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## **The aftermath of acute pulmonary embolism: approach to persistent functional limitations**

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# 2

## Essential aspects of the follow-up after an acute pulmonary embolism: an illustrated review

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## ABSTRACT

Care for patients with acute pulmonary embolism (PE) involves more than determination of the duration of anticoagulant therapy. After choosing the optimal initial management strategy based on modern risk stratification schemes, patients require focused attention aimed at prevention of major bleeding, identification of underlying (malignant) disease, prevention of cardiovascular disease and monitoring for long-term complications. The most frequent complication of PE is the so-called 'post-PE syndrome', a phenomenon of permanent functional limitations after PE occurring in up to 50% of patients. The post-PE syndrome is caused by persistent deconditioning, anxiety, and/or ventilatory or circulatory impairment as a result of acute PE. The most severe and most feared presentation of the post-PE syndrome is chronic thromboembolic pulmonary hypertension (CTEPH), a deadly disease if it remains untreated. While CTEPH may be successfully treated with pulmonary endarterectomy, balloon pulmonary angioplasty and/or pulmonary hypertension drugs, the major challenge is to diagnose CTEPH at an early stage. Poor awareness for the post-PE syndrome and in particular for CTEPH, high prevalence of persistent symptoms after PE and inefficient application of diagnostic tests in clinical practice all contribute to an unacceptable diagnostic delay and underdiagnosis. Its consequences are dire: increased mortality in patients with CTEPH, and excess health care costs, higher prevalence of depression, more unemployment and poorer quality of life in patients with post-PE syndrome in general. In this review, we provide an overview of the incidence and impact of the post-PE syndrome, and illustrate the clinical presentation, optimal diagnostic strategy as well as therapeutic options.

### List of abbreviations

BPA = balloon pulmonary angioplasty	PA = pulmonary artery
CO = carbon monoxide	PE = pulmonary embolism
COPD = chronic obstructive pulmonary disease	PEA = pulmonary endarterectomy
CPET = cardiopulmonary exercise test	PFT = pulmonary function test
CTED = chronic thromboembolic disease	PH = pulmonary hypertension
CTEPH = chronic thromboembolic pulmonary hypertension	PVR = pulmonary vascular resistance
CTPA = computed tomography pulmonary angiography	QoL = quality of life
DVT = deep vein thrombosis	RHC = right heart catheterization
ECG = electrocardiography	RV = right ventricle
i.v. = intravenous	TRPG = tricuspid regurgitation peak gradient
IQR = interquartile range	TRV = tricuspid regurgitation velocity
LV = left ventricle	VTE = venous thromboembolism
NYHA = New York Heart Association	V/Q scan = ventilation/perfusion scan



**ESSENTIAL ASPECTS OF OPTIMAL CARE AFTER ACUTE PE****DIAGNOSIS**

1



Risk stratification based on hemodynamic status



Initial treatment (reperfusion, parenteral or oral anticoagulation)



Optimal setting for initial treatment (critical care unit, regular ward, home treatment)

**INITIAL WEEKS\***

3



Screen for cancer, antiphospholipid syndrome or genetic thrombophilia in selected patients



Monitor the clinical course



Target modifiable risk factors for bleeding and VTE

**LONG-TERM FOLLOW-UP**

5



Evaluate the anticoagulant treatment periodically (e.g. risk factors for bleeding)



Monitor long-term complications (e.g. post-PE syndrome)

2

**DISCHARGE**

Provide relevant medical background information



Instruction on handling potential complications



Target modifiable risk factors for bleeding and VTE

4

**3-MONTH FOLLOW-UP**

Determine duration of anticoagulation: weighing risk of recurrence versus risk of bleeding<sup>3</sup>



Determine optimal anticoagulation drug class and dosing (if decided to continue)



Evaluate the presence of and/or risk factors for CTEPH

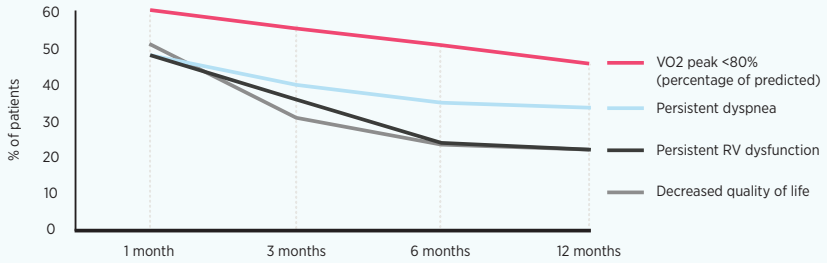


Target modifiable risk factors for cardiovascular disease

## CONSEQUENCES OF PULMONARY EMBOLISM

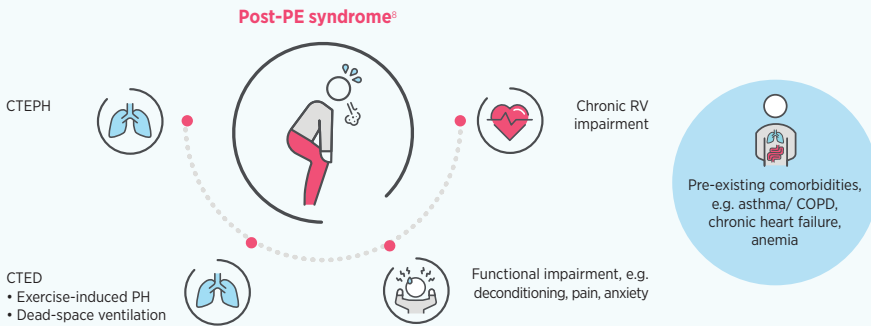
### 1

#### INCOMPLETE PHYSICAL RECOVERY AFTER PE IS COMMON<sup>4-7</sup>



### 2

#### UNDERLYING CAUSES OF PERSISTENT SYMPTOMS AFTER PE



### 3

#### IMPACT OF POST-PE SYNDROME ON A PATIENT'S DAILY LIFE

<p>↓ Quality of life, to be measured by: • quality of life questionnaires (particularly the PEmb-QoL)</p>	<p>↑ Depressive disorders, to be measured by: • e.g. Hospital Anxiety and Depression Scale (HADS)</p>
<p>↓ Functional status, to be measured by: • CPET: reduced VO2 peak, low O2 pulse (VO2/HR), cardiovascular limitation, inefficient ventilation due to increased dead-space ventilation and arterial hypoxemia • PFT: reduced diffusion capacity; alternatively restrictive or obstructive comorbidities • Post-VTE Functional Status (PVFS) Scale<sup>9</sup></p>	<p>↑ Unemployment</p>
	<p>↑ Healthcare costs</p>
	<p>↑ Mortality in case of untreated CTEPH</p>



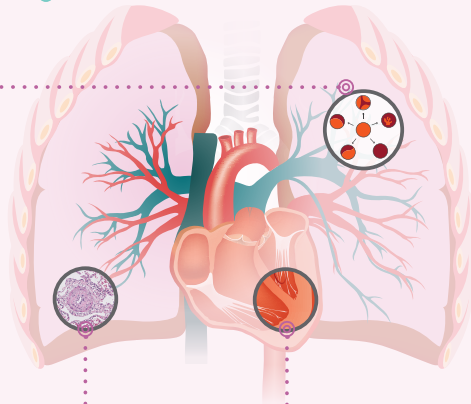
## PATHOPHYSIOLOGY OF CTEPH

### 1

#### INITIAL TRIGGER<sup>10,11</sup>

##### Persistent obstruction of proximal pulmonary arteries by organized thrombi

- Incomplete thrombus resolution may be caused by inflammation/infection and resistance to physiological fibrinolysis or reduced endogenous fibrinolytic potential
- Residual thrombi progressively evolve into a fibrotic mass, which is highly adherent to the pulmonary vascular wall in contrast to a fresh thrombus
- On CTPA or pulmonary angiography, those chronic thrombi are visible as bands, webs, stenoses and occlusions



### 2

#### COURSE OF THE DISEASE<sup>10,12</sup>

##### Small-vessel disease plays an important role in disease progression:



Nonoccluded pulmonary arteries are affected due to abnormal shear stress



Maintaining perfusion of the capillary bed is essential:

1. hypertrophy of bronchial arteries
2. anastomoses between these high-pressure systemic arteries and pulmonary vasculature distally from occlusions



Anastomoses could, in turn, increase shear stress and induce microvasculopathy, mainly in areas obstructed by organized thrombi



Molecular processes: not fully understood

##### Increased pulmonary vascular resistance is associated with chronic to finally irreversible RV dysfunction:



The RV is severely and progressively affected because of chronically increased RV afterload



1. Adaptive RV wall thickening (decreased wall stress + improved pumping capability)



2. Sustained RV overload → maladaptive RV wall thickening (increased wall stress + decreased pumping capability)



3. Imbalance between increased oxygen demand & decreased supply to the coronary arteries → ischemia, necrosis and fibrosis of the RV wall

## Capsule 4

## EPIDEMIOLOGY OF CTEPH

## 1

## CTEPH INCIDENCE\*



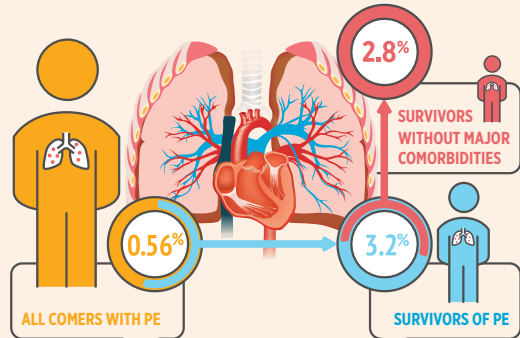
25% of CTEPH patients have no history of symptomatic PE or DVT<sup>14</sup>



Signs of CTEPH are often present on CTPA or echocardiography at the time of index PE<sup>15</sup>



Sometimes long duration between diagnosis of PE and first CTEPH symptoms (honeymoon period)



## 2

RISK FACTORS AND PREDISPOSING CONDITIONS OF CTEPH<sup>1</sup>

## Findings at the time of the acute PE event

- Recurrent PE or DVT
- Central pulmonary arterial thrombi on CTPA
- Unprovoked PE
- Diagnostic delay of PE
- Echocardiographic signs of PH/RV dysfunction
- CTPA findings suggestive of CTEPH

## Concomitant chronic diseases and conditions

- Hypothyroidism treated with thyroid hormones
- Infected chronic i.v. lines or pacemakers
- Ventriculo-atrial shunts
- History of splenectomy
- Non-O blood group
- Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
- Inflammatory bowel disease
- Chronic osteomyelitis
- Myeloproliferative disorders
- Malignancy

\* Numbers in the figure are based on a meta-analysis including 16 independent studies. Arrows indicate that the group of 'Survivors of PE' (blue) is a subset of 'All comers with PE' (yellow), whereas 'Survivors without major comorbidities' (red) is a subset of 'Survivors of PE'.<sup>13</sup>



## CLINICAL PRESENTATION AND DIAGNOSIS OF CTEPH

### 1

#### CLINICAL PRESENTATION



##### Symptoms - non-specific and often absent in early CTEPH:

- Predominant: exertional dyspnea and functional limitations;
- Other: fatigue, edema, syncope, chest pain, hemoptysis

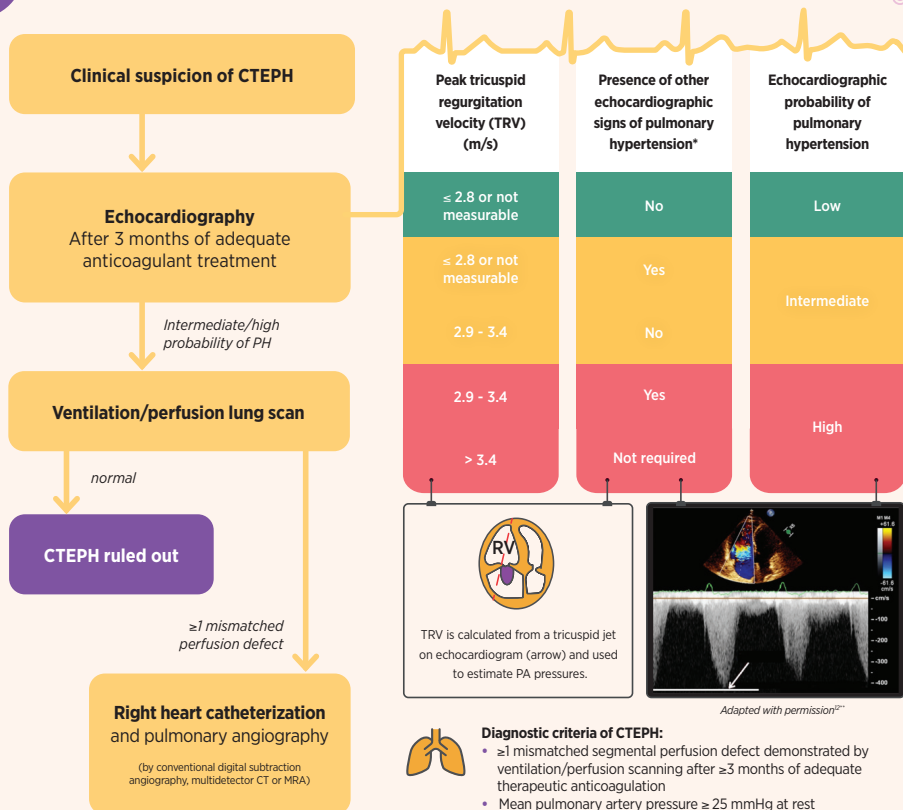


##### Clinical signs – may become evident at later stages of disease when the right ventricle (RV) fails:

- Palpable RV heave
- Closely split second heart sound with accentuation of its pulmonic component
- Tricuspid regurgitation murmur
- Jugular venous distension
- Peripheral edema
- Hepatomegaly and ascites

### 2

#### CURRENT DIAGNOSTIC ALGORITHM<sup>6</sup>



\* According to the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH'<sup>16</sup>

\*\* Copyright 2019 by Springer Open, under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).<sup>12</sup>

## TREATMENT AND PROGNOSIS OF CTEPH

### 1

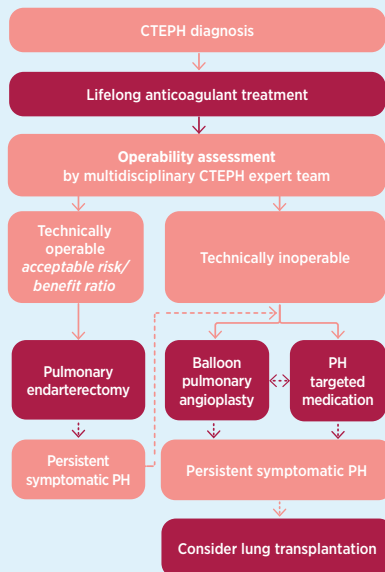
#### AIMS OF TREATMENT



- To restore normal flow distribution within the pulmonary vasculature
- To unload the right ventricle
- To prevent or treat small-vessel disease
- To prevent recurrent VTE
- To reduce functional limitations and improve quality of life

### 2

#### TREATMENT ALGORITHM<sup>®</sup>



### 3

#### OUTCOMES FOR EACH TREATMENT STRATEGY



##### 1. Lifelong anticoagulant treatment

- Best experience is with vitamin K antagonists, unclear whether DOACs are as effective and safe



##### 2. Pulmonary endarterectomy (PEA)<sup>17-24</sup>

*operability is dependent on surgical accessibility of thrombi, presence of comorbidity and patient preference*

- Mean pulmonary artery (PA) pressure: (near-)normalization in most patients
- Pulmonary vascular resistance (PVR): decrease from 700-800 to ~250 dyn·s·cm<sup>-5</sup>
- RV: immediate recovery of RV dimensions, RV systolic function restores in the majority within 1-3 years
- NYHA functional status: improvement from class III/IV to II/I in ~80%
- Quality of life: significant improvement



##### 3. Balloon pulmonary angioplasty (BPA)<sup>25-28</sup>

*a median of 4 sessions are performed per patient*

- Mean PA pressure after final BPA session: (near-)normalization in most patients
- PVR: mean reduction of 47-68%
- NYHA functional status: improvement from class III/IV to II/I in ~90%
- Quality of life: significant improvement

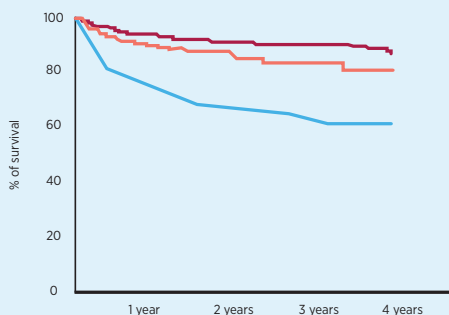


##### 4. PH targeted medication<sup>29</sup>

- 6-minute walk distance: increase from mean 351 ± 78 m to 409 ± 96 m at 1 year
- Quality of life: significant improvement

### 4

#### ESTIMATES OF SURVIVAL<sup>30-32</sup>



#### Legend:

Patients treated with PEA

Non-operated patients treated with PH targeted medication and/or BPA in the modern management era

Historical control patients treated for CTEPH between 1964 and 1979



## CURRENT CLINICAL PRACTICE PATTERNS AFTER PE

### 1

#### FOLLOW-UP AFTER PE



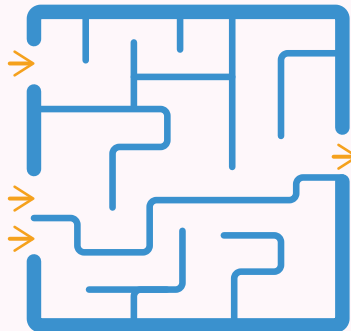
- Large practice variation
- Guidelines do not provide clear recommendations regarding diagnosis, treatment and prevention of the post-PE syndrome
- No tools available for assessing patient-relevant functional outcomes
- Timely CTEPH diagnosis is challenging because of non-specific presentation and diagnostic misclassification

### 2

#### DIAGNOSING CTEPH



- Considerable diagnostic delay of median 14 months (IQR 7.5-33)<sup>33,34</sup>
  - higher pulmonary pressures at diagnosis
  - higher risk of all-cause mortality
- History of recurrent VTE associated with a longer delay
- Insufficient healthcare utilization:
  - Only 61% of PE patients with post-PE syndrome are subjected to targeted diagnostic tests for CTEPH<sup>35</sup>
  - Before CTEPH is diagnosed, on average patients consult 4 different physicians for 13 consultations<sup>36</sup>
  - Diagnostic results suggestive of CTEPH are not always recognized
  - The recommended diagnostic algorithm for CTEPH is often not followed



### 3

#### HOW TO IMPROVE PATIENT OUTCOMES?



- Better physician and patient education
- Higher awareness for CTEPH/post-PE syndrome
- Validation and implementation of follow-up algorithms aimed at early CTEPH diagnosis
- Clear guideline recommendations for optimal follow-up after acute PE

## STRATEGIES FOR EARLIER CTEPH DIAGNOSIS

### 1

#### FOLLOW-UP AFTER PE<sup>27</sup>



Transthoracic  
echocardiography

##### Advantages

- non-invasive test
- imaging of structural as well as functional changes

##### Disadvantages

- lack of precision in estimating PA pressure, leading to both false positives and false negatives
- not cost-effective if performed as routine screening test in all patients



V/Q scan

- very high sensitivity

- poor specificity
- not cost-effective if performed as routine screening test in all patients
- radiation exposure



Algorithms of sequential  
diagnostic tests

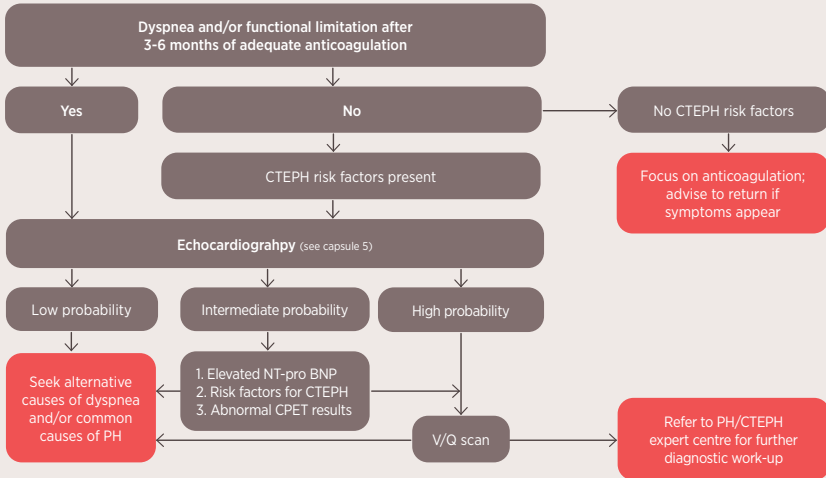
- optimal use of healthcare resources

- not (yet) formally validated in outcome studies

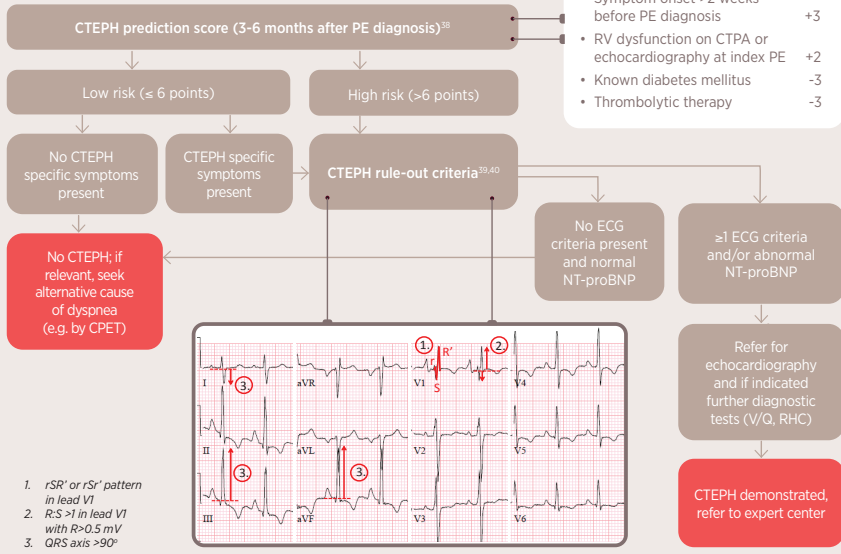
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**SUGGESTED SCREENING ALGORITHMS**

1. European Society of Cardiology 2019 suggests echocardiography in patients with risk factors for and/or symptoms of CTEPH (adapted with permission)



2. The InShape II algorithm aims to limit the number of required echocardiograms and is currently being evaluated in a prospective, multicenter outcome study in consecutive acute PE patients (NCT02555137)



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