



Universiteit
Leiden
The Netherlands

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

Boon, G.J.A.M.; Bogaard, H.J.; Klok, F.A.

Citation

Boon, G. J. A. M., Bogaard, H. J., & Klok, F. A. (2020). Essential aspects of the follow-up after acute pulmonary embolism: an illustrated review. *Research And Practice In Thrombosis And Haemostasis*, 4(6), 958-968. doi:10.1002/rth2.12404

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3627494>

Note: To cite this publication please use the final published version (if applicable).

ILLUSTRATED REVIEW

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

Gudula J. A. M. Boon MD¹  | Harm Jan Bogaard MD, PhD²  |
 Frederikus A. Klok MD, PhD¹  

¹Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

²Department of Pulmonary Diseases, Institute for Cardiovascular Research (ICaR-VU), Amsterdam University Medical Center, location VUmc, Amsterdam, The Netherlands

Correspondence

Frederikus A. Klok, Department of Thrombosis and Hemostasis, Leiden University Medical Center, Albinusdreef 2, Leiden 2300RC, The Netherlands.
 Email: f.a.klok@LUMC.nl

Handling Editor: Susan Kahn

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.

KEYWORDS

complications, early diagnosis, prognosis, pulmonary embolism, pulmonary hypertension, venous thromboembolism

Essentials

- Persistent functional limitations after acute pulmonary embolism (PE) are common and negatively impact quality of life.
- Among various causes of this post-PE syndrome, chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe presentation.
- Timely CTEPH diagnosis is a major challenge; diagnostic delay is associated with higher mortality.
- Implementation of a CTEPH screening algorithm after PE likely results in earlier CTEPH diagnosis.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
 © 2020 The Authors. *Research and Practice in Thrombosis and Haemostasis* published by Wiley Periodicals LLC on behalf of International Society on Thrombosis and Haemostasis.

Capsule 1

ESSENTIAL ASPECTS OF OPTIMAL CARE AFTER ACUTE PE

1 DIAGNOSIS



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)

3 INITIAL WEEKS²



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



Monitor the clinical course



Target modifiable risk factors for bleeding and VTE

5 LONG-TERM FOLLOW-UP



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 anti-coagulation: weighing risk of recurrence versus risk of bleeding³



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

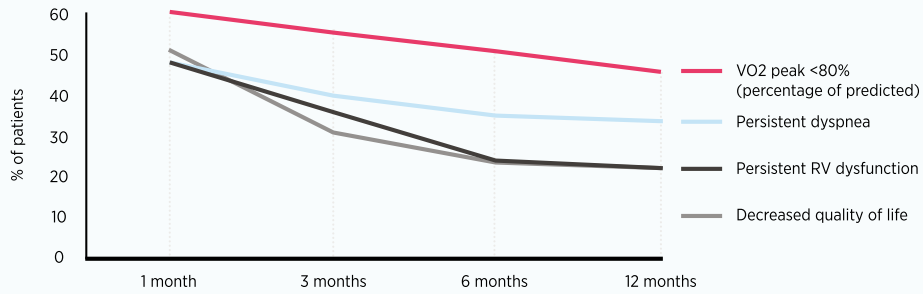
CTEPH chronic thromboembolic pulmonary hypertension
PE pulmonary embolism

Capsule 2

CONSEQUENCES OF PULMONARY EMBOLISM

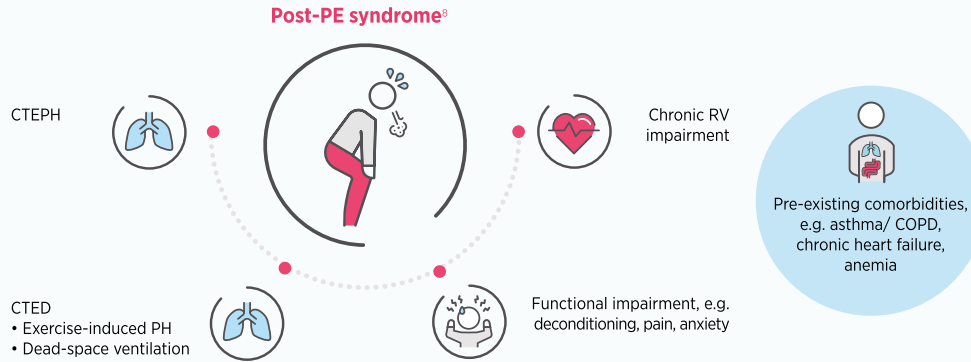
1

INCOMPLETE PHYSICAL RECOVERY AFTER PE IS COMMON¹⁻⁷



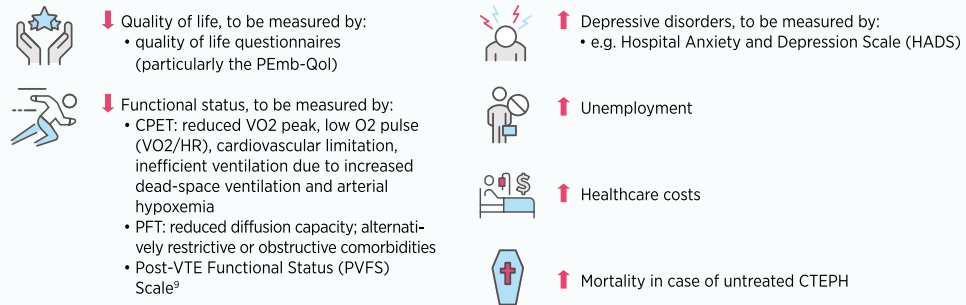
2

UNDERLYING CAUSES OF PERSISTENT SYMPTOMS AFTER PE



3

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



COPD	chronic obstructive pulmonary disease	PE	pulmonary embolism
CPET	cardiopulmonary exercise test	PFT	pulmonary function test
CTED	chronic thromboembolic disease	PH	pulmonary hypertension
CTEPH	chronic thromboembolic pulmonary hypertension		

Capsule 3

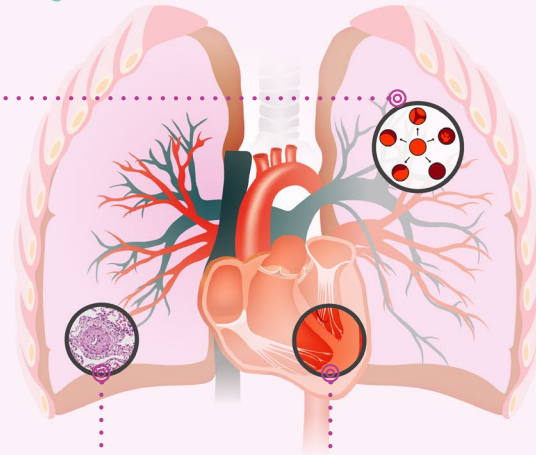
PATHOPHYSIOLOGY OF CTEPH

1

INITIAL TRIGGER^{10,11}

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^{10,12}

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

CTEPH chronic thromboembolic pulmonary hypertension
CTPA computed tomography pulmonary angiography

PE pulmonary embolism
RV right ventricle

Capsule 4

EPIDEMIOLOGY OF CTEPH

1

CTEPH INCIDENCE*



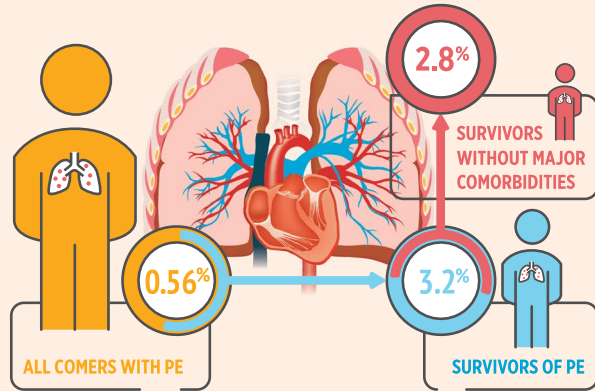
25% of CTEPH patients have no history of symptomatic PE or DVT¹⁴



Signs of CTEPH are often present on CTPA or echocardiography at the time of index PE¹⁵



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



2

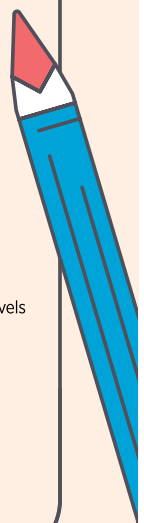
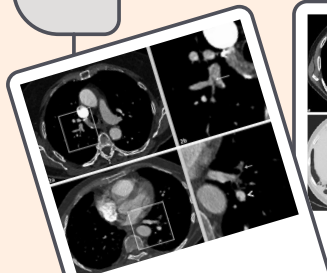
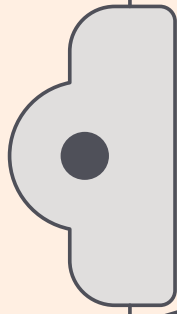
RISK FACTORS AND PREDISPOSING CONDITIONS OF CTEPH¹

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



CTEPH
CTPA
DVT
i.v.

chronic thromboembolic pulmonary hypertension
computed tomography pulmonary angiography
deep vein thrombosis
intravenous

PE
PH
RV

pulmonary embolism
pulmonary hypertension
right ventricle

* 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'.¹⁵

Capsule 5

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

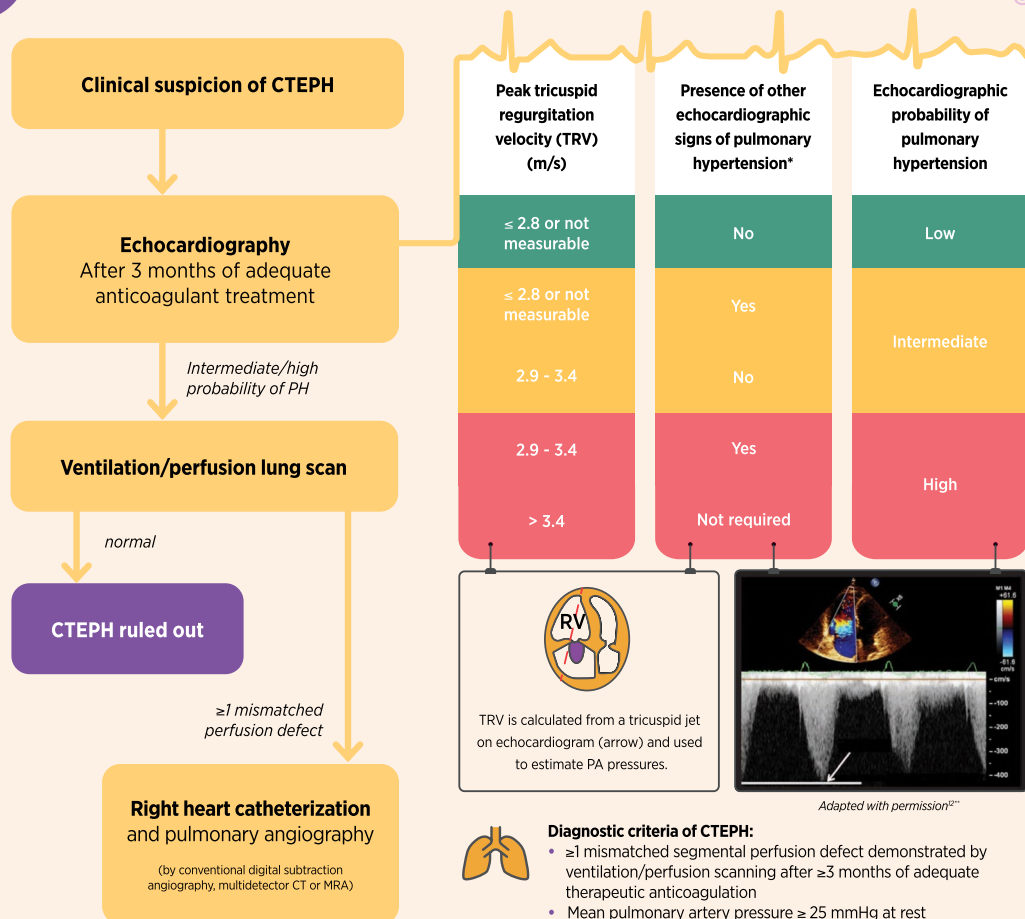


Clinical signs – may become evident at later stages of disease when the right ventricle (RV) fails:

- 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 ALGORITHM⁶



Diagnostic criteria of CTEPH:

- ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning after ≥3 months of adequate therapeutic anticoagulation
- Mean pulmonary artery pressure ≥ 25 mmHg at rest measured by invasive right heart catheterization
- Pulmonary capillary wedge pressure ≤ 15 mmHg

CTEPH chronic thromboembolic pulmonary hypertension
PA pulmonary artery
RV right ventricle
TRV tricuspid regurgitation velocity
LV left ventricle

* RV/LV diameter ratio >1.0, flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole), RV outflow doppler acceleration time <105 msec and/or midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec, PA diameter >25 mm, inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), right atrial area (end-systole) >18 cm².
 ** Copyright 2019 by Springer Open, under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).²²

Capsule 6

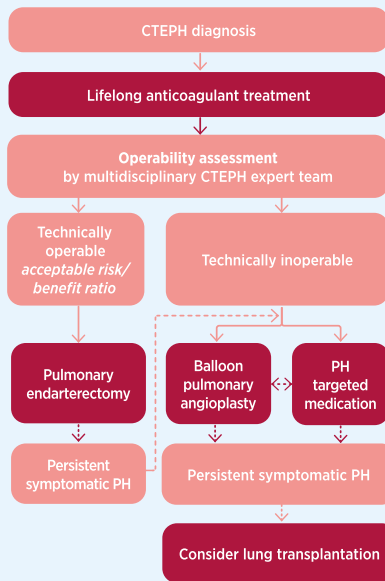
TREATMENT AND PROGNOSIS OF CTEPH

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 ALGORITHM¹⁶



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)¹⁷⁻²⁴
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⁻⁵
→ 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

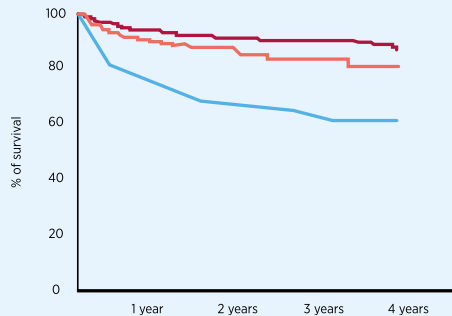


3. Balloon pulmonary angioplasty (BPA)²⁵⁻²⁸
a median of 4 sessions are performed per patient
→ Mean PA pressure after final BPA session: (near-)normalization in most patients
→ PVR: mean reduction of 47-68%
→ NYHA functional status: improvement from class III/IV to II/I in ~90%
→ Quality of life: significant improvement



4. PH targeted medication²⁹
→ 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 SURVIVAL³⁰⁻³²



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

BPA balloon pulmonary angioplasty
CTEPH chronic thromboembolic pulmonary hypertension

PA pulmonary artery
PEA pulmonary endarterectomy
PH pulmonary hypertension

CURRENT CLINICAL PRACTICE PATTERNS AFTER PE

1

FOLLOW-UP AFTER PE



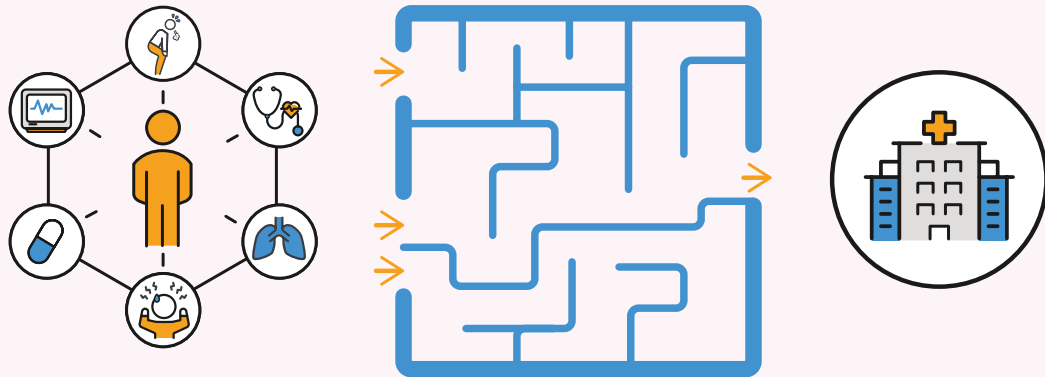
- Large practice variation
- Guidelines do not provide clear recommendations regarding diagnosis, treatment and prevention of the post-PE syndrome
- No tools available for assessing patient-relevant functional outcomes
- Timely CTEPH diagnosis is challenging because of non-specific presentation and diagnostic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

2

DIAGNOSING CTEPH



- Considerable diagnostic delay of median 14 months (IQR 7.5-33)^{33,34}
 - 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 CTEPH³⁵
 - Before CTEPH is diagnosed, on average patients consult 4 different physicians for 13 consultations³⁶
 - 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




CTEPH chronic thromboembolic pulmonary hypertension
IQR interquartile range

PE pulmonary embolism
VTE venous thromboembolism

Capsule 8

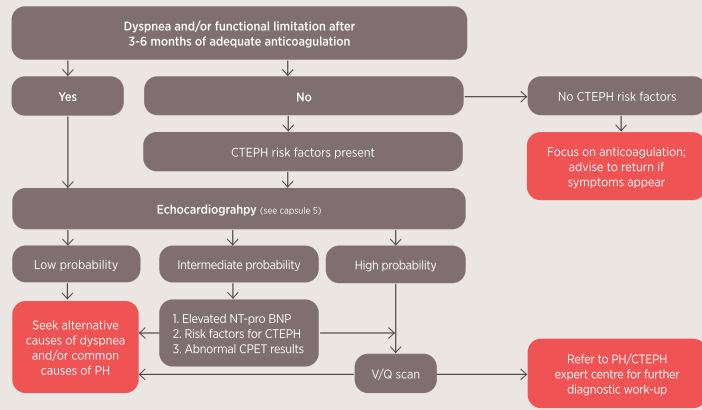
STRATEGIES FOR EARLIER CTEPH DIAGNOSIS

1 FOLLOW-UP AFTER PE³⁷

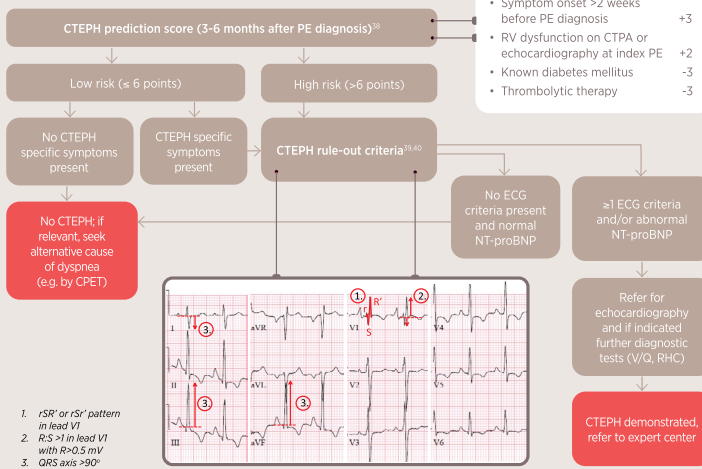
	Transthoracic echocardiography	Advantages • non-invasive test • imaging of structural as well as functional changes	Disadvantages • lack of precision in estimating PA pressure, leading to both false positives and false negatives • not cost-effective if performed as routine screening test in all patients
	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

2 SUGGESTED SCREENING ALGORITHMS

1. European Society of Cardiology 2019 suggests echocardiography in patients with risk factors for and/or symptoms of CTEPH (adapted with permission³⁸)



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 (NCT0255137)



CPET cardiopulmonary exercise test
CTEPH chronic thromboembolic pulmonary hypertension
CTPA computed tomography pulmonary angiography
ECG electrocardiography
PE pulmonary embolism
PH pulmonary hypertension
RHC right heart catheterization
VTE venous thromboembolism
V/Q scan ventilation/perfusion scan

RELATIONSHIP DISCLOSURE

GJAMB has nothing to disclose. HJB has received research grants from Bayer, Boehringer Ingelheim, Actelion, Therabel, and GSK. FK reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD, Actelion, the Dutch Heart Foundation, and the Netherlands Thrombosis Foundation.

AUTHOR CONTRIBUTIONS

FAK and GJAMB drafted the first version of the manuscript. All authors revised the review critically for important intellectual content and agree with the final version.

ORCID

Gudula J. A. M. Boon  <https://orcid.org/0000-0003-4532-436X>

Harm Jan Bogaard  <https://orcid.org/0000-0001-5371-0346>

Frederikus A. Klok  <https://orcid.org/0000-0001-9961-0754>

TWITTER

Frederikus A. Klok  @Erik_Klok_MD

REFERENCES

- 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 ERS: The Task Force for the diagnosis and management of acute pulmonary embolism of the ESC. *Eur Respir J*. 2020;41(4):543–603.
- den Exter PL, van der Hulle T, Lankeit M, Huisman MV, Klok FA. Long-term clinical course of acute pulmonary embolism. *Blood Rev*. 2013;27(4):185–92.
- Klok FA, Huisman MV. How I assess and manage the risk of bleeding during treatment of patients with venous thromboembolism. *Blood*. 2020;135(10):724–734.
- Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest*. 2009;136(5):1202–10.
- Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007;28(20):2517–24.
- Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, et al. Quality of Life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE Cohort Study. *Am J Med*. 2017;130(8):990.
- Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE Prospective Cohort Study. *Chest*. 2017;151(5):1058–68.
- Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev*. 2014;28(6):221–6.
- Boon GJAM, Barco S, Bertoletti L, Ghanima W, Huisman MV, Kahn SR, et al. Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale. *Thromb Res*. 2020;190:45–51.
- Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26(143):160112.
- Lang IM, Dorfmüller P, Vonk NA. The pathobiology of chronic thromboembolic pulmonary hypertension. *Ann Am Thorac Soc*. 2016;13(Suppl 3):S215–S221.
- Bryce YC, Perez-Johnston R, Bryce EB, Homayoon B, Santos-Martin EG. Pathophysiology of right ventricular failure in acute pulmonary embolism and chronic thromboembolic pulmonary hypertension: a pictorial essay for the interventional radiologist. *Insights Imaging*. 2019;10(1):18.
- 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.
- 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.
- Ende-Verhaar YM, Meijboom LJ, Kroft LJM, Beenen LFM, Boon GJAM, Middeldorp S, et al. Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study. *J Heart Lung Transplant*. 2019;38(7):731–8.
- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *Rev Esp Cardiol*. 2016;69(2):177.
- Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *European respiratory review: an official journal of the European Respiratory Society*. 2017;26(143):160111.
- D'Armini AM, Zanotti G, Ghio S, Magrini G, Pozzi M, Scelsi L, et al. Reverse right ventricular remodeling after pulmonary endarterectomy. *J Thorac Cardiovasc Surg*. 2007;133(1):162–8.
- Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest*. 2009;136(5):1202–10.
- Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007;28(20):2517–24.
- Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Annals Thorac Surg*. 2012;94(1):97–103.
- Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg*. 2011;141(3):702–10.
- Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Technique and outcomes of pulmonary endarterectomy surgery. *J Thorac Cardiovasc Surg*. 2008;14(5):274–82.
- Mathai SC, Ghofrani HA, Mayer E, Pepke-Zaba J, Nikkho S, Simonneau G. Quality of life in patients with chronic thromboembolic pulmonary hypertension. *Euro Respir J*. 2016;48(2):526–37.
- Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, et al. Angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. *Circ Cardiovasc Interv*. 2016;9:e00318.
- Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, et al. Pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. *Circ Cardiovasc Qual Outcomes*. 2017;10:11.

27. Darocha S, Pietura R, Pietrasik A, Norwa J, Dobosiewicz A, Piłka M, et al. Improvement in quality of life and hemodynamics in chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty. *Circulation J*. 2017;81(4):552–7.
28. Simonneau G, D'Armini AM, Ghofrani H-A, Grimminger F, Hoeper MM, Jansa P, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). *Euro Respirat J*. 2015;45(5):1293–302.
29. Riedel M, Stanek V, Widimsky J, Prerovsky I, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982;81(2):151–8.
30. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation*. 2016;133(9):859–71.
31. Taniguchi YU, Jaïs X, Jevnikar M, Boucly A, Weatherald J, Brenot P, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant*. 2019;38(8):833–42.
32. Khan MS, Amin E, Memon MM, Yamani N, Siddiqi TJ, Khan SU, et al. Meta-analysis of use of balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol*. 2019;291:134–9.
33. 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.
34. Klok FA, Barco S, Konstantinides SV, Dartevelle P, Fadel E, Jenkins D, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH registry. *The Eur Respir J*. 2018;52(6):1801687.
35. Tapson VF, Platt DM, Xia F, Teal SA, de la Orden M, Divers CH, et al. Monitoring for pulmonary hypertension following pulmonary embolism: the INFORM Study. *Am J Med*. 2016;129(9):978–85.
36. Ende-Verhaar YM, van den Hout WB, Bogaard HJ, Meijboom LJ, Huisman MV, Symersky P, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost*. 2018;16(11):2168–74.
37. Ende-Verhaar YM, Huisman MV, Klok FA. To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Thromb Res*. 2017;151:1–7.
38. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost*. 2016;14(1):121–8.
39. Klok FA, Surie S, Kempf T, Eikenboom J, van Straalen JP, van Kralingen KW, et al. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Thromb Res*. 2011;128(1):21–6.
40. Klok FA, Tesche C, Rappold L, Dellas C, Hasenfuß G, Huisman MV, et al. External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Thromb Res*. 2015;135(5):796–801.

How to cite this article: Boon GJAM, Bogaard HJ, Klok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. *Res Pract Thromb Haemost*. 2020;4:958–968. <https://doi.org/10.1002/rth2.12404>