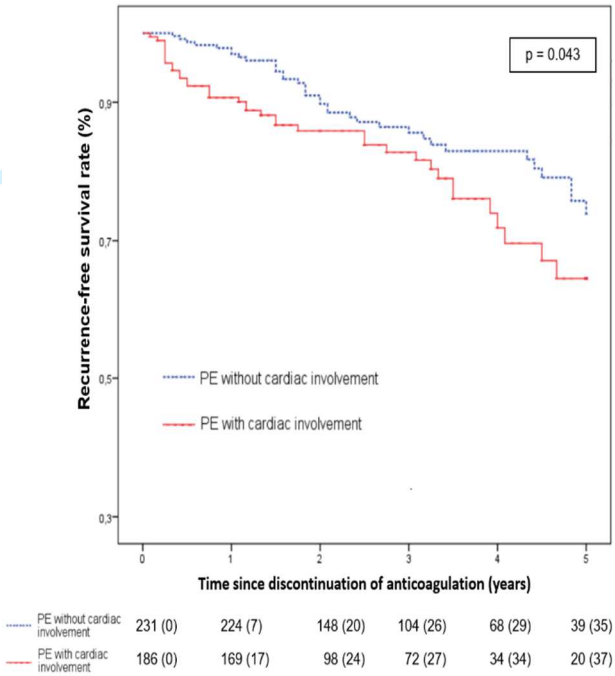

Figure 3: Recurrence-free survival following provoked PE according to severity of first PE

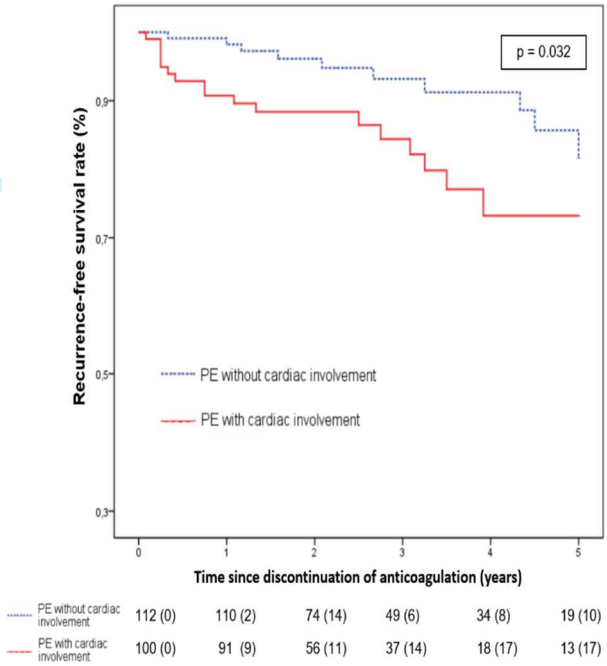

Figure 4: Recurrence-free survival following unprovoked PE according to severity of first PE