Frequency and Predictors for Chronic Thromboembolic Pulmonary Hypertension after a first Unprovoked Pulmonary Embolism: results from PADIS studies

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Frequency and Predictors for Chronic Thromboembolic Pulmonary Hypertension after a first Unprovoked Pulmonary Embolism: results from PADIS studies.

Running Head: CTEPH after unprovoked pulmonary embolism.

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**Members of the Prolongation d'un traitement par Antivitamine K pendant Dix-huit mois versus placebo au décours d'un premier épisode d'embolie pulmonaire Idiopathique traité Six mois (PADIS-PE) Study Group are listed in the Appendix.

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Abbreviations:

AUC: Area Under Curve

CI: Confidence Interval

CTEPH: Chronic Thromboembolic Pulmonary Hypertension

CTPA: Computed-Tomography Pulmonary Angioplasty

DVT: Deep Venous Thrombosis

ERS: European Respiratory Society

ESC: European Society of Cardiology

HR: Hazard Ratio

IQR: Inter Quartile Range

LAA: Lupus Anticoagulant Antibodies

NYHA: New York Health Association

PA: Pulmonary Artery

PAWP: Pulmonary Artery Wedge Pressure

PE: Pulmonary Embolism

PEA: Pulmonary Endarterectomy

PH: Pulmonary Hypertension

PVO: Pulmonary Vascular Obstruction

PY: Pack-Year

RHC: Right Heart Catheterism

RHD: Right Heart Dysfunction

ROC: Receiver Operating Characteristics

SD: Standard Deviation

sPAP: systolic Pulmonary Arterial pressure

TTE: Transthoracic Echocardiography

V/Q: Ventilation / Perfusion

VWF: Von Willebrand Factor

VT: Venous Thrombosis

WU: Wood Units

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ESSENTIALS

- Chronic thromboembolic pulmonary hypertension (CTEPH) features are not well characterized.
- CTEPH incidence and predictors were studied after a first unprovoked pulmonary embolism (PE).
- Cumulative incidence of CTEPH during 8-year follow-up was 2.8% (95%CI 0.95-4.64)
- PVO and sPAP at PE diagnosis and at 6 months were the main predictors for CTEPH diagnosis.

ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening pulmonary embolism's (PE) complication whose incidence and predictors are not precisely determined.

Objective: To determine the frequency and predictors for CTEPH after a first unprovoked PE.

Patients/Methods: In a randomized trial comparing an additional 18-month warfarin versus placebo in patients after a first unprovoked PE initially treated with vitamin K antagonist for 6 months, we applied recommended CTEPH screening strategies through 8-year follow-up to determine cumulative incidence of CTEPH. CTEPH predictors were estimated using Cox models. Pulmonary vascular obstruction (PVO) and systolic pulmonary arterial pressure (sPAP) at PE diagnosis and 6 months were studied by receiver operating curves analysis. All CTEPH cases and whether they were incident or prevalent were adjudicated.

Results: During a median follow-up of 8.7 years, 9 CTEPH cases were diagnosed among 371 patients, with a cumulative incidence of 2.8% (95% confidence interval [CI], 0.95-4.64), and of 1.31% (95%CI, 0.01-2.60) after exclusion of 5 cases adjudicated as prevalent. At PE diagnosis, PVO>45% and sPAP>56mmHg were associated with CTEPH with a hazard ratio (HR) of 33.00 (95%CI 1.64-667.00, p=0.02) and 12.50 (95%CI 2.10-74.80, p<0.01) respectively. Age>65 years, lupus anticoagulant antibodies and non-O blood groups were also predictive of CTEPH. PVO>14% and sPAP>34mmHg at

6-month were associated with CTEPH (HRs 63.90 [95%CI, 3.11-1310.00, p<0.01]and 17.2 [95%CI, 2.75-108, p<0.01]).

Conclusion: After a first unprovoked PE, CTEPH cumulative incidence was 2.8% during 8-year follow-up. PVO and sPAP at PE diagnosis and at 6 months were the main predictors for CTEPH diagnosis.

Keywords: Pulmonary Embolism; Pulmonary Hypertension; Clinical Studies; Risk Factors; Incidence.

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TEXT:

Chronic thromboembolic pulmonary hypertension (CTEPH) results from the obstruction of pulmonary arteries by persistent thrombotic material and by small pulmonary arteries remodelling, leading to an increase of pulmonary arterial pressure and of pulmonary vascular resistance, and finally pulmonary hypertension (PH) (1). In patients with an acute symptomatic pulmonary embolism (PE), CTEPH constitutes a rare life-threatening complication, with a frequency ranging from 0.56% to 6.3% (2) and a three-year survival of 35% in the absence of specific treatment. Recent guidelines from European Society of Cardiology/European Respiratory Society (ESC/ERS) recommend to evaluate for CTEPH in patients with PE after at least three months of anticoagulation based on clinical evaluation, transthoracic echocardiography (TTE) and ventilation perfusion (V/Q) lung scan assessment (3,4). Despite numerous prospective studies, CTEPH incidence (5–8) and predictors remain uncertain due to the heterogeneity of analyzed study populations and the non negligible probability that some patients were already carriers of CTEPH at the time of acute PE diagnosis. Unprovoked PE is an established CTEPH risk factor, but there are few data about CTEPH incidence in this high-risk population. Moreover, to the best of our knowledge, there is no estimation of CTEPH incidence after a first diagnosis of unprovoked PE.

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In this study, we aimed to determine cumulative incidence and predictors of CTEPH during an 8-year prospective follow-up of patients initially included in a randomized trial on extended anticoagulation duration after a first unprovoked PE (9).

STUDY DESIGN AND METHODS

Study design and population

All patients were initially included in the randomized, double-blind, multicentre "Prolonged Anticoagulation During eighteen months versus placebo after Initial Six-month treatment for a first episode of idiopathic Pulmonary Embolism" (PADIS-PE) trial which has been previously described (9) (**See Supplement and Figure S1**). Inclusion criteria were: age of 18 or older; objectively confirmed first unprovoked PE based on computerized-tomography pulmonary angiography (CTPA) or V/Q lung scan; initial treatment with vitamin K antagonist during six uninterrupted months. Main exclusion criteria were: indication for prolonged anticoagulation other than PE (e.g., CTEPH, atrial fibrillation); previous PE or deep vein thrombosis (DVT); recurrent PE during the initial six-month treatment and high bleeding risk. PE was considered as unprovoked if it occurred in the absence of major transient risk factors.

At six months after PE, patients were included and randomly assigned to receive an additional 18-month warfarin treatment or placebo and were followed during a 2-year post-treatment period. At the time of inclusion (i.e.; after the initial 6 months of anticoagulation), all patients underwent centralized frozen blood samples, leg vein ultrasound, V/Q lung scan, and trans-thoracic echocardiography according to a predefined methodology and before randomization (9).

After completing the PADIS-PE study, patients were prospectively followed-up for an additional 6-year period ("PADIS-EXTENSION" study, NCT02884934) and, at 5 years from index PE, a systematic screening for CTEPH was performed, based on a predefined algorithm including systematic TTE and V/Q lung scan, whether patients were symptomatic or not (PADIS-Pulmonary Hypertension study "PADIS-PH", NCT01894204) (**see Supplement and Figure S1**). PADIS studies were conducted in

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accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection (review board: CPP Ouest 6-778; reference number: 2012-A01570-43).

Data collection

At PE diagnosis, data from TTE, CTPA or V/Q lung scan were retrospectively collected (12). All CTPA images were reassessed by expert radiologists and signs of CTEPH such as pouching defects, webs and bands, mosaic lung perfusion were reported (10). Pulmonary vascular obstruction (PVO) was scored according to Qanadli (for CTPA) and Meyer (for V/Q lung scan) scores (11,12) (**See Supplement**).

At 6 months (i.e., at inclusion in PADIS-PE study) and at 5 years after PE (i.e., at inclusion in PADIS-PH study), data from systematic TTE and V/Q lung scan were prospectively collected; residual PVO was scored on V/Q lung scan (**See Supplement**) (12). Centralized frozen blood plasmas were taken at 6 months and thrombophilia testing was performed by biologists blinded from study treatment allocation and patients' characteristics (12) (**Table 1**).

During 8-year follow-up after inclusion in PADIS-PE study, clinical data concerning incident medical conditions, respiratory symptoms, PE recurrence and bleeding were collected through a questionnaire sent annually to participants. Interviewers were physicians in charge of the patients. In case of a suspicion of CTEPH, TTE and V/Q lung scan were performed according to physician's decision.

The probability of PH was evaluated using standardised TTE in accordance with ESC/ERS 2015 guidelines (**See Supplement)** (4). The PH probability was "high", "intermediate" or "low" depending on peak tricuspid regurgitation velocity measurement, and presence of other indirect signs of PH. Persistent perfusion defects were diagnosed if V/Q lung scan showed at least one segmental unmatched perfusion defect, corresponding to a PVO of 5% (13,14). All PVOs were estimated on all available imaging by two independent radiologists or nuclear physicians without knowledge of patients' clinical characteristics and treatment allocation.

Outcomes

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The primary outcome was the cumulative incidence of "confirmed" and "likely" CTEPH during 8-year follow-up after a first unprovoked PE. Patients were classified as having "confirmed", "likely", "ruled out" or "undetermined" CTEPH by an independent adjudication committee. All deaths were also adjudicated. Right heart catheterization was performed in case of "intermediate" or "high" PH probability on TTE: CTEPH was "confirmed" if pre-capillary PH was diagnosed on right heart catheterization, according to previous ESC 2015 guidelines (3,15) (mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest and pulmonary artery wedge pressure (PAWP) ≤15 mmHg), associated with PVO >5% on V/Q lung scan. In the absence of right heart catheterization, CTEPH was considered «likely» in patients with symptoms of PH, "intermediate" or "high" TTE probability of PH, and PVO >5%. In case of PVO >5% but incomplete TTE data, CTEPH was classified "likely" only if clinical history was highly suggestive of PH (**See Supplement**) in absence of any other cause. CTEPH was considered as "undetermined" if there were not enough data to assess diagnosis. CTEPH was "ruled out" if there was a "low" TTE probability of PH with or without perfusion defects at V/Q lung scan, or in case of post-capillary PH or normal right heart catheterization.

Secondary outcomes were the cumulative incidence of only "confirmed" CTEPH during 8-year follow-up and determination of the incident or prevalent nature of CTEPH cases.

All outcomes (CTEPH assessment as confirmed, likely, incident or prevalent) were centrally adjudicated by an independent committee based on clinical data, TTE (at PE diagnosis, 6 months, 5 years and at the time of CTEPH diagnosis), CTPA (PVO measurement at PE diagnosis, presence of specific signs of CTEPH at PE diagnosis and at the time of CTEPH diagnosis), V/Q imaging (PVO measurement at PE diagnosis, 6 months, 5 years and at the time of CTEPH diagnosis) and right heart catheterization, blinded from study treatment allocation.

Statistical analysis

Study population according to study treatment allocation in the randomized PADIS-PE study was previously described (n=371 patients) (9). Cumulative incidences of CTEPH during 8-years follow-up and their 95% confidence interval (95% CI) were estimated by Kaplan-Meier method in overall

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population. Hazard Ratios and 95%CI were calculated using unadjusted Cox model. "Undetermined" CTEPH patients were excluded from risk analyses.

For CTEPH predictors analyses, the study population was described depending on the presence of "confirmed" and "likely" CTEPH during 8-year follow-up. For continuous variables, mean and standard deviation (SD), median and interquartile range (IQR) were provided. For discrete variables, proportions were used. In order to identify potential predictors for CTEPH, an univariable analysis was performed using a Cox model adjusted on study treatment allocation. Given the expected small number of CTEPH occurrence, a full multivariable model including all potential predictors identified from univariable analysis and adjusted on study treatment allocation was not planned. For PVO and systolic pulmonary arterial pressures (sPAP) at PE diagnosis and at 6 months, the most discriminant threshold value was estimated by calculation of area under the curve (AUC) on receiver operating curve (ROC). The same method was performed to analyse the reperfusion ratio (difference between PVO values at 6 months and at PE diagnosis divided by PVO value at diagnosis). Friedman test was used to evaluate changes in PVO from PE diagnosis to the end of follow-up. A p-value of less than 0.05 was considered statistically significant. Missing data were not replaced.

Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc).

RESULTS

Population description

Between July 2007 and September 2014, 371 patients were included in the PADIS-PE trial (baseline characteristics previously described (9)). Among them, 235 were included in the PADIS-PH study at 5 years allowing systematic complete CTEPH assessment. For the remaining 136 patients, CTEPH screening was based on PADIS-PE and PADIS-EXTENSION data **(Figure 1)**. Finally, CTEPH was "undetermined" in 34 patients, which were excluded from analyses on CTEPH predictors, and "confirmed", "likely" or "ruled out" in the remaining 337 patients. Median (IQR) follow-up after index PE was 105 months (78.5-118).

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Baseline characteristics and predictors of the 337 patients with determined CTEPH assessment are presented in **Table 1**. Two (0.6%) patients had history of splenectomy, 27 (8.0%) reported a thyroid substitution therapy and five (1.5%) a chronic inflammatory disease. Non-O blood group was present in 212 (70.7%) patients. A major thrombophilia was present in 45 (14.2%) patients, including 36 (11.1%) elevated antiphospholipid antibodies. Ten (3.0%) patients had indwelling central catheters. During follow-up, 52 (15.5%) patients developed recurrent PE.

Index PE was diagnosed by CTPA in 252 (74.7%) patients and by V/Q lung scan in 82 (24.3%) and mean (SD) PVO was 35.6% (24.0); among the 92 (27.3%) patients who had TTE, mean (SD) sPAP was 41.5 mmHg (15.0).

During follow-up, mean (SD) PVO and sPAP were 8.8% (13.1) and 30.7 mmHg (8.3) at six months from index PE, respectively; and 7.5% (11.8) and 30.9 mmHg (12.1) at 8-year follow-up, respectively. Ten right heart catheterizations were performed: three confirmed CTEPH diagnosis, three excluded PH diagnosis, two diagnosed post-capillary PH, one diagnosed PH due to lung disease, and one was non-contributory (death during procedure).

CTEPH cumulative incidence

During the 8-year follow-up of the 371 patients, nine CTEPH were diagnosed, including three "confirmed" and six «likely» cases, yielding a cumulative incidence of primary outcome of 2.8% (95%CI 0.95-4.64). Among them, five cases were adjudicated as prevalent and the remaining four cases as incident. The cumulative incidences of "confirmed" and of incident CTEPH were 0.92% (95%CI 0.0-1.96) and 1.31% (95%CI 0.01-2.60), respectively (**Table 2**). The cumulative incidence of primary outcome was not different between warfarin and placebo groups (**Table 2**, **Figure 2)**.

Median (IQR) times between index PE and CTEPH diagnosis were 29.8 months (6.3-55.6) for the primary outcome, 55.0 months (42-57) for only "confirmed" cases, and 6.0 months (6.0-6.0) and 54 months (44.0-69.3) for prevalent and incident CTEPH cases, respectively.

Clinical, haemodynamic and PVO characteristics during follow-up between patients with and without CTEPH are presented in **Table 3**. Individual characteristics of patients with confirmed or likely

CTEPH are detailed in **Table S2**. Despite incomplete TTE measurements, patients 7 and 8 were classified "likely" due to suggestive clinical history and perfusion sequalae.

Predictive factors of confirmed and likely CTEPH (univariable analysis)

For this analysis, patients for whom CTEPH diagnosis was classified as "undetermined" were excluded.

Influence of variables collected at PE diagnosis. The presence of "confirmed" and "likely" CTEPH was associated with age >65 years (HR 8.78, 95%CI 1.41-54.60), non-O blood group (HR 0.24, 95%CI 0.06-0.99), lupus anticoagulant antibodies (LAA) (HR 5.22, 95%CI 1.07-25.50), sPAP determined by TTE as a continuous variable (HR 1.05 (95%CI 1.00-1.10) and PVO as a continuous variable (HR 1.06, 95%CI 1.02-1.09). Based on ROC analyses **(Figure 3)**, the most discriminant value of PVO at PE diagnosis for the risk of further CTEPH was 45% (AUC 0.80; 0.75-0.84), with a HR of 33.00 (95%CI 1.64-667.00). For sPAP at PE diagnosis, the most discriminant value was 56 mmHg (AUC 0.68; 0.58-0.77), with a HR of 12.50 (95%CI 2.10-74.80) **(Figure S2)**.

Influence of variables collected at 6 months. The presence of "confirmed" and "likely" CTEPH was associated with a higher residual PVO (HR 1.09, 95%CI 1.05-1.13), with a discriminant value of 14.0% (AUC 0.94; 0.91-0.96) in ROC analyses (HR 63.90 [95%CI 3.11-1310.00]) (**Figure 3**). Higher sPAP at 6 months was also associated with CTEPH (HR 1.12, 95%CI 1.06-1.18) (**Table 3**) with a discriminant value of 34 mmHg (AUC 0.85; 0.81-0.89) **(Figure S2).**

Mean (SD) PVOs at PE diagnosis, at 6 months and at the end of follow-up were 60.6% (8.4), 46.2% (16.9) and 44% (9.6) in CTEPH patients, respectively ($P = 0.37$), and.33.7% (23.2), 9.0% (13.2) and 7.35% (11.3) in patients without CTEPH, respectively ($P < 0.001$).

ROC curves analyse yielded an optimal reperfusion ratio threshold of 77.5% (AUC 0.82; 95%CI 0.77-0.87) for predicting CTEPH with a HR of 25.90 (95%CI 1.28-524.00) **(Figure S3)**.

DISCUSSION

In this prospective follow-up of patients with a first unprovoked symptomatic PE from a randomized trial, we estimated an overall CTEPH cumulative incidence of 2.8% at 8 years, and identified age >65

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years, lupus anticoagulant antibodies, PVO and sPAP at PE diagnosis and at 6 months from PE as predictors of this life-threatening complication.

To our knowledge, our study is the first prospective estimation of CTEPH incidence in a population of selected patients with a first unprovoked PE. The cumulative incidence of 2.8% is consistent with that of 3.2% reported in a meta-analysis (2). Nevertheless, considering a potential 6-fold increased risk of CTEPH in unprovoked PE patients (6), we could have expected a higher incidence rate. This could have several explanations. First, patients deemed to have CTEPH at six months of initial anticoagulation or having any indication for prolonged anticoagulation for causes other than PE were not included in the PADIS-PE study. Despite this, adjudication committee identified five patients who were suspected to have prevalent CTEPH at 6 months from PE: in one, sPAP was 68 mmHg at PE diagnosis with right ventricular dysfunction on TTE; in four, PH signs at PE diagnosis were present and CTEPH diagnosis was performed 5-6 months after PE diagnosis. After their exclusion, CTEPH cumulative incidence was 1.31%, which might be closer to the real CTEPH incidence after a first unprovoked PE. This highlights that the presence of pre-existing CTEPH at PE diagnosis is an important factor of CTEPH incidence over-estimation, especially suspected in case of short time between index PE and CTEPH diagnosis (16–18). Second, the non inclusion of patients with a previous PE and/or proximal DVT, a recognized CTEPH risk factor, might have reduced CTEPH incidence (19). Of note, when using current definition with mPAP >20 mmHg, PAWP ≤15 mmHg and pulmonary vascular resistance ≥3 Wood Units, no supplemental CTEPH was identified (20–22).

We found a significant association between PVO at PE diagnosis and CTEPH diagnosis, with a discriminant threshold of 45%. This association was maintained at 6 months, with a discriminant threshold of 14%, which is consistent with the observation of Pesavento *et al.*, although they used an outcome combining recurrent PE and CTEPH (23). Other studies showed that PVO at PE diagnosis was predictive of recurrent PE, with PVO cut-off of 40% and 20% in patients with a first unprovoked PE and unselected PE, respectively (14,24). Predictive values of recurrent PE have been also established for residual PVO at 6 months (25). Indeed, recurrent PE is a recognized risk factor for CTEPH, with the

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hypothesis that undiagnosed recurrent PE might contribute to persistent PVO (26). Interestingly, our findings on reperfusion rates highlighted that patients who did not improve pulmonary perfusion over 75% during the first 6-month treatment had an increased risk of CTEPH diagnosis during 8-year follow-up. In CTEPH patients, there was no difference in PVO at PE diagnosis, 6 months and 8 years of follow-up. This finding supports another pathophysiological hypothesis, related to abnormal clot resolution with thrombolysis-resistant fibrinogen variants (27). This observation, which is helpful in clinical practice to better select patients at high risk of CTEPH and emphasizes interest of V/Q lung scan at 6 months from PE, requires confirmation. Lastly, there was no significant difference in CTEPH incidence between patients allocated to an additional 18-month warfarin and those to placebo. Although the trial was not designed for this purpose, it suggests that extended anticoagulation with 18-month warfarin seems incapable to prevent later vascular remodelling in unprovoked PE patients (28).

The optimal time for CTEPH screening is not firmly known, but it has been shown that thrombus resolution reaches a plateau phase between 6 and 11 months after PE (29), with CTEPH diagnosis time ranging between 6 months and two years from PE (5,16,30,31). We found similar diagnosis timing, with a median time of 29 months before CTEPH diagnosis. However, after exclusion of the five patients with adjudicated prevalent CTEPH, the median time of diagnosis increased up to 54 months, suggesting that incident CTEPH might develop after a longer "honeymoon period" than previously described. Interestingly, for two patients whose diagnosis delay was over two years, CTEPH was confirmed after a recurrent PE. Consistent with others, older age at PE diagnosis and presence of LAA were predictive of CTEPH (27).

Our study had several limitations. First, as a part of data collecting was retrospective, only "confirmed" CTEPH classification was based on right heart catheterization measurements. For CTEPH adjudicated as "likely", only clinical data, TTE and V/Q lung scans were available, which might have led to an overestimation of CTEPH incidence. Furthermore, we used the previous ESC 2015 haemodynamic definition of PH and not the current haemodynamic definition of PH (20,22)(mPAP ≥20 mmHg at rest, PAWP ≤15 mmHg and pulmonary vascular resistance >3 wood units). However, it

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does not affect our results. Second, as about 25% of CTEPH patients have no history of symptomatic PE (32), we cannot exclude that some CTEPH were already present at PE diagnosis, although only first symptomatic PE were included in PADIS-PE. In particular, three CTEPH patients had sPAP ≥60mmHg at PE diagnosis, which is suggestive of prevalent CTEPH (33). Yet, the study design limited the number of prevalent CTEPH cases, as patients requiring prolonged anticoagulation beyond 6 months were excluded. Third, the number of CTEPH cases (n=9) was low, which weakened the accuracy of hazard ratio and the ability to identify CTEPH predictors. For example, recurrent PE was not statistically associated with CTEPH risk whereas it is a well-recognised CTEPH risk factor. The same reasoning is relevant for non-O blood groups, which are associated with CTEPH (1), whereas they were protective toward CTEPH in our study. This univariate analysis was weakened by a large proportion of missing data, making it difficult to take into account despite its statistically significance. The results should be considered as hypothesis-generation instead of confirmed association.

Strengths of our study include: a homogeneous and well characterized population of patients with a first symptomatic unprovoked PE; a low number of patients lost to follow-up and a long median follow-up of 8 years after initial 6-month anticoagulation; a blind review and validation of all outcomes by an independent centralized adjudication committee, in particular for CTEPH cases; a central assessment of PVO by independent physicians blinded from the study treatment allocation, the results of other imaging tests and the patients characteristics.

CONCLUSION

In a randomized trial including patients with a first episode of unprovoked PE, we estimated a cumulative incidence of confirmed and likely CTEPH of 2.8% during an 8-year follow-up period and a cumulative incidence of confirmed CTEPH of 1.3%. In univariable analysis, an association was found between the presence of CTEPH and the following factors: age ≥65 years, lupus anticoagulant antibodies, high PVO and sPAP at PE diagnosis and at 6 months, with discriminant PVO thresholds of 45% and 14%, respectively. Patients who did not improve pulmonary perfusion by at least 75% in the

first 6 months had a higher risk of CTEPH. External validation in a larger and prospective cohort is required.

ADDENDUM

Author contributions: Dr Couturaud had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: F. Couturaud, C. Tromeur, A. Fauché, O. Sanchez, X. Jais, F. Parent, P. Mismetti, C. Leroyer.

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Analysis and interpretation of data: All.

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Critical revision of the manuscript for important intellectual content: All.

Final approval of the manuscript: All.

Obtaining funding: F. Couturaud.

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Study supervision: F. Couturaud.

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Clinical Trial Registration: NCT01894204

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Lyon) – P. Chevarier, N. Monte**; Operation team (*Brest University Hospital*) -** F. Morvan, V. Kouassi, N. Ibrir, G. El Asri**; Lung Scintigraphy Panel -** P.Y. Salaun, P. Robin, P.Y. Le Roux; **Ultrasound Panel -** L. Bressollette, Ph. Quéhé, S. Gestin; **Computerised Tomography S*can* Panel** - M. Nonent, J. Bahuon, L. Deloire, C. Tromeur, B. Planquette,; **Echocardiography Panel** - Y. Jobic, Y. Etienne, R. Didier, F. Leven; **Central Laboratory** - L. Leroux, H. Galinat, C. Le maréchal, L. Gourhant, F. Mingant; **Investigators (*by city and in order of the number of patients enrolled*)** - *Brest* (198 patients): F. Couturaud , C. Leroyer, C. Tromeur, F. Leven, K. Lacut, E. Lemoigne, L. De Saint Martin, A. Delluc, G. Le Gal, N. Paleiron, R. Le Mao, D. Mottier; *Paris* (53 patients): O. Sanchez, G. Meyer, B. Planquette; *Grenoble* (33 patients) G. Pernod, C. Pison; *Rennes* (33 patients): P. Jego, P. Guéret; *Saint-Etienne* (21 patients): P. Mismetti, H. Décousus, S. Accassat, L. Bertoletti; *Saint-Brieux* (9 patients): E. Duhamel; *Lannion* (8 patients): K. Provost; *Le Kremlin-Bicêtre* (5 patients): F. Parent; *Quimper* (3 patients): B.

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REFERENCES

1. Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26(143):160112.

2. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu ATA, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49(2):1601792.

3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37(1):67-119.

4. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020 Jan 21;41(4):543-603.

5. Pengo V, Marchiori A, Albanese P, Iliceto S. Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism. N Engl J Med 2004;350(22):2257-64.

6. Bonderman D, Turecek P, Jakowitsch J, Weltermann A, Adlbrecht C, Schneider B, et al. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost 2003;90(09):372-6.

7. Bonderman D, Jakowitsch J, Adlbrecht C, Schemper M, Kyrle P, Schönauer V, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost 2005;93(03):512-6.

8. Bonderman D, Wilkens H, Wakounig S, Schafers HJ, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2008;33(2):325-31.

9. Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. JAMA 2015;314(1):31-40.

10. Remy-Jardin M, Ryerson CJ, Schiebler ML, Leung ANC, Wild JM, Hoeper MM, et al. Imaging of pulmonary hypertension in adults: a position paper from the Fleischner Society. Eur Respir J 2021;57(1):2004455.

11. Meyer G, Collignon MA, Guinet F, Jeffrey AA, Barritault L, Sors H. Comparison of perfusion lung scanning and angiography in the estimation of vascular obstruction in acute pulmonary embolism. Eur J Nucl Med 1990;17(6-8):315-9.

12. Qanadli SD, El Hajjam M, Vieillard-Baron A, Joseph T, Mesurolle B, Oliva VL, et al. New CT Index to Quantify Arterial Obstruction in Pulmonary Embolism: Comparison with Angiographic Index and Echocardiography. AJR Am J Roentgenol 2001;176(6):1415-20.

Accepted Article

13. den Exter PL, van Es J, Kroft LJM, Erkens PMG, Douma RA, Mos ICM, et al. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thromb Haemost 2015;114(07):26-34.

14. Tromeur C, Sanchez O, Presles E, Pernod G, Bertoletti L, Jego P, et al. Risk factors for recurrent venous thromboembolism after unprovoked pulmonary embolism: the PADIS-PE randomised trial. Eur Respir J 2018;51(1):1701202.

15. Authors/Task Force Members, Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30(20):2493-537.

16. Guérin L, Couturaud F, Parent F, Revel MP, Gillaizeau F, Planquette B, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014;112(09):598-605.

17. Klok FA, Couturaud F, Delcroix M, Humbert M. Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Eur Respir J 2020;2000189.

18. Rashidi F, Parvizi R, Bilejani E, Mahmoodian B, Rahimi F, Koohi A. Evaluation of the Incidence of Chronic Thromboembolic Pulmonary Hypertension 1 Year After First Episode of Acute Pulmonary Embolism: A Cohort Study. Lung 2020;198(1):59-64.

19. Berghaus TM, Barac M, von Scheidt W, Schwaiblmair M. Echocardiographic evaluation for pulmonary hypertension after recurrent pulmonary embolism. Thromb Res 2011;128(6):e144-7.

20. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1):1801913.

21. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. Eur Respir J 2020;2002828.

22. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53(1):1801915.

23. Pesavento R, Filippi L, Palla A, Visonà A, Bova C, Marzolo M, et al. Impact of residual pulmonary obstruction on the long-term outcome of patients with pulmonary embolism. Eur Respir J 2017;49(5):1601980.

24. Picart G, Robin P, Tromeur C, Orione C, Raj L, Ferrière N, et al. Predictors of residual pulmonary vascular obstruction after pulmonary embolism: Results from a prospective cohort study. Thromb Res 2020;194:1-7.

25. Planquette B, Ferré A, Peron J, Vial-Dupuy A, Pastre J, Mourin G, et al. Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism. A single center cohort study. Thromb Res 2016;148:70-5.

26. Sanchez O, Helley D, Couchon S, Roux A, Delaval A, Trinquart L, et al. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemost 2010;8(6):1248-55.

27. Planquette B, Sanchez O, Marsh JJ, Chiles PG, Emmerich J, Le Gal G, et al. Fibrinogen and the prediction of residual obstruction manifested after pulmonary embolism treatment. Eur Respir J 2018;52(5):1801467.

28. Moser KM, Bioor CM. Pulmonary Vascular Lesions Occurring in Patients With Chronic Major Vessel Thromboembolic Pulmonary Hypertension. Chest 1993;103(3):685-92.

29. Nijkeuter M, Hovens MMC, Davidson BL, Huisman MV. Resolution of Thromboemboli in Patients With Acute Pulmonary Embolism. Chest 2006;129(1):192-7.

30. Martinez C, Wallenhorst C, Teal S, Cohen AT, Peacock AJ. Incidence and risk factors of chronic thromboembolic pulmonary hypertension following venous thromboembolism, a population-based cohort study in England. Pulm Circ 2018;8(3):204589401879135.

31. Tromeur C, Jaïs X, Mercier O, Couturaud F, Montani D, Savale L, et al. Factors predicting outcome after pulmonary endarterectomy. PLoS ONE 2018;13(6):e0198198.

32. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic Thromboembolic Pulmonary Hypertension (CTEPH): Results From an International Prospective Registry. Circulation 2011;124(18):1973-81.

33. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971;28(3):288-94.

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Table 1. Baseline characteristics at PE diagnosis

Characteristics	CTEPH n=9	No CTEPH n=328	Hazard Ratio (95% CI)	p-value
Clinical Characteristics				
Age, mean (SD), y	73.9 (9.7)	57.7 (17.8)	**1.07 (1.02-1.14)**	**0.0112**
> 65 years, no (%)	8 (88.9)	125 (38.1)	**8.78 (1.41-54.6)**	**0.020**
Women, no (%)	6 (66.7)	168 (51.2)	1.52 (0.39-6.04)	0.548
Body-mass index, mean (SD), Kg/m^2	25.2 (6.5)	27.4 (5.5)	0.91 (0.80-1.05)	0.202
Oestrogen contraceptive pill, no (%)	0 (0.0)	51 (15.5)	0.29 (0.01-5.86)	0.421
Medical conditions and comorbidities				
Previous cancer, no. (%)	1 (11.1)	24 (7.3)	2.57 (0.41-16.0)	0.312
Previous distal deep VT or superficial VT, no. (%)	1 (11.1)	26 (7.9)	1.72 (0.27-10.8)	0.563
Chronic heart failure, no. (%)	0 (0.0)	11 (3.4)	1.95 (0.10-38.7)	0.662
Chronic respiratory failure, no. (%)	4 (44.4)	67 (20.4)	2.99 (0.80-11.2)	0.102
Smoking status, mean (SD), PY	5 (14.1)	7 (14.7)	0.99 (0.93-1.05)	0.677
CTEPH-associated risk factors				
Associated conditions and diseases				
History of splenectomy, no. (%)	0 (0.0)	2 (0.6)	*	-
Thyroid substitution therapy, no. (%)	2 (22.2)	25 (7.6)	3.21 (0.70-14.8)	0.135
Chronic inflammatory disease, no. (%)	0 (0.0)	5 (1.5)	*	-
Ventriculo-atrial shunt, no. (%)	0 (0.0)	0 (0.0)	*	-
Non-O blood groups, no. (%)	3 (37.5)	209 (71.6)	**0.24 (0.06-0.99)**	**0.0477**
Thrombophilic disorders†				
Minor thrombophilia	2 (25)	75 (24)	1.10 (0.23-5.19)	0.908
Heterozygous factor V Leiden	0 (0.0)	32 (10.0)	0.45 (0.02-9.06)	0.600
Heterozygous G20210A prothrombin gene variant	1 (11.1)	19 (6.0)	2.06 (0.33-13.1)	0.442
Elevated factor VIII (99th percentile)	1 (12.5)	33 (10.2)	1.89 (0.30-12.1)	0.500
Major thrombophilia	3 (37.5)	42 (13.5)	**5.33 (1.25-22.8)**	**0.024**
Antithrombin deficiency	1 (12.5)	3 (0.9)	*	-
Protein C deficiency	0 (0.0)	4 (1.2)	*	-
Protein S deficiency	0 (0.0)	1 (0.3)	*	-
Homozygous factor V Leiden	0 (0.0)	0 (0.0)	*	-
Heterozygous factor V Leiden and heterozygous factor G20210A prothrombin gene variant	0 (0.0)	1 (0.4)	*	-
Antiphospholipid antibodies	2 (25.0)	34 (10.7)	4.36 (0.89-21.3)	0.068
Anticardiolipin antibodies (99th percentile)	0 (0.0)	5 (1.60)	*	-
Lupus anticoagulant	2 (25.0)	30 (9.3)	**5.22 (1.07-25.5)**	**0.041**
Chronic intra-venous material, no. (%)	0 (0.0)	10 (3.1)	*	-
Pace-maker, no. (%)	0 (0.0)	9 (2.70)	*	-
Chronic venous catheter, no. (%)	0 (0.0)	1 (0.30)	*	-
Index pulmonary embolism description				
Associated deep vein thrombosis, no. (%)	3 (42.9)	99 (31.2)	1.52 (0.340-6.81)	0.582
Echocardiographic at PE diagnosis				
Echocardiographic signs of PH / RVD, no. (%)	4 (66.7)	38 (38.4)	3.46 (0.65-18.5)	0.147
sPAP, mean (SD)	51.6 (19.0)	40.9 (14.6)	1.05 (1.00-1.10)	0.053
sPAP at diagnosis > 60 mmHg, no. (%)	3 (60.0)	9 (10.3)	**12.5 (2.10-74.8)**	**0.005**
Initial PVO (as continuous variable), mean (SD)	60.5 (9.2)	34.8 (23.9)	**1.06 (1.02-1.09)**	**0.004**
Pulmonary embolism treatment				
Fibrinolysis, no. (%)	1 (11.1)	5 (1.5)	*	-
Low molecular weight heparin, no. (%)	5 (55.6)	203 (61.9)	0.79 (0.21-2.93)	0.720
Unfractionned heparin, no. (%)	1 (11.1)	52 (15.9)	0.89 (0.14-5.58)	0.903
Pentasaccharide, no. (%)	4 (44.4)	101 (30.8)	1.60 (0.42-6.00)	0.489
Inferior vena cava filter, no. (%)	1 (11.1)	12 (3.7)	5.02 (0.80-31.3)	0.084

Abbreviations: VT: Venous Thrombosis; PY: Pack-Year; PE: Pulmonary Embolism; PH: Pulmonary Hypertension; RHD: Right Heart Dysfunction; sPAP: systolic Pulmonary Arterial Pression; CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PA: Pulmonary Artery; PVO: Pulmonary Vascular Obstruction; SD: Standard Deviation.

*prevalence<3%

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

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Table 2. Cumulative incidence depending on CTEPH adjudication

	Overall population n=371	Warfarin n=184	Placebo n=187	Hazard Ratio (95%CI)	p-value
Primary Outcome					
Cumulative incidence, % (95%CI)	2.8% (0.95-4.64)	4.48% (1.12-7.85)	1.17% (0.00-2.79)	3.69 (0.77-17.75)	0.08
Secondary outcomes					
Cumulative incidence of confirmed CTEPH (%, 95%CI)	0.92% (0.00-1.96)	0.67% (0.00-1.98)	1.17% (0.00-2.79)	0.54 (0.05-5.91)	0.61
Cumulative incidence of incident CTEPH (%, 95%CI)*	1.31% (0.01-2.60)	1.47% (0.00-3.52)	1.16% (0.00-2.75)	1.05 (0.15-7.46)	0.96

Abbreviations: CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; CI: Confidence Interval.

* 5 patients with probable CTEPH at inclusion were excluded: 1 patient had TTE signs of PH at PE diagnosis, 4 patients had TTE signs of PH at PE diagnosis and/or CTEPH diagnosis between 3 and 6 months after PE.

Table 3. Patients characteristics during follow-up

Characteristics	CTEPH n = 9	No CTEPH n = 328	HR (95% CI)	p-value
NYHA > II, no. (%)*	1 (33.3)	11 (5.6)	8.57 (0.82-89.3)	0.072
Recurrent PE, no. (%)†	3 (33.3)	49 (15.0)	3.48 (0.87-13.8)	0.077
At 6-month follow-up (n=325)				
PVO, mean (SD) ‡	39.5 (15.9)	8.0 (12.1)	**1.09 (1.05-1.13)**	**< 0.0001**
sPAP, mean (SD) §	42.7 (9.6)	30.2 (8.0)	**1.12 (1.06-1.18)**	**< 0.0001**
At 8-year follow-up (n=222)				
PVO, mean (SD) ‡	37.5 (15.2)	6.9 (11.0)	**1.12 (1.05-1.18)**	**0.0002**
sPAP, mean (SD) §	75.0 (16.1)	30.0 (10.5)	**1.10 (1.03-1.17)**	**0.003**

Abbreviations: sPAP: systolic Pulmonary Arterial Pression; CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PVO: Pulmonary Vascular Obstruction; CI: Confidence Interval; NYHA: New York Heart Association; PE: Pulmonary Embolism; SD: Standard Deviation.

* At the time of inclusion in PADIS-PH and PADIS-EXTENSION

† Recurrent pulmonary embolism between inclusion in PADIS-PE study and inclusion in PADIS-PH and PADIS-EXTENSION

‡ PVO was measured based on ventilation perfusion lung scan

§ sPAP was estimated on trans-thoracic echography

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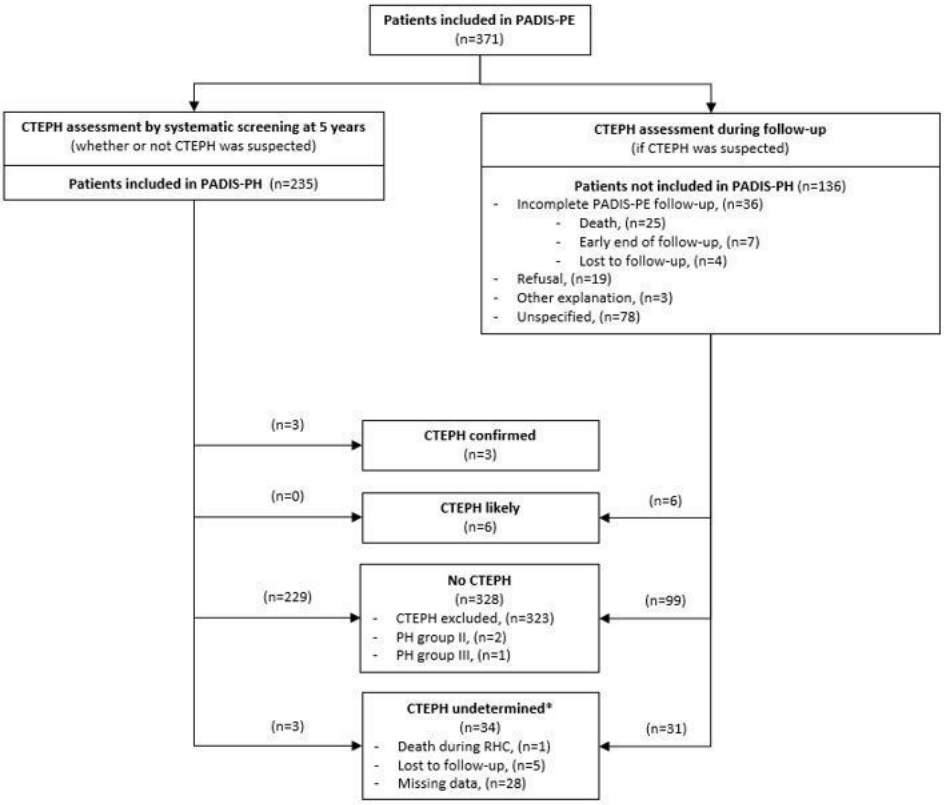
Figure 1. Study flow-chart



Abbreviations: PE: Pulmonary Embolism; PH: Pulmonary Hypertension; RHC: Right Heart Catheterization; CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension.

*Patients in "CTEPH undetermined" category (n=34) were included in cumulative incidence analyses, but not in risk analyses.

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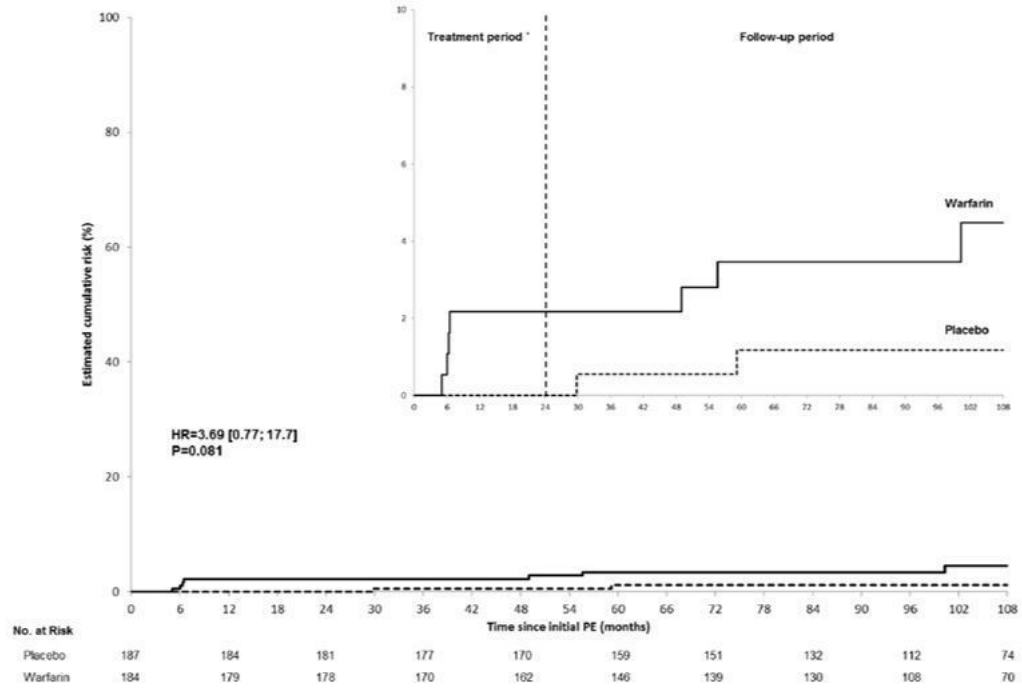
Figure 2. Cumulative CTEPH incidence depending on study treatment allocation in the PADIS-PE study



Abbreviations: CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PE: Pulmonary Embolism; HR: Hazard Ratio.

*The treatment period consists of a 6-month active treatment period and an 18-month extension of either active treatment for the warfarin group or placebo for the placebo group.

JTH_15866_Figure 2.JPG

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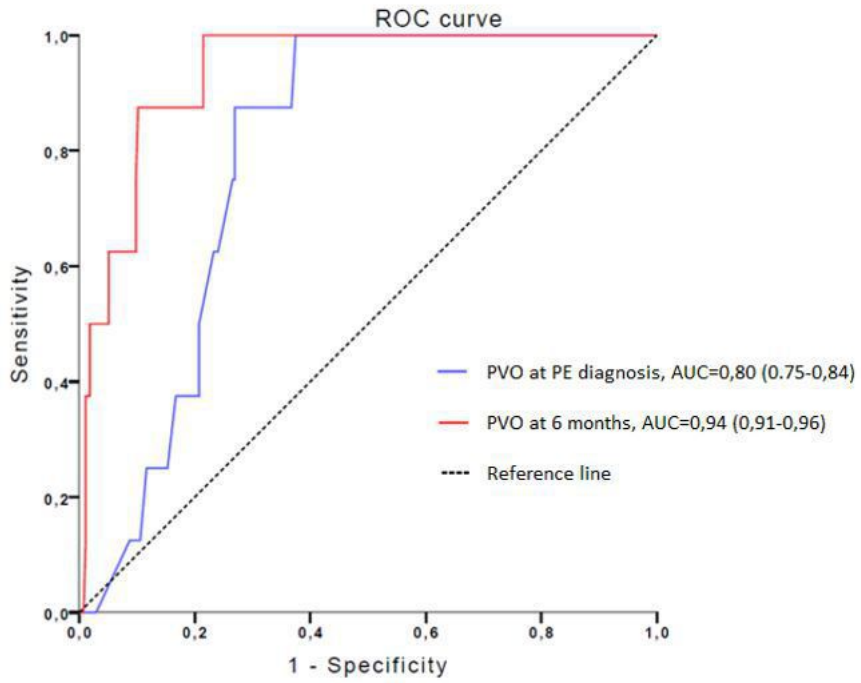
Figure 3. ROC curves for PVO at diagnosis and at 6-month follow-up



	PVO (%)	HR (95% CI) for CTEPH	p-value
PVO at PE diagnosis	45.0	33.0 (1.64-667)	0.023
PVO at 6 months	14.0	63.9 (3.11-1310)	0.007

Abbreviations: PE: HR: Hazard Ratio; Pulmonary Embolism; PVO: Pulmonary Vascular Obstruction; ROC: Receiver Operating Characteristics.

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