## L'hypertension pulmonaire thrombo-embolique chronique

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#### **DEFINITION**

#### Chronic thrombo-embolic pulmonary disease (CTEPD)

- symptomatic patients
- mismatched perfusion defects on V/Q scan and with signs of chronic, organized, fibrotic clots on CTPA
- after at least 3 months of therapeutic anticoagulation

CTEPD with pulmonary hypertension (PH) = **Chronic thrombo-embolic pulmonary hypertension (CTEPH)** 

#### **DEFINITION - CLASSIFICATION**

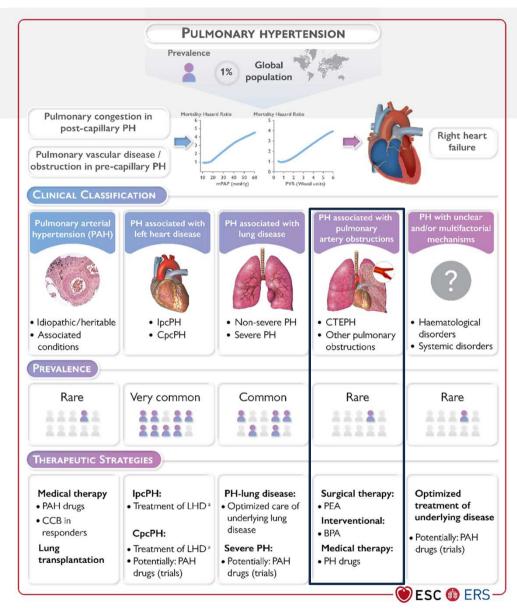
Pulmonary hypertension (PH)

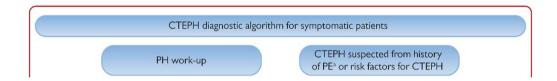
mPAP >20 mmHg

**GROUP 4 PH** associated with pulmonary artery obstructions

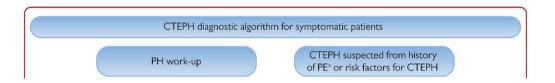
4.1 Chronic thrombo-embolic PH

**4.2** Other pulmonary artery obstructions

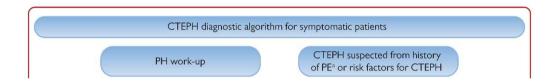




- Assessment of pulmonary hypertension: 55% of cases
- Follow-up after pulmonary embolism: ≤5% of cases
- At the time of acute pulmonary embolism with abnormally high pulmonary artery pressure (PAPs>60mmHg)



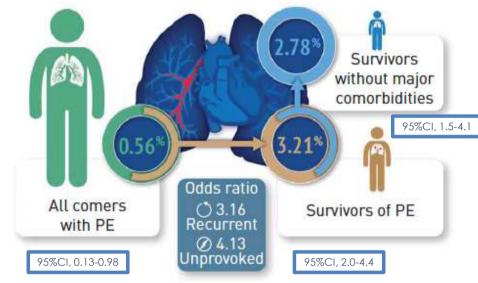
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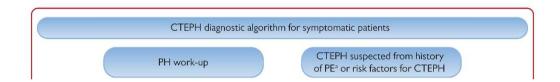
#### Follow-up after pulmonary embolism:

- Incidence of **3.7** per 1000 patients per year with a cumulative incidence of **0.79**%.(1)
- Cumulative incidence CTEPH **2.3%** (95%CI, 1.2-4.4%) (FOCUS study) (2)
- Cumulative incidence of **2.8**% with a median follow-up of 8 years in patients with unprovoked PE (PADIS Study).
  - 1. Coguoz et al, Eur Respir J 2018;
  - 2. Valerio L et al. Eur Heart J. 2022;43(36):3387-3398
  - 3. Fauché et al, J Thromb Haemost 2022.



Risk factor	Odds Ratio	95% CI
Unprovoked PE	4.1	2.1–8.2
Recurrent VTE	3.2	1.7–5.9

Ende-Verhaar YM et al. Eur Respir J 2017;49:1601792.



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#### In the context of acute PE, CTEPH should be considered:

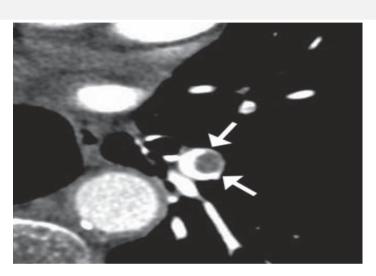
- 1. If radiological signs suggest CTEPH on the CTPA performed to diagnose PE (thrombus adhering to the vascular wall, webs, bands, PA retraction/dilatation, mosaic perfusion and enlarged bronchial arteries), and/or if estimated sPAP is >60 mmHg on echo
- 2. When dyspnoea or functional limitations persist in the clinical course post-PE
- 3. In asymptomatic patients with risk factors for CTEPH or a high CTEPH prediction score

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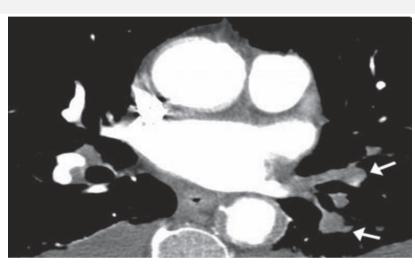
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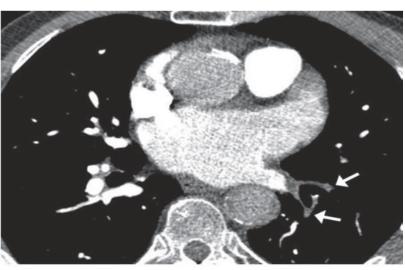
## **ACUTE PE**











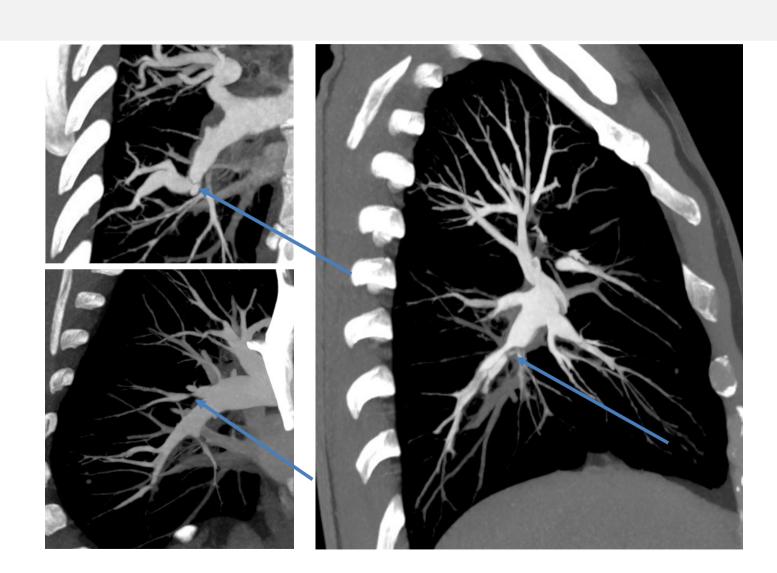
## **CT** features of chronic obstruction of pulmonary arteries

CT Features	Acute PE	Chronic PE
Mediastinal images		
Partial filling defects	Yes	Yes
Complete filling defects	Yes	Yes
Arterial retraction		Yes
Reperfusion channels		Yes
Webs, bands		Yes
Focal stenosis		Yes
Enlarged bronchial arteries		Yes
Enlarged nonbronchial		Yes
systemic arteries		
Pleural abnormalities	Yes (effusion)	Yes
ung images		
Lung infarction/sequelae	Yes (subpleural, wedge-shaped consolidation)	Yes (nonspecific fibrotic infiltration/cysts)
Bronchial dilatation		Yes (adjacent to severely stenosed arteries)
Mosaic perfusion		Yes

# CT features of chronic obstruction of pulmonary arteries

#### **Direct signs:**

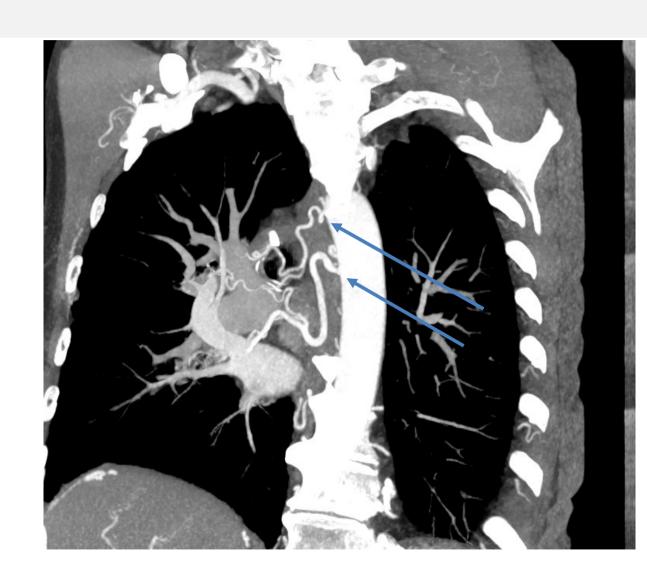
- Arterial retraction
- Webs, bands
- Focal stenosis



# CT features of chronic obstruction of pulmonary arteries

#### **Indirect signs:**

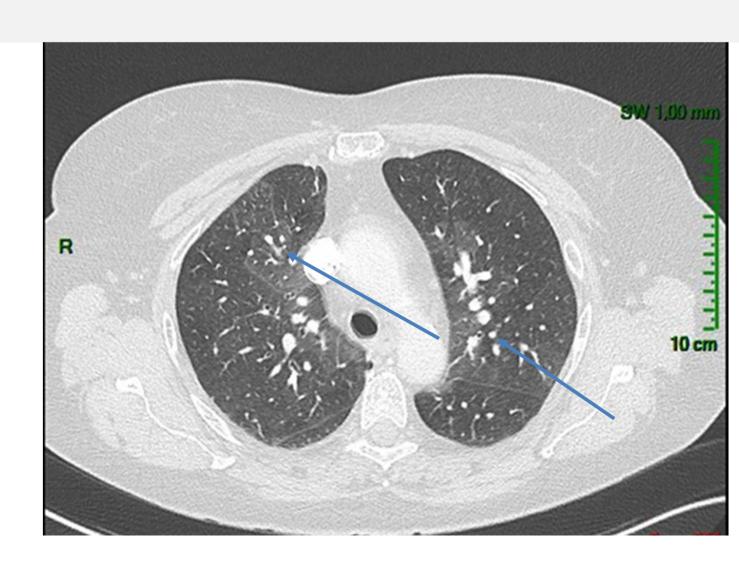
- Enlarged bronchial arteries
- Mosaic perfusion



# CT features of chronic obstruction of pulmonary arteries

#### **Indirect signs:**

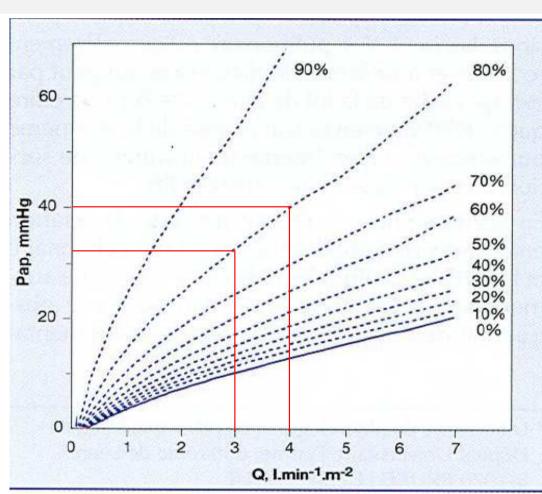
- Enlarged bronchial arteries
- Mosaic perfusion



#### Radiologic parameters of a future CTEPH diagnosis in clinical course of acute PE

≥ 3 signs: Se 70% (95%CI, 55-82) Sp 96% (86-100)

	Scored in number of	Scored in number of	Univariate	analysis	Multivari	ate analysis
Scored radiologic parameter		controls $(n = 50)$	OR	95% CI	OR	95% CI
Signs of chronic PE						
Intravascular webs	29	4	48	13-177	209	4.2 to >1,00
Thrombus attached to the vascular wall	34	14	44	9.2-207		
Complete arterial occlusion	30	25	5.0	1.8-14		
Arterial retraction	28	6	26	8.0-82	47	1.9 to >1,00
Post-stenotic vascular dilatation	2	0	Infinite			
Pulmonary infarction	21	12	4.4	1.8-11		
Parenchymal bands	10	4	4.4	1.3-16		
Signs of PH	10,000	***	***************************************			
Dilatation of the main pulmonary artery	28	8	18	6.2-55	14	0.82-248
RV hypertrophy	14	0	Infinite		Infinite	
Flattening of the interventricular septum	27	7	18	6.1-55	9.9	0.61-161
Dilated bronchial arteries	21	5	13	4.0-39	19	0.71-516
Mosaic perfusion	23	4	20	6.0-69		



Patient	t Initial PE				During f	ollow-up	
	Age (years)	sPAP (mmHg)	RV/LV	MRC	VTR (m/s)	sPAP (mmHg)	RV/LV
1	71	45	0.9	2	3.8	73	1.1

## 57% with CTEPH at initial PE

6	75	62	0.5	2	2.8	56	0.72
7	72	102	0.8	2	4	81	1.1
Mean	75	75	0.97				
± SD	4	20	0.3				

## sPAP is >60 mmHg on echo:

Suspicion of chronic pulmonary embolism

Mélot C et al. Am J Physiol 1995

Guerin L et al. Thromb Haemost 2014;112:598-605.

In the context of acute PE, CTEPH should be considered:

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Findings related to the acute PE event (at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (at PE diagnosis or 3–6-month FU)
Previous episodes of PE or DVT	Ventriculo-atrial shunts
Large pulmonary arterial thrombi on CTPA	Infected chronic i.v. lines or pacemakers
Echo signs of PH/RV dysfunction	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease	Antiphospholipid syndrome
	Non-O blood group
	History of cancer
	Myeloproliferative disorders
	Inflammatory bowel disease
	Chronic osteomyelitis

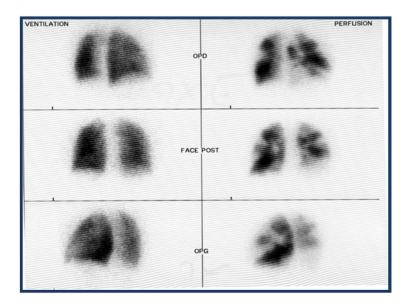
## Ventilation/perfusion scintigraphy remains the most effective tool in excluding CTEPD

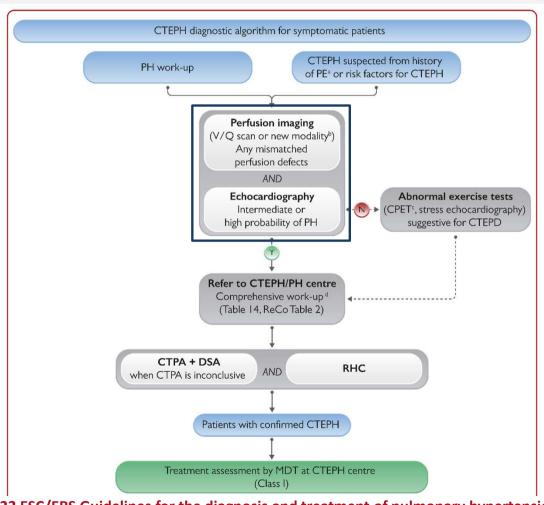
Sensibility: 96-99% Specificity: 90-95%

Negative predictive value: 98,5%

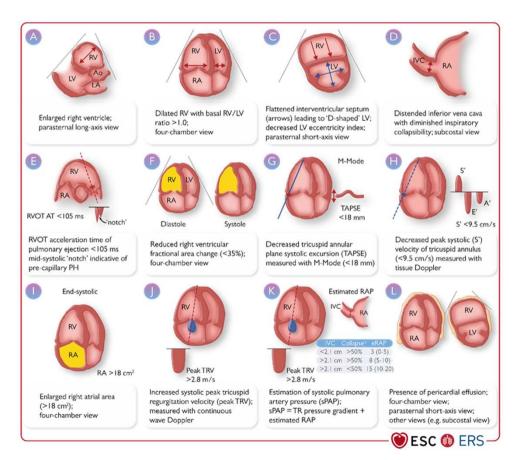
V/Q scintigraphy does not anatomically localize the extent

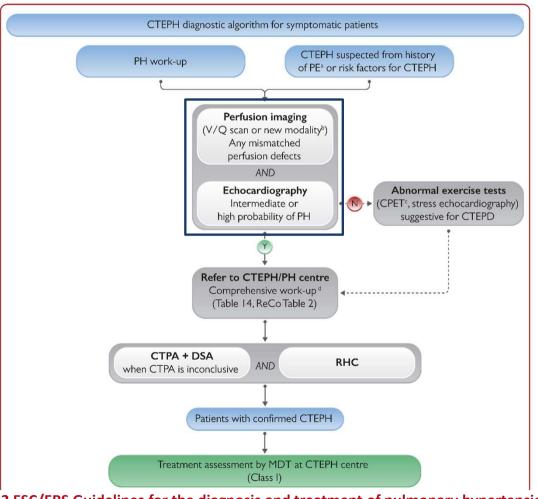
of disease





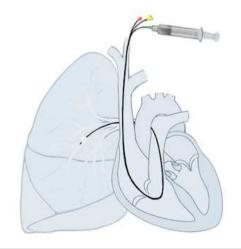
## **Echocardiography**





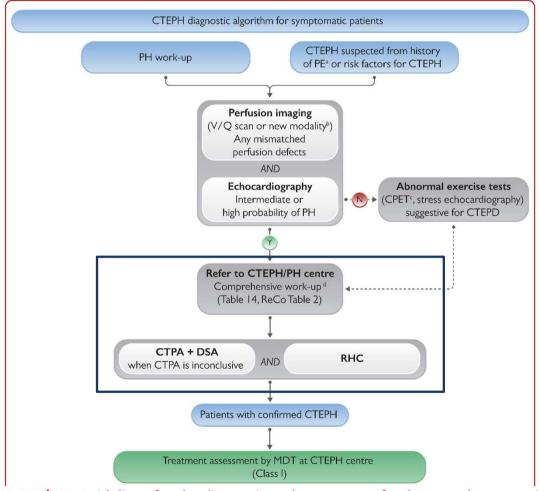
#### Referred to CTEPH/PH centre

# Right heart catheterisation (RHC)



**Pre-capillary PH** 

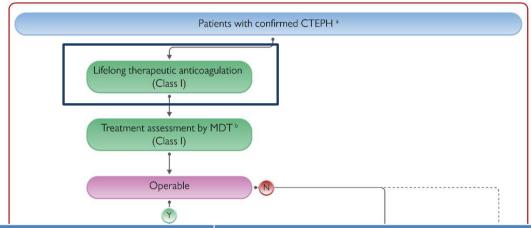
mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU



Lifelong therapeutic anticoagulation is recommended for patients with CTEPH

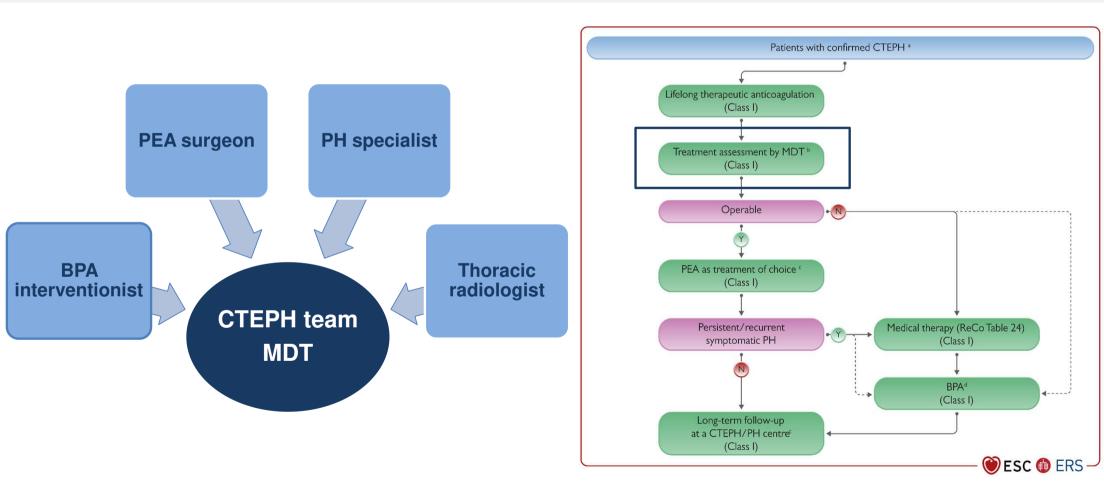
Vitamin K antagonists (VKAs) or Direct oral anticoagulants (NOACs)? No randomized controlled trial.

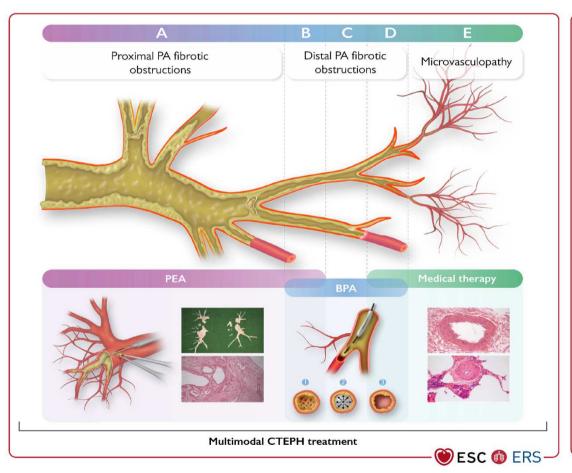
NOACs are less effective than VKAs in antiphospholipid syndrome (APS) (10% of CTEPH) (1,2).

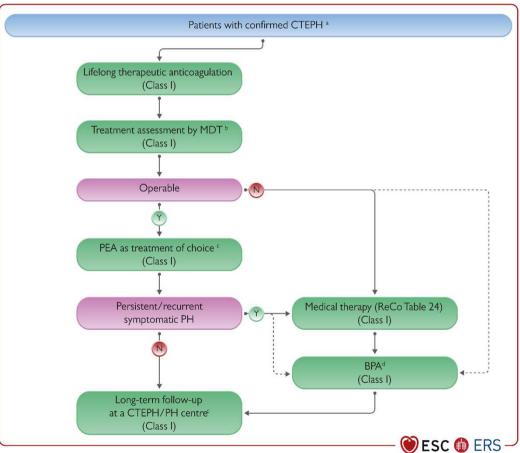


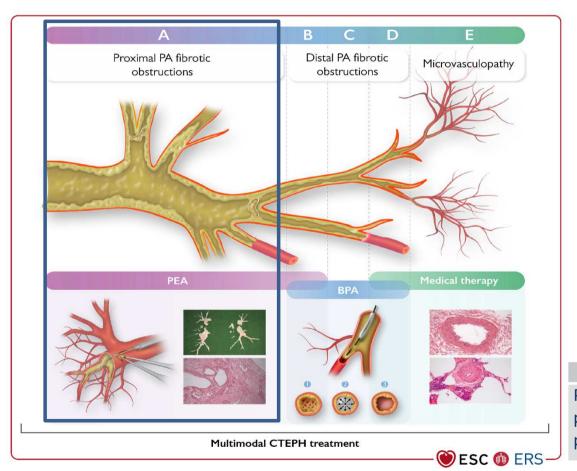
EXPERT registry	Hemorrhagic events		Embolic/thrombotic events	
Rates, n (%)	VKA group (n = 683)	NOAC group (n = 198)	VKA group (n = 683)	NOAC group (n = 198)
Any event	78 (11.4)	24 (12.1)	15 (2.2)	<u>6 (3.0)</u>
Drug discontinuation due to event	2 (0.3)	0 (0)	1 (0.1)	0 (0)
Any serious event	40 (5.9)	11 (5.6)	14 (2.0)	5 (2.5)
Discontinuation due to serious event	2 (0.3)	0 (0)	1 (0.1)	0 (0)
Event-related death	8 (1.2)	1 (0.5)	2 (0.3)	0 (0)

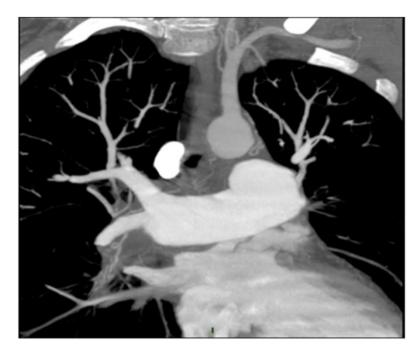
<sup>1. 2022</sup> ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension; 2. Pengo V et al. Blood 2018; 2. Ordi-Ros J et al. Ann Intern Med 2019;



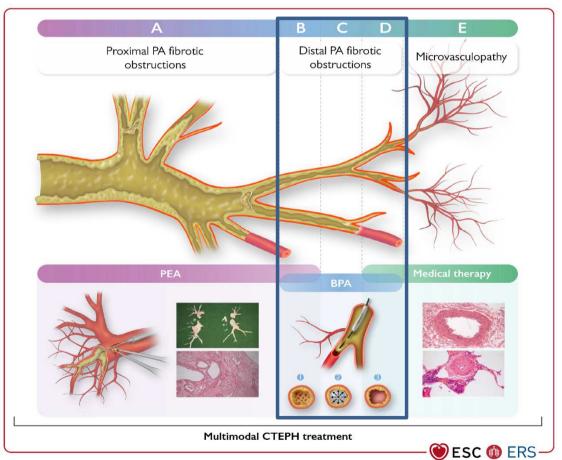






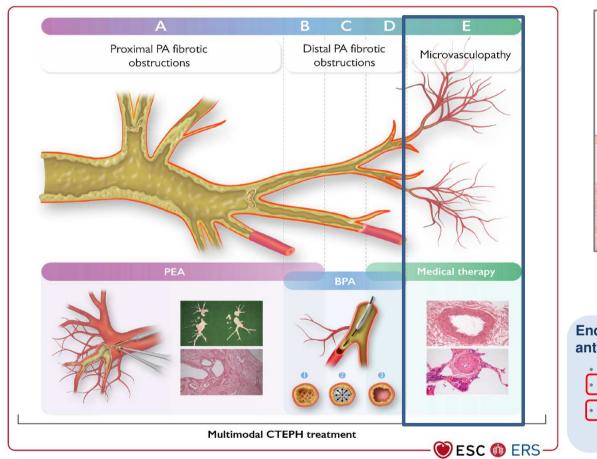


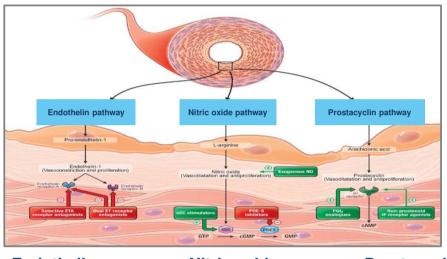
2022 Guidelines	Class
PEA is recommended as the treatment of choice for	
patients with CTEPH and fibrotic obstructions within	100
pulmonary arteries accessible by surgery	





BPA is recommended in patients who are technically inoperable





Endothelin pathway

Endothelin receptor antagonists
• Ambrisentan

Bosentan<sup>1</sup>
Macitentan<sup>4</sup>

Nitric oxide pathway

**PDE5** inhibitors

Sildenafil<sup>2</sup>
 Tadalafil

sGC stimulators

Riociguat<sup>3</sup>

Prostacyclin pathway

**Prostanoids** 

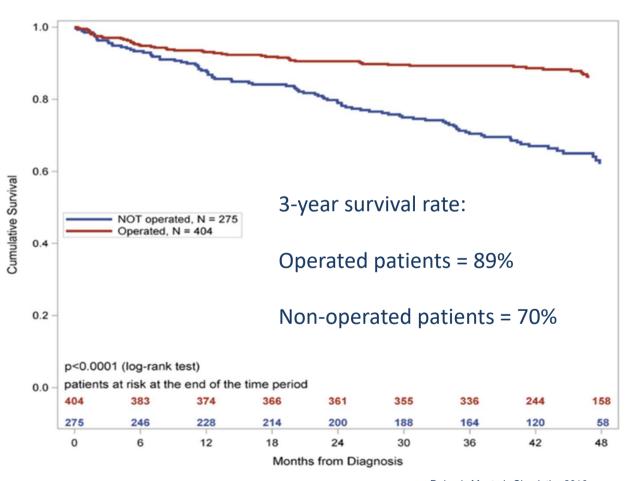
Epoprostenol iv
 Treprostinil sc<sup>5</sup>

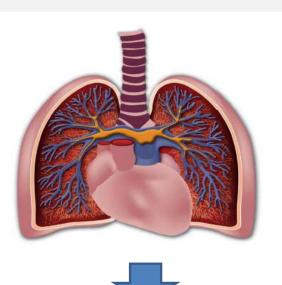
Non-prostanoid IP receptor agonist

Selexipag<sup>6</sup>

1. Jaïs X et al. J Am Coll Cardiol 2008; 2. Suntharalingam J et al. Chest 2008; 3. Ghofrani HA et al. NEJM 2013; 4. Ghofrani HA et al. Lancet Respit Med 2017; 5. Sadushi-Kolici R, et al. Lancet Respir Med 2018; Ogo T, et al. Eur Respir J 2021.

### **PEA – Pulmonary endarterectomy**

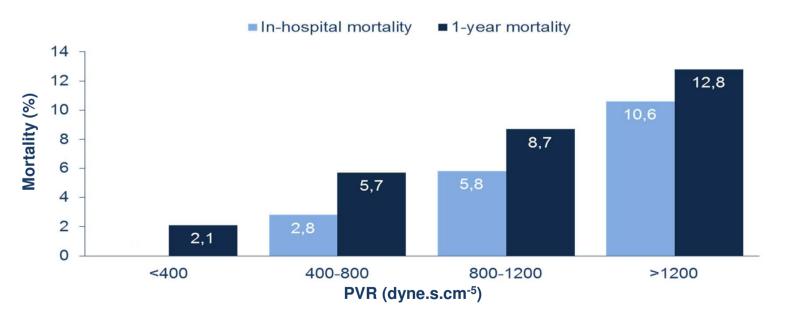


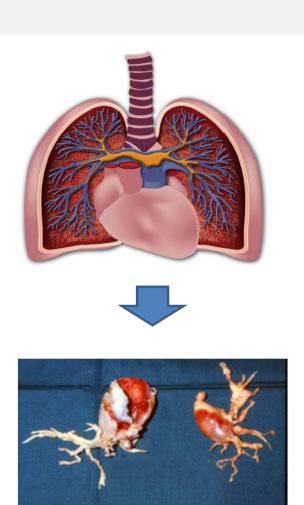




Delcroix M, et al. Circulation 2016

Perioperative mortality is less than 5% in experienced centers, but there is an increase in mortality when preoperative PVR is >800-1200 dyn.s.cm-5 (1,2)



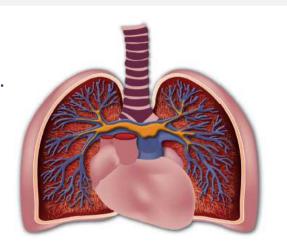


(1) Dartevelle P, et al. Eur Respir J 2004; (2) Mayer E, et al. J Thorac Cardiovasc Surg 2011.

Using medical therapy in patients with high pre-operative PVR to improve pulmonary haemodynamics before PEA is common practice but still controversial...

No randomized controlled trial.

Studies	N	Before PEA PVR (dyn.s.cm <sup>-5</sup> )	After PEA RVP (dyn.s.cm <sup>-5</sup> )	Efficacy
Corsico AG, et al. AJRCCM 2008	157	1140	349	-69%
Freed DH JTCVS 2011	314	805	301	-63%
Madani MM Ann Thorac Surg 2012	500	719	253	-65%
Mayer E JTCVS 2012	386	698	235	-66%
Skoro-Sajer N Thorax 2014	110	770	280	-64%
Cannon JE Circulation 2016	880	830	317	-62%





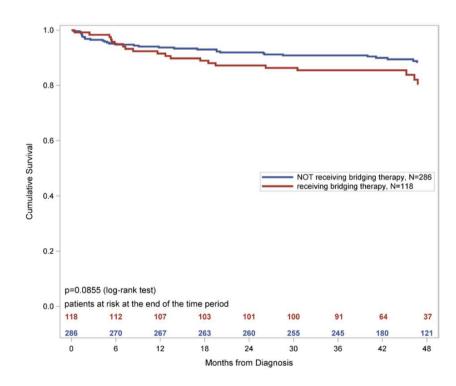


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Significant delay for referral

	PHT Group (n=111)	Control Group (n=244)	Р
Median age, y (IQR)	51 (39–62.5)	52 (37–64)	0.84
Sex, M/F	52/59	121/123	0.63
Median time to referral, mo (IQR)	8.9 (4–13)	4.4 (2.5–7)	<0.01
Anticoagulation	110 (99.1)	240 (98.4)	0.89
Diuretic	65 (58.6)	114 (46.7)	0.04
Spironolactone	24 (21.6)	18 (7.4)	< 0.01
Digoxin	16 (14.4)	15 (6.1)	0.01
Dopamine	3 (2.7)	2 (0.8)	0.16



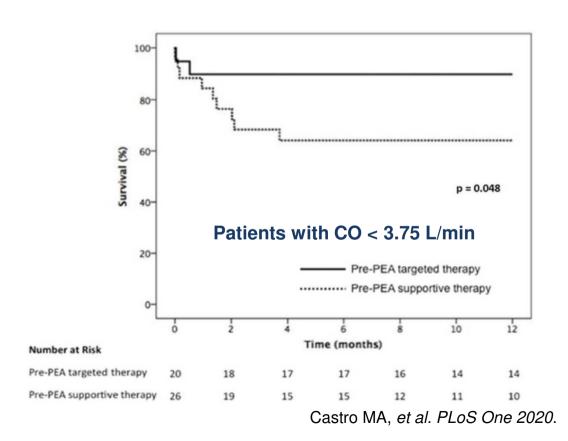
Jensen KW, et al. Circulation 2009;120:1248-54.

Delcroix M, et al. Circulation 2016;133:859-71.

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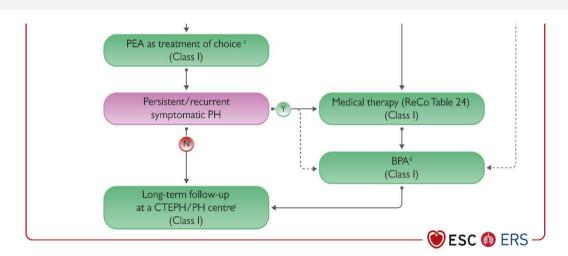
- 108 patients who underwent PEA (2013-2017)



#### PEA – persistent / recurrent PH post PEA

#### On 880 operated patients in England

28 % Patients	< 20 mmHg after PEA
21 % Patients	21 – 24 mmHg after PEA
51 % Patients	> 25 mmHg after PEA



#### Time point of measurement

- 3-6 months after surgery

### Haemodynamic criteria

- mPAP ≥ 30 mmHg
   associated with initiation of medical therapy
- mPAP ≥ 38 mmHg and PVR ≥ 425 dyn.s.cm<sup>-5</sup>
   predict worse long-term survival

Cannon JE et al. Circulation 2016

#### **MULTIMODAL APPROACH IN OPERABLE FORMS**

#### Medical therapy after PEA in patients with persistent PH

Riociguat is recommended for symptomatic patients with persistent/recurrent PH after PEA	1
Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have persistent/recurrent PH after PEA	IIb

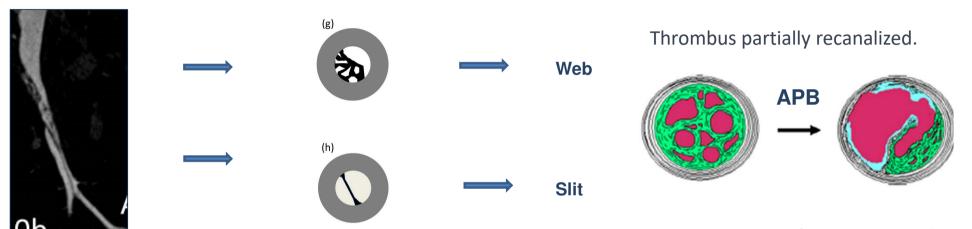
#### Additional BPA after PEA in patients with persistent PH

Author	Year	Patients (n)	Time from PEA to BPA (months)	Medical treatment before BPA	Before BPA PVR (dyn.s.cm <sup>-5</sup> )	After BPA PVR (dyn.s.cm <sup>-5</sup> )	Treatment effect
Shimura	2015	9	49.2 (2.7-7.9)	?	1250 (624-1512)	448 (280-520)	-64%
Yanaka	2018	10	7.3±2.3	20%	386±42	242±39	-37%
Araszkiewicz	2019	15	28.1±25.8	100%	552±185	344±124	-38%

BPA is recommended in patients who have residual PH after PEA and distal obstructions amenable to BPA

1

## **BPA** – Baloon pulmonary angioplasty



Sugiyama M, et al. Jpn J Radiol 2014

#### Hemodynamic effects of APB and mortality.

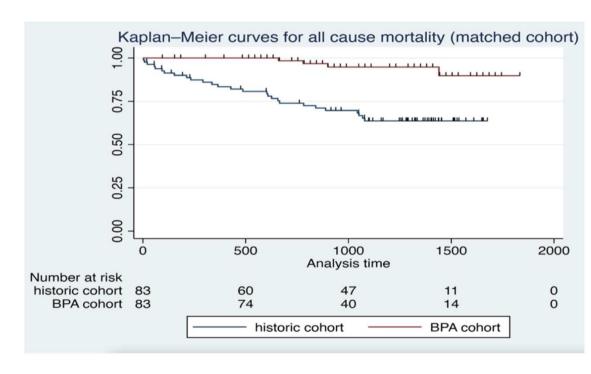
	N	Before BPA PVR (dyn.s.cm <sup>-5</sup> )	After BPA PVR (dyn.s.cm <sup>-5</sup> )	Treatment effect	30-day mortality
Ogo, 2017	80	880±424	408±184	-54%	0%
Ogawa, 2017	249	854±451	360±223	-58%	3%
Olsson, 2017	56	591±286	440±279	-26%	1.8%
Brenot, 2018	184	604±226	329±177	-43%	2.2%

Ogo T, et al. Eur J Radiol 2017; Ogawa A et al. Circ Cardiovasc Qual Outcomes 2017; Olsson KM et al. Eur Respir J 2017; Brenot P et al. Eur Respir J 2019.

### **BPA - Multimodal treatment in non operable CTEPH**

Evaluation of the impact of sequential combination of riociguat/angioplasty on prognosis.

83 patients treated with riociguat/angioplasty compared to a historical cohort of 83 matched patients from an international registry (51.5% receiving targeted therapy for PAH).



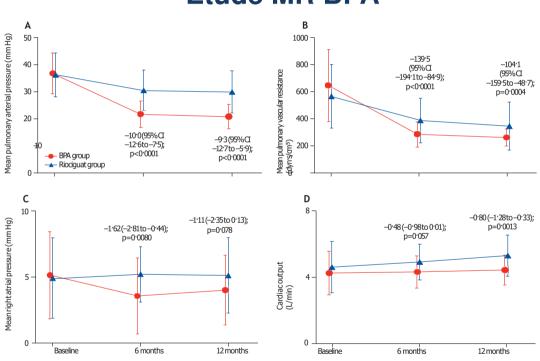
Wiedenroth CB et al. J Heart Lung Transplant 2022.

#### **BPA** – Randomized control trials

#### **Etude RACE** At week 26 geometric mean PVR decreased to At week 26 geometric mean PVR decreased to 39.9% of baseline value in the BPA group 66.7% of baseline value in the Rio group 100 % of baseline PVR at week 26\* Riociguat **BPA** 80 N = 52N = 5370 60 50 30 20 10 -

	Riociguat (N = 53)	BPA (N = 52)
Patients with ≥1 AE – n (%)	38 (72)	33 (63)
Patients with ≥1 SAE – n (%)	14 (26)	26 (50)
Patients with ≥1 treatment-related SAE – n (%)	5 (9)	22 (42)

## **Etude MR BPA**



Adverse events (haemoptysis or pulmonary haemorrhage) 14/32 patients (44%) in the BPA group 1/29 patients (4%) in the riociguat

## **BPA - Complications**

#### **Vascular lesions:**

- Perforation of the pulmonary artery
- Dissection of the pulmonary artery
- Rupture of the pulmonary artery



RACE STUDY	First-line Riociguat then BPA(N = 36)	First-line BPA (N = 52)	P value
Patients with ≥1 SAE related to BPA– n (%)	5 (14)	22 (42)	0.0045
Patients with ≥1 severe BPA procedure-related complication– n (%)	3 (8)	18 (35)	0.0045

#### Predictive variables for complications related to BPA (multivariate analysis): meanPAP>45 mmHg (OR 1.202, 95% CI 1.048-1.378; p=0.0084)

<sup>1.</sup> Ejiri K et al. Circ Cardiovasc Interv 2018. 2. Jaïs X et al. Lancet Respir Med 2022

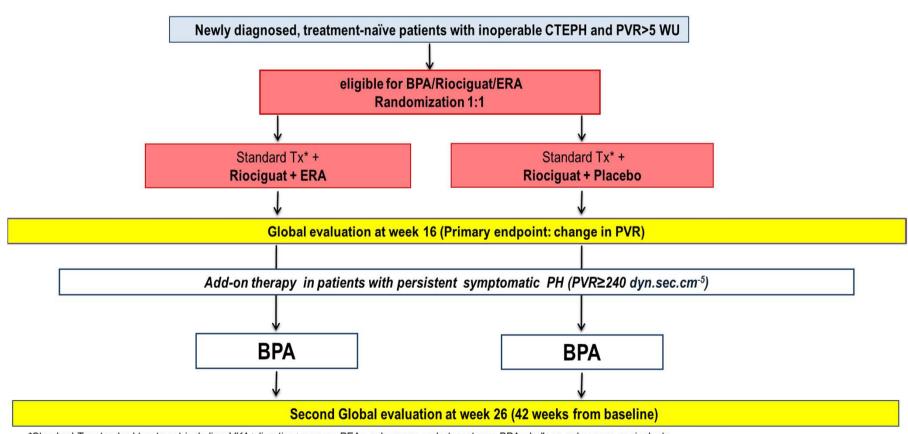
## **BPA – Multimodal treatment in non operable CTEPH**

Impact of riociguat treatment prior to angioplasty on angioplasty-related complications in patients with PVR > 4 UW

Recommendations	Quality of evidence	Strength of recommendation	Class	Level
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention	Very low	Conditional	lla	В

### **BPA - Multimodal treatment in non operable CTEPH**

Initial dual oral combination therapy vs initial oral monotherapy prior to BPA (IMPACT-CTEPH)



<sup>\*</sup>Standard Tx: standard treatment including VKA±diuretics±oxygen; PEA= pulmonary endarterectomy; BPA= balloon pulmonary angioplasty

#### MULTIMODAL APPROACH, THERAPEUTIC GOALS AND FOLLOW-UP

A multi-modality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH

Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy

- No data or consensus on what is the therapeutic target after PEA/BPA or medical therapy in CTEPH.
- Most experts accept achieving a good FC (WHO FC I-II) and/or normalization or near normalization of haemodynamics at rest, obtained 3-6 months post-procedure, and improvement in quality of life.
- Follow-up should include RHC 3-6 months after intervention (PEA or last BPA)

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#### THE KEY MESSAGES

#### 1. Consider CTEPH if:

- 1. Experiencing persistent symptoms after a PE.
- 2. Signs of chronic PE on CTPA.
- 3. Having risk factors of CTEPH.
- 2. Follow the algorithm for CTEPH diagnosis
- 3. Refer to a CTEPH/PH Center for a Multimodal Approach
- 4. CTEPH is a potentially curable condition

## Merci de l'attention!

## COUP DE SANG A LA SPIF!

N'oubliez pas les vaisseaux pulmonaires

> Samedi 7 octobre 2023 Espace Chaptal (PARIS 9<sup>e</sup>)