

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

Online Data Supplement

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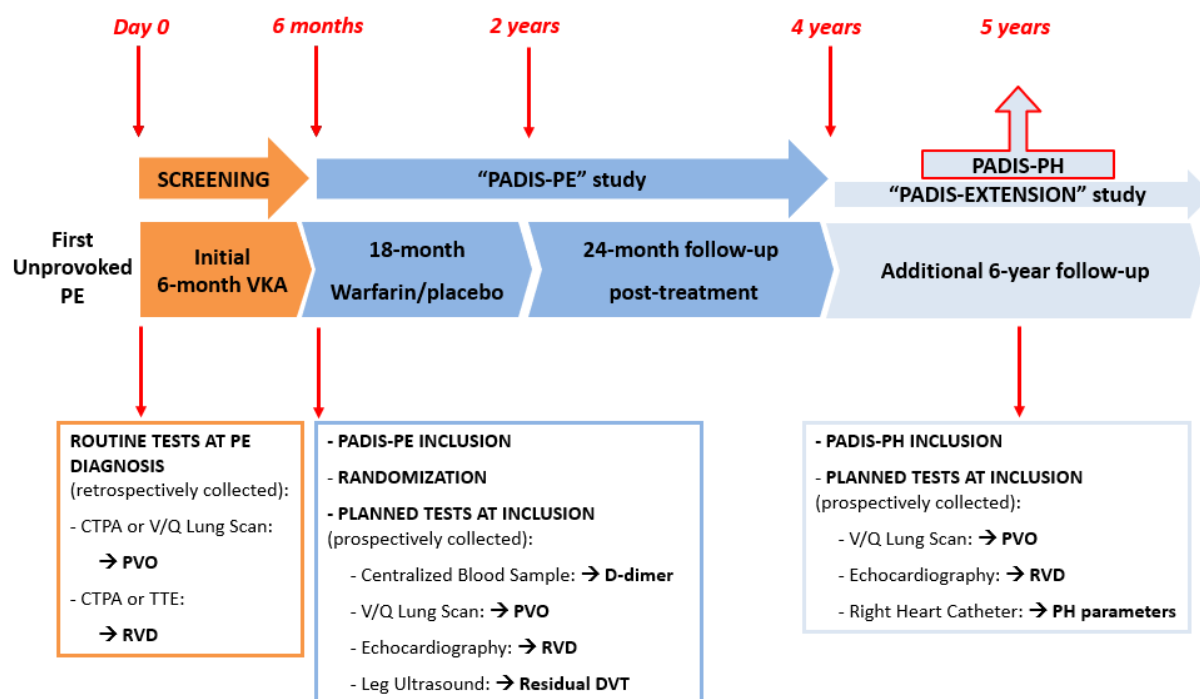
PADIS studies

- PADIS-PULMONARY EMBOLISM ("PADIS-PE" - NCT00740883) is a randomized, double-blind, multicentric trial conducted from July 2007 to September 2014, in order to determine the benefits and harms of an additional 18-month treatment with warfarin versus placebo, after an initial 6-month treatment of Vitamin K Antagonist (VKA). Inclusion criteria were: patients aged 18 years or older; first episode of symptomatic objectively diagnosed pulmonary embolism (PE) by computerized-tomography pulmonary angiography (CTPA) or ventilation perfusion (V/Q) lung scan; initial 6-month treatment with a VKA; unprovoked PE, which was defined as PE occurring in the absence of major transient risk factor within 3 months of diagnosis. Main exclusion criteria were previously confirmed PE or proximal deep vein thrombosis (DVT), indication for prolonged VKA therapy for other reason than venous thromboembolism (VT) or contra-indication for VKA therapy. The primary outcome was the composite of recurrent VT or major bleeding at 18 months after randomization. All patients underwent V/Q lung scan and trans-thoracic echocardiography (TTE) at study inclusion (6 months after PE). A follow-up period of 24 months was conducted after treatment discontinuation.

- PADIS-EXTENSION (NCT02884934) is an observational prospective study. It aimed to estimate the risk of PE recurrence and complications such as chronic thromboembolism pulmonary hypertension (CTEPH) over 6 years of follow-up after a first unprovoked PE, initially treated by 6 or 18 months of VKA. Inclusion criteria was: patients included in PADIS-PE trial. Primary outcome was diagnosis of symptomatic recurrent PE. During study period every patient was followed yearly, through a standardized questionnaire or medical appointments. PE recurrence was confirmed by CTPA or V/Q lung scan.

- PADIS-PULMONARY HYPERTENSION ("PADIS-PH" - NCT01894204) is an interventional trial, which attempted to determine the frequency and risk factors of CTEPH 5 years after a first unprovoked PE. Main outcome was the frequency of CTEPH. Inclusion criteria was: patients who had ended PADIS-PE follow-up. Patients underwent V/Q lung scan and TTE after the inclusion, at five years from PE. Data from PADIS-EXTENSION 6-year follow-up were also used to determine the probability of CTEPH.

Figure S1. PADIS studies



Abbreviations: PE: Pulmonary Embolism; PH: Pulmonary Hypertension; VKA: Vitamin K Antagonist; V/Q: ventilation/perfusion; RVD: Right Ventricular Dysfunction; TTE: Transthoracic Echocardiography; PVO: Pulmonary Vascular Obstruction; DVT: Deep Vein Thrombosis.

Echocardiographic probability of pulmonary hypertension

A standardized protocol was applied to determine probability of pulmonary hypertension from TTE performed at index PE diagnosis, at 6 months from PE (PADIS-PE inclusion) and at 5 years from PE (PADIS-PH inclusion). This protocol was in accordance with future ESC/ERC 2015 guidelines (1).

PH evaluation was based on the measure of peak tricuspid regurgitation velocity (TRV) by continuous wave Doppler, and the presence of other indirect signs of PH: right/left ventricles diameters ratio above unity; flattening of the interventricular septum; decreased right ventricular outflow Doppler acceleration time; increased early diastolic pulmonary regurgitation velocity; dilatation of pulmonary artery or inferior vena cava or right atrium.

TTE probability of PH was «low» if peak TRV was 2.8 meters per second (m/s) or less without other sign of PH. The probability was «intermediate» if these signs were present and in case of peak TRV between 2.9 and 3.4m/s without other sign of PH. The probability was «high» if peak TRV was between 2.9 and 3.4m/s with presence of other signs of PH, or if TRV was strictly above 3.4m/s.

Table S1. Clinical presentation suggestive of CTEPH

Symptoms*	Physical signs*	Other
Shortness of breath	Peripheral oedema	Absence of symptoms or physical signs suggesting other cause of PH
Fatigue	Elevated jugular venous pressure	
Weakness	Left parasternal lift	
Angina	Right ventricular third heart sound	
Syncope	Tricuspid regurgitation murmur	
Haemoptysis	Pulmonary regurgitation murmur	

*This non-exhaustive list was used to classify patients in “likely” CTEPH category if neither V/Q lung scan nor TTE were performed.

Pulmonary vascular obstruction

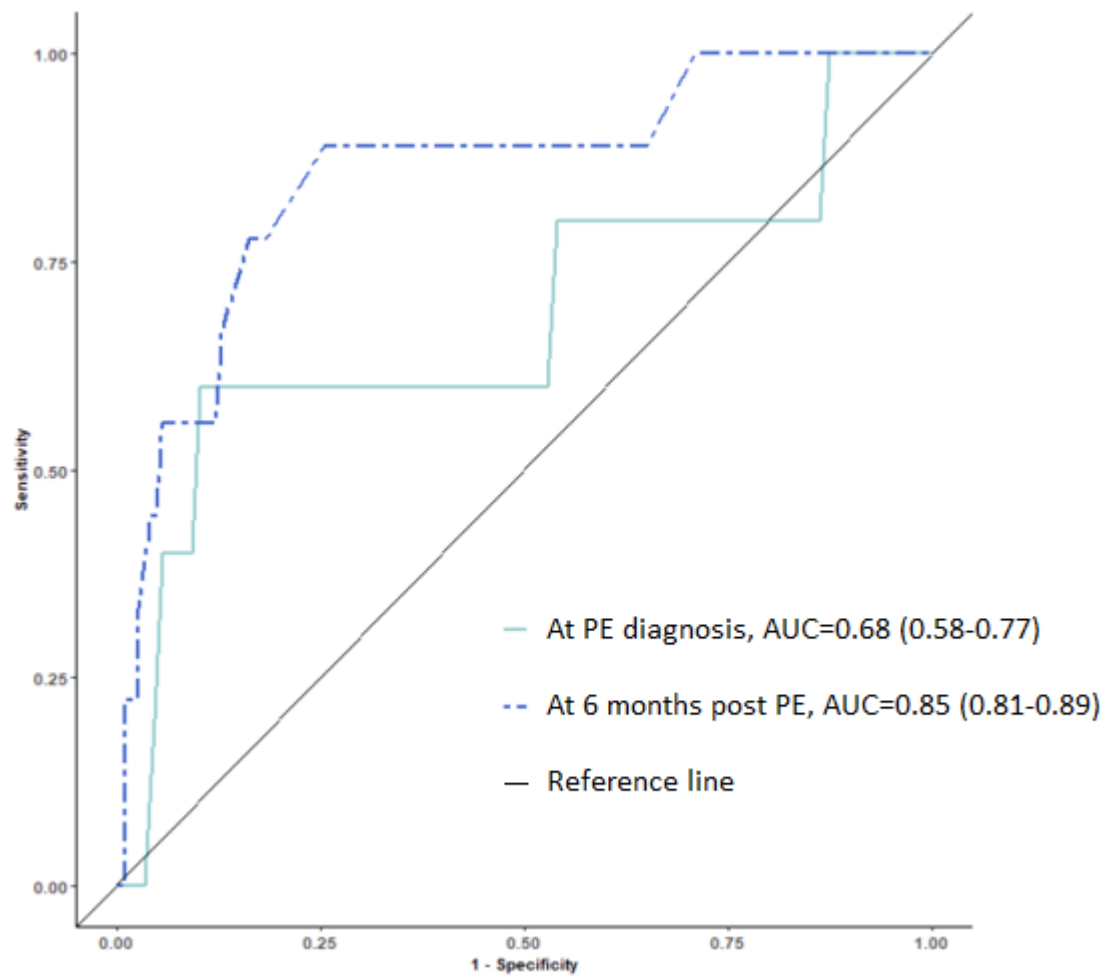
Pulmonary vascular obstruction index (PVO) was measured at index PE diagnosis on V/Q lung scans or on CTPA. At 6 months from PE (inclusion in PADIS-PE trial), and at 5 years from (inclusion in PADIS-PH trial) PE, PVO were measured on V/Q lung scans.

PVO were calculated using validated scores which are correlated with Miller index (2).

For PVO measured on V/Q lung scans, Meyer score was used (3): each lobe was assigned a weight based on the regional distribution of pulmonary blood flow in the supine position (right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12% and left upper lobe 13%). For each lobe, a semi-quantitative perfusion score (0, 0.25, 0.5, 0.75 or 1) was estimated from the film density in the anterior, posterior and oblique views by comparison with the photo density of an apparently normally perfused area. Each lobar perfusion score was then calculated by multiplying the weight by perfusion score and the overall perfusion score was determined by summing the six separate lobar perfusion scores. The percentage of vascular obstruction was then calculated.

For PVO measured on CTPA, each lung was divided in 10 segmental arteries (3 to the upper lobes, 2 to the middle lobe and to the lingula and 5 to the lower lobes) as previously described by Qanadli *et al.* (4). The presence of an embolus in a segmental artery was scored 1 point and emboli in the most proximal arterial level were scored a value equal to the number of segmental arteries arising distally. In order to evaluate the residual perfusion distal to the embolus, a weighting factor was assigned to each value, depending on the degree of vascular obstruction (factor equal to zero when no embolus was observed or 1 with partially occlusive embolus or 2 with complete occlusion). The maximal pulmonary vascular obstruction score was 40 per patient and results were expressed as percentage of vascular obstruction.

Figure S2. ROC curves for sPAP at diagnosis and at 6-month follow-up

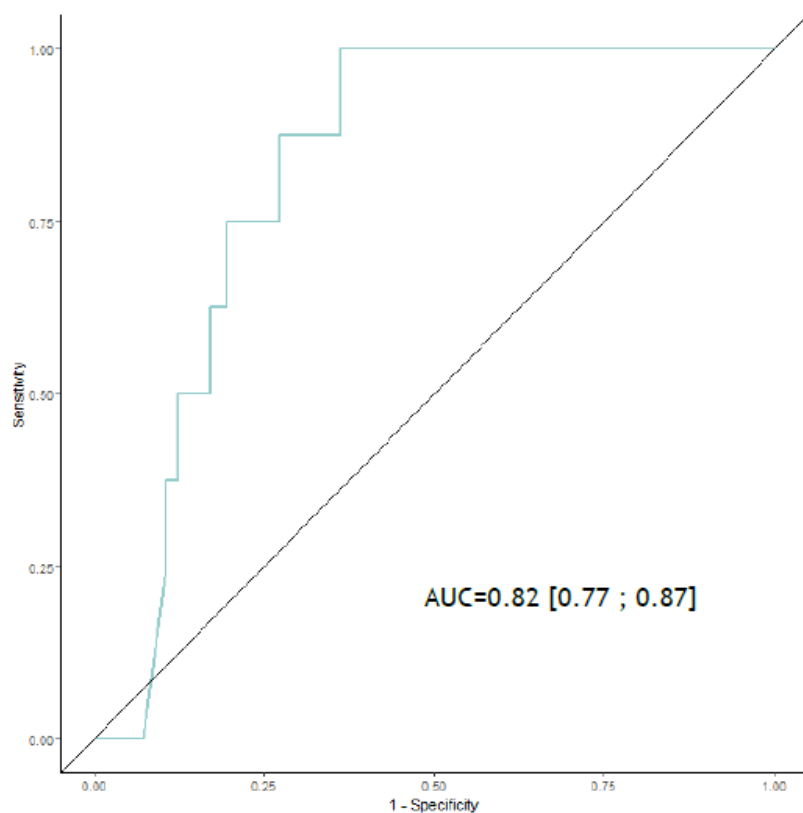


	sPAP (mmHg)	CTEPH risk HR (95% CI)	p-value
sPAP* at PE diagnosis	56.0	12.5 (2.10-74.8)	<0.01
sPAP* at 6 months	34.0	17.2 (2.75-108)	<0.01

Abbreviations: CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PE: HR: Hazard Ratio; Pulmonary Embolism; sPAP: systolic Pulmonary Vascular Obstruction Index; ROC: Receiver Operating Characteristics; CI: Confidence Interval; AUC: Area Under Curve

*sPAP calculated on transthoracic echocardiography.

Figure S3. ROC curve for reperfusion index between PE diagnosis and 6-month follow-up



Reperfusion index (%)	CTEPH risk HR (95% CI)	p-value
77.5	25.9 (1.28-524)	0.03

Abbreviations: CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PE: Pulmonary Embolism; HR: Hazard Ratio; ROC: Receiver Operating Characteristics; CI: Confidence Interval; AUC: Area Under Curve.

Table S2. Detailed characteristics of CTEPH cases

Characteristics	Patients with CTEPH “likely” or “confirmed”								
	1	2	3	4	5	6	7	8	9
CTEPH diagnosis category	Confirmed	Likely	Likely	Likely	Likely	Confirmed	Likely	Likely	Confirmed
CTEPH diagnosis delay from index PE, months	55	6	5	6	6	59	49	100	29
CTEPH chronology	Prevalent	Prevalent	Prevalent	Prevalent	Prevalent	Incident	Incident	Incident	Incident
Clinical Characteristics									
Age, y	80	85	85	79	55	76	81	74	67
Gender	Female	Female	Female	Male	Male	Male	Female	Female	Female
Body-mass index, Kg/m ²	23.9	26.7	21.1	38.2	16.3	26.0	20.7	22.8	31.5
NYHA dyspnoea scale	3	-	-	-	-	1	-	-	2
Oestrogen contraceptive pill	No	No	No	No	No	No	No	No	No
Medical conditions and comorbidities									
Previous cancer	No	No	No	No	Yes	No	No	No	No
Previous distal deep VT or superficial VT	No	No	No	No	Yes	No	No	No	No
Chronic heart failure	No	No	No	No	No	No	No	No	No
Chronic respiratory failure	No	No	Yes	Yes	No	Yes	No	Yes	No
Smoking status, pack-year	0	0	0	0	40	0	0	0	-
CTEPH-associated risk factors									
Recurrent PE	No	Yes	No	No	No	Yes	No	No	Yes
Time-to-recurrence, mths	-	23	-	-	-	42	-	-	13
Associated conditions and diseases									
History of splenectomy	No	No	No	No	No	No	No	No	No
Thyroid substitution therapy	No	Yes	No	No	No	No	Yes	No	No
Chronic inflammatory disease	No	No	No	No	No	No	No	No	No
Ventriculo-atrial shunt	No	No	No	No	No	No	No	No	No
Blood group	O	O	O	O	B	O	AB	A	-
Thrombophilic disorders									
Minor thrombophilia									
Heterozygous factor V Leiden	No	No	No	No	No	No	No	No	No
Heterozygous G20210A prothrombin gene variant	No	No	No	No	No	No	No	No	Yes
Elevated factor VIII (99th percentile)	No	No	Yes	No	No	No	-	No	No
Major thrombophilia									
Antithrombin deficiency	No	No	No	Yes	No	No	-	No	No
Protein C deficiency	No	No	No	No	No	No	-	No	No
Protein S deficiency	No	No	No	No	No	No	-	No	No
Homozygous factor V Leiden	No	No	No	No	No	No	No	No	No
Heterozygous factor V Leiden and heterozygous factor G20210A prothrombin gene variant	No	No	No	No	No	No	No	No	No
Antiphospholipid antibodies	No	No	No	No	No	Yes	-	No	Yes
Anticardiolipin antibodies (99th percentile)	No	No	No	No	No	No	-	No	No
Lupus anticoagulant	No	No	No	No	No	Yes	-	No	Yes
Chronic intra-venous material									
Pace-maker	No	No	No	No	No	No	No	No	No
Chronic venous catheter	No	No	No	No	No	No	No	No	No
Index pulmonary embolism description									
Associated deep vein thrombosis	No	Yes	No	Yes	No	Yes	No	-	-
Echocardiographic signs of PH / RVD	Yes	Yes	Yes	-	Yes	-	-	-	-
CTPA findings of pre-existing CTEPH	-	-	-	-	No	No	No	No	No
Pulmonary embolism treatment									
Fibrinolysis	No	No	No	No	No	No	No	No	Yes
Low molecular weight heparin	No	No	Yes	No	Yes	No	Yes	Yes	Yes
Unfractionated heparin	No	No	No	No	No	No	No	Yes	No
Pentasaccharide	Yes	Yes	No	Yes	No	Yes	No	No	No
Inferior vena cava filter	No	Yes	No	No	No	No	No	No	No
Haemodynamic characteristics									
Right Heart Catheterism	Yes	No	No	No	No	Yes	No	No	Yes
sPAP / dPAP / mPAP, mmHg	-/-/37	-	-	-	-	55/19/29	-	-	88/32/49
Precapillary pressure, mmHg	3	-	-	-	-	9	-	-	14
PAWP, mmHg	12.6	-	-	-	-	4	-	-	10.3

CI, L/min/m ²	2.7	-	-	-	-	2.61	-	-	1.68
TTE sPAP (mmHg)									
At index PE diagnosis	68	67	60	26	-	37	-	-	-
At 6 months follow-up	56	48	46	38	44	37	54	26	35
At the end of follow-up	77	-	-	-	-	58	-	-	90
Pulmonary Vascular Obstruction Index									
PVO at diagnosis	54	62.5	75	57.8	57.5	70	55	45	67.5
PVO at 6 months follow-up	54	14.25	38	57.8	45.3	26.8	54	26.3	-
PVO at the end of follow-up	54	-	-	34.8	-	43.3	-	-	18
CTEPH management									
PEA	No	No	No	No	No	Yes	No	No	Yes
Time-to PEA (months)	-	-	-	-	-	4.5	-	-	4.6
Balloon angioplasty	No	No	No	No	No	No	No	No	No
Specific PH therapy	Yes	No	No	No	No	No	No	No	No

Abbreviations: VT: Venous Thrombosis; PE: Pulmonary Embolism; PH: Pulmonary Hypertension; RVD: Right Ventricular Dysfunction; sPAP: systolic Pulmonary Arterial Pression; CTPA: Computerized Tomography Pulmonary Angiography; CTEPH: Chronic ThromboEmbolic Pulmonary Hypertension; PA: Pulmonary Artery; Ao: Aorta; PVO: Pulmonary Vascular Obstruction; PAWP: Pulmonary Artery Wedge Pressure; WU: Wood Units; NYHA: New York Heart Association; CI: Cardiac Index; TTE: TransThoracic Echocardiography; PEA: Pulmonary Endarterectomy

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