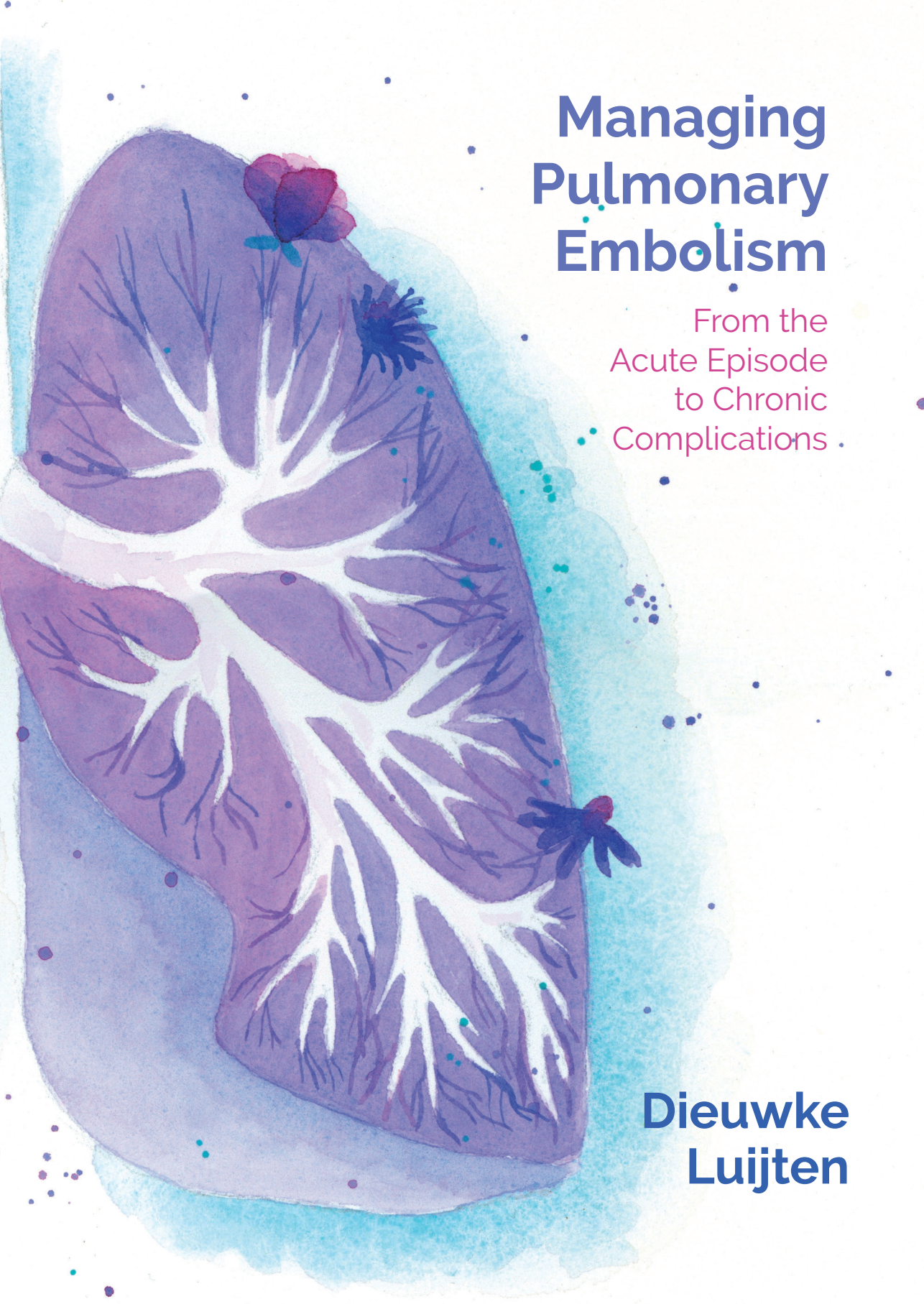

Managing Pulmonary Embolism

From the Acute Episode to Chronic Complications

Dieuwke Luijten

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Financial support for printing this thesis was kindly provided by Trombosestichting Nederland, LEO Pharma B.V., Stago BNL B.V., Boehringer Ingelheim B.V. and ChipSoft.

The studies performed in this thesis were performed at the Department of Thrombosis and Hemostasis of the Leiden University Medical Center, Leiden, the Netherlands.

ISBN/EAN: 978-94-6522-233-2

Cover design: Evelien Jagtman
Layout: Dieuwke Luijten
Printing: Ridderprint, www.ridderprint.nl

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op vrijdag 5 september 2025
klokke 13:00 uur

door

Dieuwke Luijten
geboren te ‘s-Hertogenbosch
in 1996

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Contents

1

Introduction

Acute pulmonary embolism (PE) is a condition where a blood clot occludes the pulmonary arterial system.[1] The clinical presentation of acute PE comprises a broad spectrum of symptoms and levels of hemodynamic compromise, from life-threatening obstructive shock to incidental findings on Computed Tomography (CT) scans ordered for an indication other than suspected PE. In acute PE, if 30-50% or more of the pulmonary arterial bed is occluded, the pulmonary artery pressure increases relevantly, leading to dilation of the thin-walled right ventricle, reduced contractility and decreased cardiac output, eventually resulting in right heart failure, obstructive shock and -if left untreated- death.[2, 3] Typically, acute PE patients should be treated with anticoagulants to prevent further clot formation or recurrence.[1] However, the treatment of PE encompasses more than the administration of anticoagulants alone. Patients with a severe pulmonary embolism, who are at high risk of death, should receive primary reperfusion therapy. On the other hand, patients with a so-called low risk PE may be directly discharged home without hospitalization. Hence, adequate risk stratification at diagnosis is one of the cornerstones of proper PE management.

Table 1: Risk classification according to the ESC

ESC risk classification	Hemodynamically unstable	sPESI>0 or PESI class III-IV	RV dysfunction on TTE or CTPA	Abnormal troponin levels	Treatment recommendation
Low risk PE	-	-	-	(-)	Early discharge/home treatment
Intermediate-low risk PE	-	+	One (or none) positive		Hospitalize
	-	-	One positive		
Intermediate-high risk PE	-	+	+	+	Monitoring; consider rescue reperfusion if deterioration
High risk PE	+	(+)	+	(+)	Reperfusion treatment/ hemodynamic support

+ present, - absent, ( ) measurement optional. Abbreviations: CTPA computed tomography pulmonary angiogram, ESC European Society of Cardiology, PE pulmonary embolism, PESI pulmonary embolism severity index, RV right ventricular, TTE trans thoracic echocardiography.

The European Society of Cardiology (ESC) recommends classifying patients in low, intermediate or high risk groups, and treat them accordingly (**Table 1**).[3]

However, recent studies have provided evidence supporting alternative management decisions beyond these guidelines.

The first part of this thesis focusses on improving the management of PE in the acute episode. **Chapter 2** provides an introduction to contemporary PE management with a focus on four important treatment decisions: (1) advanced reperfusion treatment in hemodynamically stable acute PE patients considered to be at high-risk of decompensation and death, (2) the treatment of subsegmental PE, (3) home treatment for hemodynamically stable PE patients with signs of right ventricle (RV) dysfunction, and (4) the optimal approach for identification and treatment of the post-PE syndrome.

Various tools exist to select PE patients for home treatment, but these tools have been tested in relatively small cohorts, leaving some subgroups underrepresented. In **Chapter 3** we performed an Individual Patient Data Meta-Analysis (IPDMA) combining data from previous studies into a large cohort to evaluate the safety of home treatment in specific subgroups relevant for decision making in daily practice.

Older patients are one of these subgroups, making correct management decisions in older PE patients is complex because they are often underrepresented in clinical trials, present with several comorbidities and have an associated increased risk of adverse outcome. Additionally, prevalent hypertension may make vital sign cut-offs and risk classifications developed for younger populations inaccurate. In **Chapter 4**, we evaluate risk classification in older acute PE patients, as well as the outcomes of subsequent management decisions, focusing on home treatment, reperfusion treatment, and mortality prediction.

If a patient survives the acute PE episode, the focus of care shifts to preventing and managing chronic complications, which is the topic of the second part of this thesis. Up to 50% of patients report persistent symptoms despite receiving adequate anticoagulant therapy for at least three months. This incomplete recovery is framed in the concept of the post-PE syndrome (PPES).[4-7] **Chapter 5** gives an overview of the definition, characteristics, diagnosis, and management of PPES. There are four main aetiologies captured within PPES: residual pulmonary vascular obstruction causing 1) chronic thromboembolic pulmonary hypertension (CTEPH) or 2) chronic thromboembolic pulmonary disease (CTEPD) without

pulmonary hypertension (PH) at rest; 3) incomplete recovery of the right ventricle (i.e. post-PE cardiac impairment) without residual pulmonary vascular obstruction and 4) post-PE functional impairment without residual vascular obstruction or measurable abnormal cardiopulmonary limitations during exercise.[7-9]

In post-PE functional impairment, the combination of fear of recurrence or complications as well as counselling to be cautious when performing exercise shortly after the diagnosis can lead to inactivity and deconditioning. Given the suggested benefits of early exercise training programs to prevent post-PE functional impairment, there is a pressing need for a deeper understanding of the safety considerations and underlying pathophysiology associated with engaging in exercise shortly after PE diagnosis. To address this need, **Chapter 6** investigates the safety and physiological response to exercise 2-4 weeks after PE diagnosis through cardiopulmonary exercise testing in 100 patients.

CTEPH is the most severe presentation of PPES, where chronic thrombi cause increased pulmonary artery pressure and right ventricular failure. A CTEPH diagnosis is confirmed by mismatched perfusion defects on ventilation-perfusion (V/Q) scan in combination with a mean pulmonary artery pressure of ≥20 mmHg, pulmonary capillary wedge pressure of ≤15 mmHg, and pulmonary vascular resistance of >2 Woods units measured during right heart catheterization (RHC).[10, 11] Reducing the diagnostic delay of CTEPH after acute PE improves survival and quality of life.[12] Screening strategies for CTEPH in acute PE patients can help achieve earlier diagnoses. To design and implement such algorithms, it is crucial to know the exact incidence of CTEPH following acute PE. In **Chapter 7** we present a systematic review and meta-analysis updating the incidence of CTEPH based on current literature.

One algorithm designed to identify CTEPH early after acute PE is the InShape II algorithm. The InShape II algorithm is one of the few follow-up algorithms that has been prospectively validated.[13] According to the algorithm, patients with either a high-pretest probability of CTEPH, as assessed with the CTEPH prediction score, or suggestive symptoms of CTEPH are subjected to the "CTEPH rule-out criteria", consisting of electrocardiogram (ECG) reading for the presence of RV overload and NTproBNP measurement.[13-15] CTEPH is ruled out if both are normal, otherwise echocardiography is necessary. This algorithm has been proven safe and efficient with an indication for echocardiography in only 19% of patients and a diagnostic failure rate of 0.29%. However, this algorithm might be further improved. In **Chapter 8** we evaluated the diagnostic performance of the ECG-derived

ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) for the detection of CTEPH and its incremental diagnostic value as new rule-out criteria within the InShape II algorithm. Another approach to improve the InShape II algorithm might be by using the dedicated evaluation of the computed tomography pulmonary angiogram (CTPA) used to diagnose the initial PE, for signs of CTEPH.[16-19] In **Chapter 9**, the incorporation of advanced CTPA reading in the InShape II algorithm, either as an additional test or as a replacement of one of the existing components was evaluated.

In addition to the InShape II algorithm and the algorithm presented in **Chapter 9**, several other screening methods are available for detecting CTEPH following acute PE. While all these algorithms aim to minimize diagnostic delays, their performance and cost may vary. In **Chapter 10**, we conducted a cost-effectiveness analysis of 11 PE follow-up algorithms and a hypothetical scenario without a dedicated follow-up algorithm to identify which approach is most cost-effective.

Having explored the diagnostic strategies for CTEPH detection in the preceding chapters, it becomes evident that while CTEPH represents a severe manifestation of PPES, it accounts for only a fraction of patients with persistent symptoms following acute PE. To address the needs of other patients experiencing PPES, it is crucial to delve deeper into the factors contributing to persistent symptoms in this population. Notably, up to 50% of acute PE patients exhibit incomplete thrombus resolution during follow-up. Therefore, in **Chapter 11**, we conducted a systematic review and meta-analysis to explore the association between pulmonary perfusion defects or residual vascular obstruction and functional recovery after PE.

Finally, we shift the focus from diagnosing CTEPH to the management of CTEPH. For CTEPH, pulmonary endarterectomy (PEA) is the treatment of choice.[20-22] PEA has been shown to significantly improve hemodynamics and exercise tolerance in CTEPH patients with low early mortality rates, particularly when performed in specialized centres.[20, 23, 24] Unfortunately, residual increased pulmonary artery pressure (i.e. residual PH) may still occur after PEA, leading to poorer long-term outcomes.[25, 26] Currently, repeated right heart catheterization is the gold standard for diagnosing residual PH post-PEA. One potential non-invasive alternative is the above-described VG-RVPO.[27-29] In **Chapter 12**, we assess the diagnostic accuracy of the VG-RVPO in detecting residual PH in CTEPH patients after PEA.

REFERENCES

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature Reviews Disease Primers 2018: 4(1): 18028.
2. McIntyre KMandSasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971: 28(3): 288-294.
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) 2019: 1901647.
4. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest 2017: 151(5): 1058-1068.
5. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
6. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010: 104(11): 1744-1749.
7. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014: 28(6): 221-226.
8. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2022: 43(3): 183-189.
9. Boon G, Bogaard HJandKlok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. Research and practice in thrombosis and haemostasis 2020: 4(6): 958-968.
10. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by 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 for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). European Heart Journal 2022: 43(38): 3618-3731.
11. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
12. Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Research 2021: 7(3): 00719-02020.
13. Boon G, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021: 76(10): 1002-1009.
14. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016: 14(1): 121-128.
15. Klok FA, Surie S, Kempf T, 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): 21-26.
16. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014: 112(3): 598-605.

17. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
18. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. AJR Am J Roentgenol 2020: 215(4): 800-806.
19. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. Eur Respir J 2021.
20. Delcroix M, Torbicki A, Gopalan D, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. The European respiratory journal 2020: 57(6): 2002828.
21. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). The European respiratory journal 2019: 54(3): 1901647.
22. Galiè N, Humbert M, Vachiery J-L, 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 2015: 37(1): 67-119.
23. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. Circulation 2011: 123(16): 1788-1830.
24. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013: 62(25 Suppl): D92-99.
25. Cannon JE, Su L, Kiely DG, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. Circulation 2016: 133(18): 1761-1771.
26. Quadery SR, Swift AJ, Billings CG, et al. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. Eur Respir J 2018: 52(3).
27. Kamphuis VP, Haeck MLA, Wagner GS, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of Electrocardiology 2014: 47(2): 175-182.
28. Meijer FMM, Kies P, Jongbloed MRM, et al. ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients. Int J Cardiol 2018: 273: 203-206.
29. Henkens IR, Mouchaers KTB, Vonk-Noordegraaf A, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. Am J Physiol Heart Circ Physiol 2008: 294(5): H2150-H2157.

2

Clinical controversies in the management of acute pulmonary embolism

Evaluation of four important but controversial aspects of acute pulmonary embolism management, that are still subject of debate and research

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Thijs E. van Mens and Menno V. Huisman

Expert Rev Respir Med. 2023 Mar;17(3):181-189

ABSTRACT

Introduction: Acute pulmonary embolism (PE) is a disease with a broad spectrum of clinical presentations. While some patients can be treated at home or may even be left untreated, other patients require an aggressive approach with reperfusion treatment.

Areas covered: (1) advanced reperfusion treatment in hemodynamically stable acute PE patients considered to be at high risk of decompensation and death, (2) the treatment of subsegmental pulmonary embolism, (3) outpatient treatment for hemodynamically stable PE patients with signs of right ventricle (RV) dysfunction, and (4) the optimal approach to identification and treatment of the post-PE syndrome.

Expert opinion: Outside clinical trials, hemodynamically stable acute PE patients should not be treated with primary reperfusion therapy. Thrombolysis and/or catheter directed therapy are only to be considered as rescue treatment. Subsegmental PE can be left untreated in selected low risk patients, after proximal deep vein thrombosis has been ruled out. Patients with an sPESI or Hestia score of 0 criteria can be treated at home, independent of the presence of RV overload. Lastly, healthcare providers should be aware of the post-PE syndrome and diagnose chronic thromboembolic pulmonary disease (CTEPD) as early as possible. Persistently symptomatic patients without CTEPD benefit from exercise training and cardiopulmonary rehabilitation.

INTRODUCTION

Acute pulmonary embolism (PE) is a disease with a broad spectrum of clinical presentations. Important improvements in the diagnosis and treatment of acute PE have been made in recent years.[1] Advanced imaging techniques have resulted in improved acute PE detection, and new risk stratification and interventional techniques have been introduced, overall resulting in a decreased PE-related mortality.[2, 3] Important questions regarding the optimal management of acute PE remain nonetheless, especially at both extremes of the disease severity spectrum. In this review, we focus on four important but controversial aspects of acute PE management that are still subject of debate and research**:** (1) advanced reperfusion treatment in hemodynamically stable acute PE patients considered to be at high risk of decompensation and death, (2) the treatment of subsegmental pulmonary embolism (SSPE), (3) outpatient treatment for hemodynamically stable acute PE patients with signs of right ventricle (RV) dysfunction, and (4) the optimal approach to identify and treat post-PE syndrome in PE survivors.

Reperfusion therapy in stable acute PE patients

There is a general consensus that, to increase survival chances, acute PE associated with hemodynamic instability or frank obstructive shock at presentation is a clear indication for immediate reperfusion therapy.[3] However, whether hemodynamically stable acute PE patients with signs of RV dysfunction and myocardial injury, who are also at increased risk of decompensation and death, referred to as intermediate-high-risk acute PE[4], may also benefit from reperfusion therapy is an ongoing point of debate. This debate is fuelled by the introduction of catheter-based reperfusion techniques.

The Pulmonary Embolism Thrombolysis (PEITHO) trial was designed to gain more knowledge regarding the efficacy and safety of systemic thrombolysis in intermediate-high-risk acute PE patients.[3] In this trial, 1005 acute PE patients with RV dysfunction on Computed Tomography Pulmonary Angiography (CTPA) and a positive troponin test were randomized between standard anticoagulation therapy with heparin versus anticoagulation with a single-bolus injection of tenecteplase (30–50 mg depending on the body weight). Tenecteplase indeed prevented death or hemodynamic decompensation (incidence within 7 days of 2.6% in the tenecteplase group versus 5.6% in placebo group; odds ratio [OR] 0.44;

95% confidence interval [CI] 0.23 to 0.87); however, the risk for major extracranial bleeding was increased with 6.3% in the tenecteplase group versus 1.2% in the placebo group, and hemorrhagic stroke occurred 2.0% in the tenecteplase group versus 0.2% in the placebo group. Therefore, the benefits of treatment did not outweigh its risks, and the current guidelines do not recommend systemic thrombolysis in intermediate-high-risk acute PE patients as a first-line treatment option.[5, 6] However, a post-hoc analysis of the PEITHO study showed that in intermediate-high-risk acute PE with at least two clinical criteria of severity (i.e. a systolic blood pressure ≤110 mmHg, a respiratory rate > 20 breaths/min, chronic heart failure, and/or cancer), tenecteplase treatment would have resulted in an adverse event rate of 7.6% compared to 20.3% for the placebo group.[7] This result suggests that further risk stratification of patients in the intermediate-high-risk category may help to select patients for whom the risk–benefit ratio of reperfusion therapy would support immediate application of the latter. While clinical signs of severity are likely important for further risk stratification, it is important to bear in mind that clot burden as a sole parameter has no beneficial role in selecting hemodynamically stable acute PE patients at risk for deterioration since a high clot burden is not associated with increased adverse events in hemodynamically stable acute PE.[8]

It has been proposed that reduced dose thrombolytic therapy may avoid the risk of bleeding while preserving the increased rate of thrombus resolution. Several small studies have been performed to investigate the safety and efficacy of reduced dose systemic thrombolysis. Two studies have shown that reduced systemic thrombolysis (recombinant tissue plasminogen activator at 0.5–0.6 mg/kg) is more effective than placebo in the normalization of perfusion defects and that systemic thrombolysis resulted in a reduced combined endpoint of persistent pulmonary hypertension or recurrent PE.[9, 10] Moreover, three randomized studies suggested that a reduced dose of thrombolytic treatment (recombinant tissue plasminogen activator at 0.5–0.6 mg/kg or at 50 g per 2 hours) was equally effective as full dose in prevention of death, change in total pulmonary resistance, and residual vascular obstruction.[11-13] In a network meta-analysis, low-dose thrombolysis was indeed associated with the lowest probability of dying and bleeding compared to other reperfusion options.[14] The ongoing PEITHO-3 trial (NCT04430569) is formally evaluating the efficacy and safety of a reduced-dose alteplase regimen (0.6 mg/kg) with standard heparin anticoagulation in patients with intermediate-high-risk PE and at least one clinical criterion of severity (i.e. a

systolic blood pressure ≤110mmHg, a respiratory rate >20 breaths/min, and/or chronic heart failure) and will ultimately determine the role of half-dose thrombolysis in the management of intermediate-high-risk acute PE.[15]

Over the last decade, multiple percutaneous catheter-directed therapies (CDTs) have been introduced. CDT is a local technique aiming for thrombus resolution based on thrombus fragmentation, thrombus aspiration, rheolytic thrombectomy (i.e. disruption and removal of the thrombus using a pressure gradient or local thrombolysis), or local (ultrasound accelerated) thrombolysis.[16] Studies have shown that CDT results in a decrease in RV overload compared to anticoagulation alone, along with low rates of major bleeding (ranging 0–10%).[15, 17-21] However, evidence is limited since most studies were observational or single-arm cohort studies. There is also limited evidence on complication rates of CDT beyond major bleeding or death. Clinical studies have reported a complication rate of ~0–4%.[22] Complication rates of CDT performed by inexperienced physicians are unknown, but a higher rate can be expected. The few small, randomized trials performed were not designed to establish differences in clinically relevant outcomes, such as death or hemodynamic deterioration to shock. Larger randomized controlled trials are needed to prove efficacy beyond doubt, before these costly therapies become routine care for intermediate-high risk acute PE patients. Currently ongoing trials investigating the efficacy and safety of CDT include the HI-PEITHO trial (NCT04790370) and the PEERLES study (NCT05111613).[22, 23] The HI-PEITHO trial randomizes intermediate-high-risk acute PE patients with at least two clinical criteria of severity (i.e. heart rate ≥100 bpm, systolic blood pressure ≤110 mmHg, respiratory rate > 20/min, and/or oxygen saturation on pulse oximetry <90% on room air) to treatment with a standardized protocol of ultrasound-facilitated catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone.[23] The PEERLESS study randomizes intermediate-high-risk acute PE patients to mechanical thrombectomy using the FlowTriever system versus catheter-directed thrombolysis with any commercially CDT system.[24] Another treatment option is surgical embolectomy, but there is little evidence on the safety and efficacy in (intermediate) high-risk acute PE since only non-randomized studies have been performed. Surgical embolectomy is therefore currently only recommended in patients with a high-risk acute PE who deteriorated after thrombolysis or have a contra-indication for thrombolysis.[3] While awaiting the results of currently ongoing clinical trials, a multidisciplinary

rapid-response team, also known as PE response teams (PERT), facilitates clinical decision-making in patients with intermediate-high-risk acute PE.[25]

Treatment of subsegmental pulmonary embolism

An SSPE is an embolus located in single or multiple subsegmental pulmonary arteries.[26, 27] It is currently debated whether SSPE is an indication for anticoagulant treatment. There are several arguments why SSPE can be left untreated. First, advances in the radiological diagnosis of PE have resulted in an increased incidence of SSPE. Because this increase in the number of PE diagnosis was associated with a decreasing trend in PE mortality, SSPE has been hypothesized to be 'overdiagnosis'.[1, 28-33] The fact that imaging artifacts are often misclassified as SSPE is supportive of this concept.[34-37] Second, it can be argued that the presence of small thrombi in the pulmonary system provided that proximal deep vein thrombosis (DVT) is not present may be a physiological finding as the pulmonary system might act as a filter to prevent thrombotic tissue entering the arterial system.[38, 39]

Multiple small observational studies have shown that patients with isolated SSPE may be left untreated with a low incidence of symptomatic recurrent venous thromboembolism (VTE).[35, 40-44] A recent large multicentre prospective cohort study showed a recurrent VTE rate of 3.1% (8 out of 266 patients; 95%CI 1.6–6.1; none of the eight recurrences observed were fatal) which led to premature stop of recruitment since the predefined inferiority stopping rule was met; the primary study hypothesis was that this recurrence rate would be below 3.0%.[25]

A potential explanation for the observed difference between the available studies is that, until recently, a universal SSPE diagnosis was lacking. A Delphi analysis was performed in order to establish a uniform diagnostic definition for SSPE: "A contrast defect in a subsegmental artery, i.e. the first arterial branch division of any segmental artery independent of artery diameter, visible in at least two subsequent axial slices, using a Computed Tomography scanner with a desired maximum collimator width of ≤1 mm".[45] This universal diagnosis likely helps the reliable and reproducible identification of SSPE, and should be the basis of future studies.

Another important factor in SSPE treatment is the selection of which SSPE patients can potentially be left untreated since there are multiple factors determining the risk of recurrent VTE besides location and size. SSPE patients with

a malignancy or previous VTE should not be left untreated since the expected recurrence rate is higher, even when this diagnosis was incidental.[46-51] Also, SSPE patients presenting with hypoxemia should not be left untreated since an isolated SSPE may become clinically relevant in patients with pre-existing cardiopulmonary disease.[44, 52] In the previously described cohort study, 435 of 749 SSPE patients (58%) were excluded from the study and treated with anticoagulants due to the presence of (among others) one of the previously described criteria.[52] Finally, SSPE patients with a simultaneous DVT should not be left untreated. DVT is an important predictor for recurrent VTE and PE-related mortality and therefore requires anticoagulation.[44, 53] For SSPE patients with concomitant DVT who receive anticoagulation for the DVT, there is no need to discuss if there is an indication for anticoagulation for the SSPE, since this treatment is already indicated based on the DVT. In the previously described cohort study, six out of 292 SSPE patients with no other risk factors for recurrent VTE were found to have (non-symptomatic) proximal DVT (2.1%) and 22 had (non-symptomatic) distal DVT (7.5%) upon bilateral compression ultrasonography, highlighting the importance of ruling out DVT in SSPE patients when considering leaving them untreated.[54] The safe-SSPE trial (NCT04263038) is currently investigating the incidence of recurrent VTE, recovery of complaints, and functional performance in selected SSPE patients randomized to either placebo or rivaroxaban.[3]

Home treatment

The 2019 ESC guideline recommends classifying patients according to their risk of early (in hospital or 30-day) death and treating patients accordingly.[55] The PESI score and simplified PESI (sPESI) are prediction models that can identify low-risk acute PE patients with a 30-day mortality of ~1.0%.[56, 57] The PESI score can be used to select patients eligible for outpatient treatment since a randomized controlled trial showed non-inferiority for outpatient treatment versus hospitalization in low-risk patients according to an ad hoc decision rule in patients with PESI class I–II.[58] The Hestia criteria are an alternative tool to select patients eligible for outpatient treatment. This is a pragmatic list of 11 reasons why patients would require hospitalization, e.g. need for advanced reperfusion therapy, oxygen therapy, or intravenous analgesics. The Hestia criteria are a checklist rather than a prediction score (**Table 1**).

Table 1: Hestia criteria and sPESI score for eligibility of home-treatment.

Hestia	Answer	sPESI	Points
Is the patient hemodynamically unstable? [a]	Yes/No	Age >80 years	1
Is thrombolysis or embolectomy necessary?	Yes/No	History of cancer	1
Active bleeding or high risk of bleeding? [b]	Yes/No	Chronic cardiopulmonary disease	1
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?	Yes/No	Systolic blood pressure <100mmHg	1
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No	Heart rate ≥110 b.p.m.	1
Severe pain needing intravenous pain medication for more than 24 h?	Yes/No	Arterial oxygen saturation <90%	1
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes/No		
Does the patient have a creatinine clearance of < 30 mL/min? [c]	Yes/No		
Does the patient have severe liver impairment? [d]	Yes/No		
Is the patient pregnant?	Yes/No		
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No		
If all questions can be answered with 'No' the patient has a negative Hestia and is eligible for home treatment		If the sPESI score is 0 points, a patient is eligible for home treatment.	

[a] Include the following criteria, but leave these to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats min^{-1}; condition requiring admission to an intensive care unit. [b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (< 4 weeks ago), recent operation (< 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 · 109 L^{-1}),uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg). [c] Calculated creatinine clearance according to the Cockroft–Gault formula. [d]Left to the discretion of the physician.

Patients that were negative for all 11 Hestia criteria were treated as outpatients with low molecular weight heparin (LMWH) or LMWH plus a vitamin K antagonist (VKA) in a prospective cohort study, with a 90-day overall mortality of 1.0%.[59, 60] The Vesta study randomized patients who were negative for all Hestia criteria between direct discharge versus additional N-terminal pro–brain natriuretic peptide (NT-proBNP) assessment. Patients with an NT-proBNP below 500 ng/L were also treated at home. All patients received LMWH and VKAs.

Due to the low number of adverse events, this study was unable to show incremental value of NT-proBNP testing in patients who are negative for all Hestia criteria.[61] The HOME-PE trial randomized patients between Hestia and sPESI for selection for outpatient treatment with LWMH, VKAs, or directs oral anticoagulants and showed that the rate of 30-day combined end-point (i.e. recurrent VTE, bleeding, or all-cause death) for patients treated at home was low (1.3% for Hestia and 1.1% for sPESI). Moreover, in the overall population, the rate of this endpoint was comparable in both groups (3.8% for Hestia versus 3.6% for sPESI), showing that both strategies are safe and effective in selecting patients for outpatient treatment.[3]

Notably, both Hestia and (s)PESI do not incorporate an explicit assessment of RV function (**Table 1**). Whether low-risk patients (according to Hestia and/or [s]PESI) with RV dysfunction can be treated as outpatients remain a point of debate. According to the 2019 ESC guidelines, assessment of RV dysfunction is obligatory before considering outpatient treatment: patients with none of the Hestia criteria, PESI I–II, or sPESI 0 but with RV dysfunction are characterized as intermediate-risk acute PE.[62] Hospitalization is recommended for this patient category. This recommendation was partly based on a meta-analysis suggesting that RV dysfunction is associated with a high risk of early all-cause mortality even in selected low-risk patients according to the PESI score (OR 4.2 95%CI 1.4–12.6).[63] The HoT-PE study evaluated the safety and efficacy of early discharge (up to two nights of hospital stay were permitted) in low-risk patients (according to adapted Hestia criteria) who had no signs of RV dysfunction or intracardiac thrombi. Of the 2854 acute PE patients evaluated for study inclusion, 300 patients had negative Hestia criteria but the presence of RV dysfunction or free-floating thrombi and were therefore excluded from the trial and treated as inpatients. In the 525 patients selected for early discharge, a 0.6% incidence of recurrent non-fatal VTE and a 1.2% incidence of major bleeding were observed, suggesting that early discharge is safe in these selected low-risk patients.[64] However, the studies included in the previously mentioned meta-analysis were mainly observational, and no systematic treatment decisions were made based on the (s)PESI score or signs of RV dysfunction. Therefore, we cannot simply conclude that early all-cause mortality would improve if all low-risk patients with RV dysfunction are hospitalized. In addition, patients excluded from HoT-PE due to the presence of RV dysfunction were not systematically followed, and details regarding their prognosis were unavailable.

Interestingly, an analysis of the combined Hestia and Vesta study, where RV dysfunction on CTPA was assessed post-hoc (i.e. RV/left ventricle ratio >1), showed that 30% of the patients treated at home had RV dysfunction, and the incidence of adverse events did not differ between outpatients with or without RV dysfunction (2.7% vs 2.3%, respectively).[61] Also, in the HOME-PE study, 90 of the 739 (12.2%) patients treated at home had RV dysfunction; none of these patients returned to the hospital because of hemodynamic deterioration or experienced PE recurrence of PE-related death.[65] Moreover, the post-hoc assessed troponin T levels in the Vesta study showed no difference in all-cause death after 3 months for home treated patients with or without an elevated troponin T level (1.7% vs 1.7% respectively).[66] Identifying low-risk patients based on Hestia (or [s]PESI) alone - even when signs of RV dysfunction are present- seems therefore adequate for the selection of patients who are eligible for outpatient treatment. This is explained by the fact that preselection based on Hestia and/or sPESI already results in an acceptable low adverse event rate, thus diluting the additional value in the absence of RV dysfunction.

In routine Dutch clinical practice, 46% of the patients are treated at home (ranging from 13% to 83% for individual hospitals).[67] Using patient-level data of the YEARS study, health-care utilization and costs were compared between hospitalized and home-treated patients. Patients who were treated as outpatients had a mean hospitalization duration of 0.69 days compared to 4.3 days for patients who were hospitalized. This correlated with an average cost of hospitalized patients of €3,209 versus €1,512 per patient treated at home, adjusted for potential confounders, emphasizing the cost-effectiveness of treating acute PE patients as outpatients.[68] More importantly, outpatient treatment results in a high level of patient satisfaction.[69]

Long-term consequences after acute PE

Survivors of acute PE often report persistent symptoms, new psychosocial problems, and/or persistent limitations in their daily activities.[70-73] These patients qualify as having post-pulmonary embolism syndrome (PPES) which is defined as new or progressive dyspnea, exercise intolerance, and/or impaired functional or mental status after at least 3 months of adequate anticoagulation following acute PE, which cannot be explained by other (preexisting) comorbidities.[73] Up to 16–47% of the acute PE patients report persistent limitations and/or dyspnea qualifying for PPES.[69, 74, 75] The exact incidence of PPES remains unclear since

different criteria have been used to define the presence of PPES and PPES incidence evaluation has been performed at different time points following acute PE diagnosis. Post-PE syndrome has four largely distinct clinical presentations: (1) chronic thromboembolic pulmonary disease (CTEPD) with pulmonary hypertension, i.e. chronic thromboembolic pulmonary hypertension (CTEPH), (2) CTEPD without pulmonary hypertension, (3) post-PE cardiac dysfunction (characterized as persistent RV impairment), and (4) post-PE functional impairment.[76-78] Importantly, awareness of PPES and early diagnosis of especially CTEPH will most likely lead to better health outcomes of PE survivors.[76, 79]

During follow-up of acute PE, systematic and routine evaluation of the symptom burden and quality of life (QoL) will greatly facilitate the early identification of patients who require additional treatment beyond anticoagulation. Patient reported outcome measures (PROMs) are helpful tools for this purpose, for example, by measuring dyspnea (Medical Research Council [MRC] dyspnea scale[3, 80]) or functional limitations (Post-VTE Functional Status [PVFS] scale[81, 82]). However, other validated tools to objectify persistent symptoms or functional limitations can also be used. An international workgroup (ICHOM) established a core set of outcome measures with matching instruments that encompass the most relevant outcomes. Implementation of this core set will help in shifting the focus.[83]

In patients with persistent symptoms and functional limitations, further classification of PPES should be performed. Since an early diagnosis of CTEPH will result in improved survival and better QoL, early diagnosis is of utmost importance.[78, 84, 85] A CTEPH diagnosis is confirmed by mismatched perfusion defects in ventilation-perfusion (V/Q) scan in combination with a mean pulmonary artery pressure of ≥20 mmHg, pulmonary capillary wedge pressure of ≤15 mmHg, and pulmonary vascular resistance of >2 woods-units measured with right heart catheterization (RHC).[3, 86] There are several strategies to select patients who should be subjected to V/Q scan and RHC. The ESC guidelines recommend performing echocardiography in all patients with persistent dyspnea, functional limitations, or risk factors for CTEPH. Patients with intermediate to high probability of pulmonary hypertension on echocardiography require further evaluation.[85,87] A strategy to limit the number of patients referred for echocardiography is the InShape II algorithm, which consists of a CTEPH prediction score and the CTEPH rule-out criteria.[79, 88-91] Moreover, there are several radiological signs on CTPA that

are highly specific for CTEPH and can contribute in early identification of patients who require focused diagnostic evaluation early in the course of disease.[72, 92-95]

Decreased daily physical activity after a PE diagnosis, anxiety, and post-thrombotic panic syndrome, as well as fear for recurrences or complications all result in deconditioning with persistent symptoms and functional limitations as a result; these patients are referred to as having post-PE functional impairment.[69-71, 73, 96-99] Exercise treatment or cardiopulmonary rehabilitation is a potential treatment option for these patients. A Dutch study showed that in patients with persistent moderate-to-severe dyspnea >3 months after acute PE, a 12-week rehabilitation program resulted in significant improvement in training intensity and PE-specific QoL.[100] An Austrian study showed that a 6-week rehabilitation course initiated after a median of 19 weeks following an acute PE diagnosis resulted in improvement in the 6-minute walk test and self-reported health.[101] While rehabilitation seems effective in the treatment of PPES, it has been suggested that exercise training early after PE diagnosis may prevent deconditioning and resulting loss of QoL. Several studies have shown that exercise training is safe in acute PE patients.[100, 102-106] Two studies randomized acute PE patients to early initiation of exercise training versus no exercise training.[102, 106] The first study showed significant improvement of estimated VO_2max, RV/left ventricle ratio, and health-related QoL in the exercise training group, while no improvement was found in the control group.[102] The second study showed a greater improvement in incremental Shuttle Walk Test and PE-specific QoL for the exercise group compared to the control group. However, group differences were small.[3] A potential explanation for the less than convincing findings of these two studies was that unselected post-PE patients without considering persistent symptoms were included, potentially diluting the effects of early exercise training. The currently ongoing PE@HOME study (Dutch trial register NL9615) is randomizing acute PE patients with persistent symptoms and function limitation after 2–3 weeks (i.e. MRC ≥2 and PVFS ≥ 2) to an 8-week home-based exercise program versus no exercise program. This study will provide more knowledge on optimal patient counselling regarding prevention of post-PE syndrome.

Expert opinion

We have discussed four important aspects of acute PE management that are still subject of debate and research (**Figure 1**). When treating a patient with acute PE, the first step should be the assessment of the need for reperfusion treatment. We

argue that the first-line treatment of intermediate-high-risk PE outside clinical trials remains anticoagulant treatment. Full-dose systemic thrombolysis is associated with a too high risk of major bleeding to be considered as primary treatment in this patient category; CDT cannot be recommended yet as randomized studies, using relevant clinical outcomes, are lacking. Only if intermediate-high-risk patients show progress to hemodynamic instability or obstructive shock despite adequate anticoagulant treatment, systemic thrombolytic treatment or CDT should be considered as rescue treatment.[15, 54] Decisions regarding rescue treatment are best discussed in a PERT to facilitate consistent decision-making. Reduced dose systemic thrombolysis, catheter-directed thrombolysis, and mechanical thrombectomy are currently being evaluated in large, randomized studies. Results from these trials will provide us with more information regarding the future role of primary reperfusion treatment for hemodynamically stable acute intermediate-high PE patients.

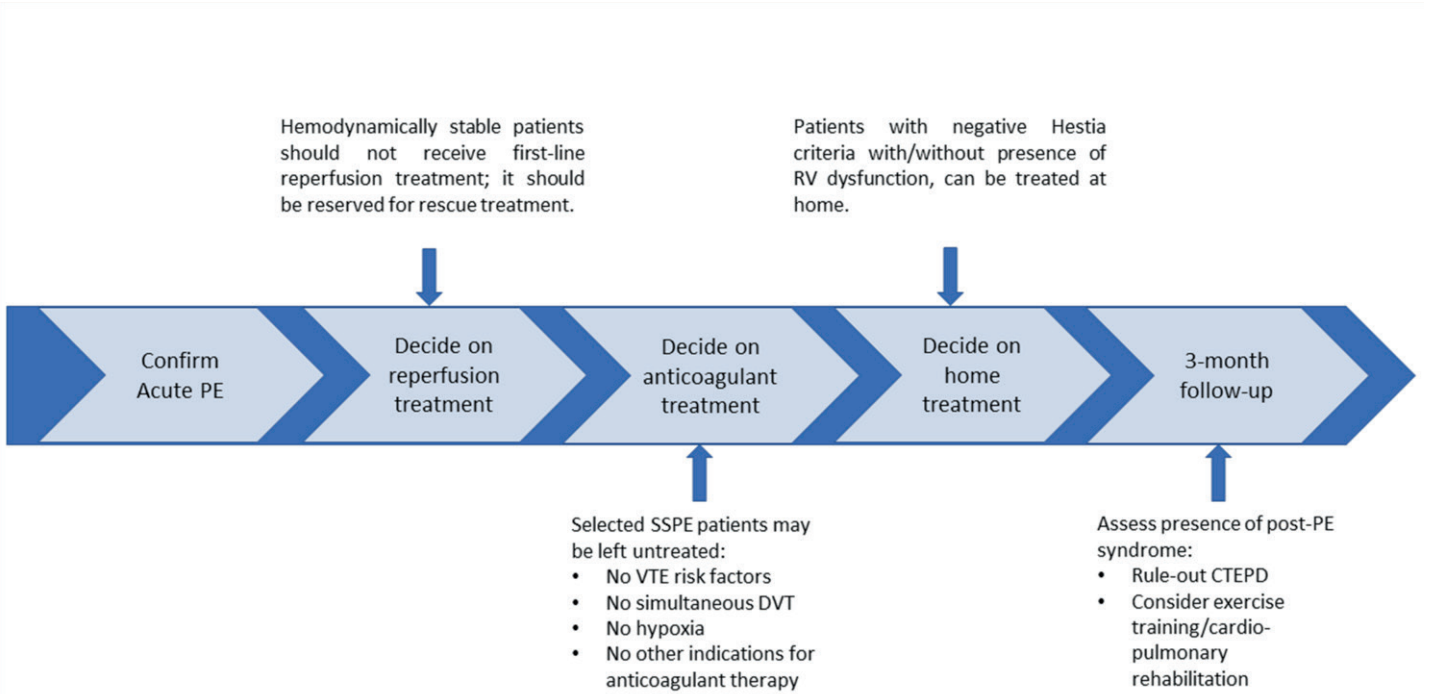
In those patients not requiring reperfusion treatment, the need for anticoagulant treatment should be weighed. There are several arguments as to why SSPE may potentially be left untreated. When considering not starting anticoagulant treatment in an SSPE patient, the following should be considered (1) the universal SSPE definition should be used, confirmed by an experienced radiologist, (2) patients with risk factors for recurrent VTE (e.g. pregnancy, cancer, trauma, recent surgery, prior VTE, and antiphospholipid syndrome), or patients presenting with hypoxemia should receive treatment if the bleeding risk is acceptable, and (3) SSPE patients with a simultaneous DVT should receive anticoagulation as well. Excluding non-symptomatic DVT in SSPE patients using the same diagnostic strategy to exclude symptomatic DVT in a patient without SSPE is therefore advised. There is no evidence for the additional value of venography or ultrasonography of pelvic veins in SSPE patients. However, since compression ultrasonography is the cornerstone of DVT diagnosis in patients without SSPS, we also advise performing a bilateral compression ultrasonography to exclude DVT in SSPE patients. The currently ongoing safe-SSPE study will hopefully provide more precise guidance in the management of SSPE patients.[103]

After confirmation of the indication for anticoagulant treatment, the need for hospitalization should be determined. Outpatient treatment of acute PE is safe, cost-effective, and results in a high level of patient satisfaction. When selecting eligible patients for outpatient treatment, the Hestia criteria or sPESI can be used, with or without assessment of RV dysfunction. In our practice, we apply the Hestia

criteria. sPESI is an alternative clinical decision rule, although it was designed as a prediction score for all-cause death rather than a clinical tool to evaluate potential home-treatment. In the HOME-PE trial 28.5% of the patients with an sPESI of 0 were ultimately hospitalized based on overruling by the treating physicians, highlighting that sPESI therefore should always be combined with other clinical (Hestia like) criteria to evaluate the feasibility of home treatment.

Finally, there is increased awareness of all aspects of the prognosis of PE patients. The ICHOM standard set of outcome measures can help to assess all important patient outcomes. Patients with persistent symptoms and/or functional limitations qualify as PPES. If so, the first priority is to evaluate the presence of CTEPD. For patients with post-PE impairment, dedicated exercise training likely improves QoL and functional abilities. The ongoing PE@HOME study will give us more insight into the role of exercise training initiated shortly after PE diagnosis in the prevention of PPES. There is currently no evidence on the relationship between different types of anticoagulant treatment or treatment adherence and the development of PPES.

Figure 1: Pathway of acute pulmonary embolism treatment



REFERENCES

1. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med 2020: 8(3): 277-287.
2. Dronkers CE, Klok FAandHuisman MV. Current and future perspectives in imaging of venous thromboembolism. J Thromb Haemost 2016: 14(9): 1696-1710.
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) 2019: 1901647.
4. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism. New England Journal of Medicine 2014: 370(15): 1402-1411.
5. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020: 4(19): 4693-4738.
6. Barco S, Vicaut E, Klok FA, et al. Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials. European Respiratory Journal 2018: 51(1): 1701775.
7. Hariharan P, Dudzinski DM, Rosovsky R, et al. Relation Among Clot Burden, Right-Sided Heart Strain, and Adverse Events After Acute Pulmonary Embolism. The American Journal of Cardiology 2016: 118(10): 1568-1573.
8. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 1990: 98(6): 1473-1479.
9. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013: 111(2): 273-277.
10. Goldhaber SZ, Agnelli GandLevine MN. Reduced Dose Bolus Alteplase vs Conventional Alteplase Infusion for Pulmonary Embolism Thrombolysis: An International Multicenter Randomized Trial. Chest 1994: 106(3): 718-724.
11. Sors H, Pacouret G, Azarian R, et al. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. Chest 1994: 106(3): 712-717.
12. Wang C, Zhai Z, Yang Y, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest 2010: 137(2): 254-262.
13. Jimenez D, Martin-Saborido C, Muriel A, et al. Efficacy and safety outcomes of recanalisation procedures in patients with acute symptomatic pulmonary embolism: systematic review and network meta-analysis. Thorax 2018: 73(5): 464-471.
14. Sanchez O, Charles-Nelson A, Ageno W, et al. Reduced-Dose Intravenous Thrombolysis for Acute Intermediate-High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. Thromb Haemost 2022: 122(5): 857-866.
15. Pruszczyk P, Klok FA, Kucher N, et al. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention 2022: 18(8): e623-e638.
16. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014: 129(4): 479-486.

17. Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv 2015: 8(10): 1382-1392.
18. Tapson VF, Sterling K, Jones N, et al. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial. JACC Cardiovasc Interv 2018: 11(14): 1401-1410.
19. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. JACC Cardiovasc Interv 2021: 14(12): 1364-1373.
20. Sista AK, Horowitz JM, Tapson VF, et al. Indigo Aspiration System for Treatment of Pulmonary Embolism: Results of the EXTRACT-PE Trial. JACC Cardiovasc Interv 2021: 14(3): 319-329.
21. Tu T, Toma C, Tapson VF, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv 2019: 12(9): 859-869.
22. Klok FA, Piazza G, Sharp ASP, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study. Am Heart J 2022: 251: 43-53.
23. The PEERLESS Study. https://ClinicalTrials.gov/show/NCT05111613.
24. Meneveau N, Séronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006: 129(4): 1043-1050.
25. den Exter PL, Kroft LJM, Gonsalves C, et al. Establishing diagnostic criteria and treatment of subsegmental pulmonary embolism: A Delphi analysis of experts. Research and practice in thrombosis and haemostasis 2020: 4(8): 1251-1261.
26. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature Reviews Disease Primers 2018: 4(1): 18028.
27. Wiener RS, Schwartz LMandWoloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011: 171(9): 831-837.
28. Wiener RS, Schwartz LMandWoloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. Bmj 2013: 347: f3368.
29. Carrier MandKlok FA. Symptomatic subsegmental pulmonary embolism: to treat or not to treat? Hematology American Society of Hematology Education Program 2017: 2017(1): 237-241.
30. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood 2013: 122(7): 1144-1149; quiz 1329.
31. Swan D, Hitchen S, Klok FA, et al. The problem of under-diagnosis and over-diagnosis of pulmonary embolism. Thromb Res 2019: 177: 122-129.
32. van der Pol LM, Bistervels IM, van Mens TE, et al. Lower prevalence of subsegmental pulmonary embolism after application of the YEARS diagnostic algorithm. British journal of haematology 2018: 183(4): 629-635.
33. Goodman LR. Small pulmonary emboli: what do we know? Radiology 2005: 234(3): 654-658.
34. Ghanima W, Nielssen BE, Holmen LO, et al. Multidetector computed tomography (MDCT) in the diagnosis of pulmonary embolism: interobserver agreement among radiologists with varied levels of experience. Acta Radiol 2007: 48(2): 165-170.
35. Pena E, Kimpton M, Dennie C, et al. Difference in interpretation of computed tomography pulmonary angiography diagnosis of subsegmental thrombosis in patients with suspected pulmonary embolism. J Thromb Haemost 2012: 10(3): 496-498.
36. Miller WT, Jr., Marinari LA, Barbosa E, Jr., et al. Small pulmonary artery defects are not reliable indicators of pulmonary embolism. Ann Am Thorac Soc 2015: 12(7): 1022-1029.
37. Gurney JW. No fooling around: direct visualization of pulmonary embolism. Radiology 1993: 188(3): 618-619.

38. Schoepf UJandCostello P. CT angiography for diagnosis of pulmonary embolism: state of the art. Radiology 2004: 230(2): 329-337.
39. Goy J, Lee J, Levine O, et al. Sub-segmental pulmonary embolism in three academic teaching hospitals: a review of management and outcomes. J Thromb Haemost 2015: 13(2): 214-218.
40. Mehta D, Barnett M, Zhou L, et al. Management and outcomes of single subsegmental pulmonary embolus: a retrospective audit at North Shore Hospital, New Zealand. Intern Med J 2014: 44(9): 872-876.
41. Donato AA, Khoche S, Santora J, et al. Clinical outcomes in patients with isolated subsegmental pulmonary emboli diagnosed by multidetector CT pulmonary angiography. Thromb Res 2010: 126(4): e266-270.
42. Cha SI, Shin KM, Lee JW, et al. Clinical characteristics of patients with peripheral pulmonary embolism. Respiration 2010: 80(6): 500-508.
43. Eyer BA, Goodman LRandWashington L. Clinicians' response to radiologists' reports of isolated subsegmental pulmonary embolism or inconclusive interpretation of pulmonary embolism using MDCT. AJR Am J Roentgenol 2005: 184(2): 623-628.
44. Le Gal G, Kovacs MJ, Bertoletti L, et al. Risk for Recurrent Venous Thromboembolism in Patients With Subsegmental Pulmonary Embolism Managed Without Anticoagulation. Annals of Internal Medicine 2021: 175(1): 29-35.
45. van der Hulle T, den Exter PL, Planquette B, et al. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. J Thromb Haemost 2016: 14(1): 105-113.
46. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007: 92(2): 199-205.
47. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med 2010: 170(19): 1710-1716.
48. den Exter PL, Kroft LJ, van der Hulle T, et al. Embolic burden of incidental pulmonary embolism diagnosed on routinely performed contrast-enhanced computed tomography imaging in cancer patients. J Thromb Haemost 2013: 11(8): 1620-1622.
49. den Exter PL, van der Hulle T, Hartmann IJ, et al. Reliability of diagnosing incidental pulmonary embolism in cancer patients. Thromb Res 2015: 136(3): 531-534.
50. Klok FAandHuisman MV. Management of incidental pulmonary embolism. The European respiratory journal 2017: 49(6).
51. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016: 149(2): 315-352.
52. Stein PD, Goodman LR, Hull RD, et al. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. Clin Appl Thromb Hemost 2012: 18(1): 20-26.
53. Jiménez D, Aujesky D, Díaz G, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med 2010: 181(9): 983-991.
54. Baumgartner C, Klok FA, Carrier M, et al. Clinical Surveillance vs. Anticoagulation For low-risk patiEnts with isolated SubSegmental Pulmonary Embolism: protocol for a multicentre randomised placebo-controlled non-inferiority trial (SAFE-SSPE). BMJ open 2020: 10(11): e040151.
55. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005: 172(8): 1041-1046.

56. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010: 170(15): 1383-1389.
57. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011: 378(9785): 41-48.
58. Zondag W, Hiddinga BI, Crobach MJT, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 2013: 41(3): 588-592.
59. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011: 9(8): 1500-1507.
60. den Exter PL, Zondag W, Klok FA, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial. Am J Respir Crit Care Med 2016: 194(8): 998-1006.
61. Roy PM, Penaloza A, Hugli O, et al. Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. Eur Heart J 2021: 42(33): 3146-3157.
62. Barco S, Mahmoudpour SH, Planquette B, et al. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2019: 40(11): 902-910.
63. Barco S, Schmidtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. Eur Heart J 2020: 41(4): 509-518.
64. Hendriks SV, Klok FA, den Exter PL, et al. Right Ventricle-to-Left Ventricle Diameter Ratio Measurement Seems to Have No Role in Low-Risk Patients with Pulmonary Embolism Treated at Home Triaged by Hestia Criteria. Am J Respir Crit Care Med 2020: 202(1): 138-141.
65. Hendriks SV, Lankeit M, den Exter PL, et al. Uncertain Value of High-sensitive Troponin T for Selecting Patients With Acute Pulmonary Embolism for Outpatient Treatment by Hestia Criteria. Acad Emerg Med 2020: 27(10): 1043-1046.
66. Hendriks SV, Bavalia R, van Bemmel T, et al. Current practice patterns of outpatient management of acute pulmonary embolism: A post-hoc analysis of the YEARS study. Thromb Res 2020: 193: 60-65.
67. Hendriks SV, van den Hout WB, van Bemmel T, et al. Home Treatment Compared to Initial Hospitalization in Normotensive Patients with Acute Pulmonary Embolism in the Netherlands: A Cost Analysis. Thromb Haemost 2022: 122(3): 427-433.
68. Bledsoe JR, Woller SC, Stevens SM, et al. Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. Chest 2018: 154(2): 249-256.
69. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
70. Klok FAandBarco S. Follow-up after acute Pulmonary Embolism. Hamostaseologie 2018: 38(1): 22-32.
71. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014: 28(6): 221-226.
72. Boon GJAM, Huisman MVandKlok FA. Determinants and Management of the Post-Pulmonary Embolism Syndrome. Seminars in respiratory and critical care medicine 2021: 42(02): 299-307.
73. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest 2017: 151(5): 1058-1068.

74. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010: 104(11): 1744-1749.
75. Le Gal G CM, Castellucci LA, et al. for the ISTHCDE Task Force. Development and implementation of common data elements for venous thromboembolism research:Official Communication from the SSC of the ISTH. J Thromb Haemost 2021: 19: 297–303.
76. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2022: 43(3): 183-189.
77. Boon G, Bogaard HJandKlok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. Research and practice in thrombosis and haemostasis 2020: 4(6): 958-968.
78. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. The European respiratory journal 2018: 52(6): 1801687.
79. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014: 112(3): 598-605.
80. Klok FA, Barco SandSiegerink B. Measuring functional limitations after venous thromboembolism: A call to action. Thromb Res 2019: 178: 59-62.
81. Boon GJAM, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale. Thromb Res 2020: 190: 45-51.
82. Gwozdz AM, de Jong CMM, Fialho LS, et al. Development of an international standard set of outcome measures for patients with venous thromboembolism: an International Consortium for Health Outcomes Measurement consensus recommendation. The Lancet Haematology 2022: 9(9): e698-e706.
83. Delcroix M, Torbicki A, Gopalan D, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. The European respiratory journal 2020: 57(6): 2002828.
84. Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Research 2021: 7(3): 00719-02020.
85. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by 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 for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). European Heart Journal 2022: 43(38): 3618-3731.
86. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
87. Klok FA, Surie S, Kempf T, 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): 21-26.
88. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016: 14(1): 121-128.
89. Boon G, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax Published Online First: 23 March 2021.

90. Ende-Verhaar YM, Huisman MVandKlok FA. To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Res 2017: 151: 1-7.
91. Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a Simple Noninvasive Screening Algorithm for Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism. TH Open 2018: 2(1): e89-e95.
92. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
93. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021.
94. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2022: 32(4): 2178-2187.
95. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 58(6).
96. Albaghdadi MS, Dudzinski DM, Giordano N, et al. Cardiopulmonary Exercise Testing in Patients Following Massive and Submassive Pulmonary Embolism. J Am Heart Assoc 2018: 7(5).
97. Kirchberger I, Ruile S, Linseisen J, et al. The lived experience with pulmonary embolism: A qualitative study using focus groups. Respir Med 2020: 167: 105978.
98. Danielsbacka JS, Rostberg L, Olsén MF, et al. "Whole life changed" - Experiences of how symptoms derived from acute pulmonary embolism affects life. A qualitative interview study. Thromb Res 2021: 205: 56-62.
99. Boon GJAM, Janssen SMJ, Barco S, et al. Efficacy and safety of a 12-week outpatient pulmonary rehabilitation program in Post-PE Syndrome. Thromb Res 2021: 206: 66-75.
100. Nopp S, Klok FA, Moik F, et al. Outpatient Pulmonary Rehabilitation in Patients with Persisting Symptoms after Pulmonary Embolism. Journal of clinical medicine 2020: 9(6): 1811.
101. Cires-Drouet RS, Mayorga-Carlin M, Toursavadkohi S, et al. Safety of exercise therapy after acute pulmonary embolism. Phlebology 2020: 35(10): 824-832.
102. Rolving N, Brocki BC, Bloch-Nielsen JR, et al. Effect of a Physiotherapist-Guided Home-Based Exercise Intervention on Physical Capacity and Patient-Reported Outcomes Among Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. JAMA network open 2020: 3(2): e200064.
103. Amoury M, Noack F, Kleeberg K, et al. Prognosis of patients with pulmonary embolism after rehabilitation. Vascular health and risk management 2018: 14: 183-187.
104. Noack F, Schmidt B, Amoury M, et al. Feasibility and safety of rehabilitation after venous thromboembolism. Vascular health and risk management 2015: 11: 397-401.
105. Lakoski SG, Savage PD, Berkman AM, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. J Thromb Haemost 2015: 13(7): 1238-1244.
106. Ghram A, Jenab Y, Soori R, et al. High-Intensity Interval Training in Patients with Pulmonary Embolism: A Randomized Controlled Trial. Med Sci Sports Exerc 2021: 53(10): 2037-2044.

Supplementary file

3

Safety of treating acute pulmonary embolism at home: an individual patient data meta-analysis

Dieuwke Luijten, Delphine Douillet, Kim Luijken, Cecile Tromeur, Andrea Penaloza, Olivier Hugli, Drahomir Aujesky, Stefano Barco, Joseph R. Bledsoe, Kyle E. Chang, Francis Couturaud, Paul L. den Exter, Carme Font, Menno V. Huisman, David Jimenez, Christopher Kabrhel, Jeffrey A. Kline, Stavros Konstantinides, Thijs van Mens, Remedios Otero, W. Frank Peacock, Olivier Sanchez, William B. Stubblefield, Luca Valerio, David R. Vinson, Philip Wells, Maarten van Smeden, Pierre-Marie Roy and Frederikus A. Klok

Eur Heart J. 2024 Aug 21;45(32):2933-2950

ABSTRACT

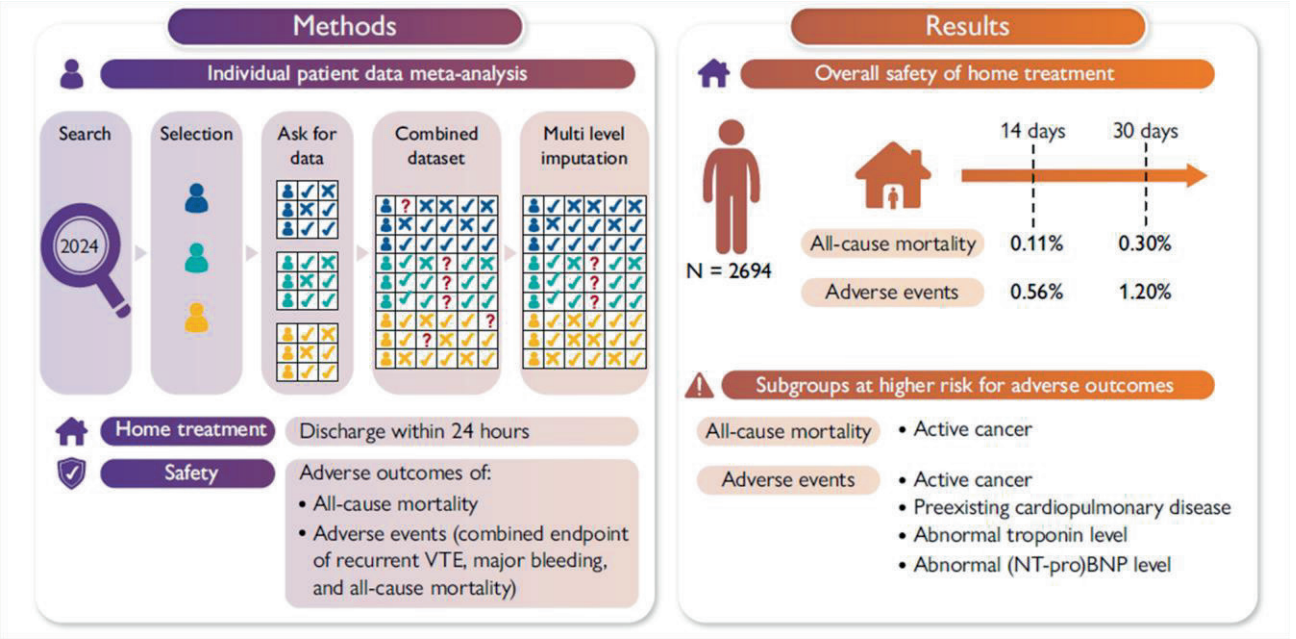
Background and Aims: Home treatment is considered safe in acute pulmonary embolism (PE) patients selected by a validated triage tool (e.g. simplified PE severity index score or Hestia rule), but there is uncertainty regarding the applicability in underrepresented subgroups. The aim was to evaluate the safety of home treatment by performing an individual patient-level data meta-analysis.

Methods: Ten prospective cohort studies or randomized controlled trials were identified in a systematic search, totalling 2694 PE patients treated at home (discharged within 24 h) and identified by a predefined triage tool. The 14- and 30-day incidences of all-cause mortality and adverse events (combined endpoint of recurrent venous thromboembolism, major bleeding, and/or all-cause mortality) were evaluated. The relative risk (RR) for 14- and 30-day mortalities and adverse events is calculated in subgroups using a random effects model.

Results: The 14- and 30-day mortalities were 0.11% (95% confidence interval (CI) 0.0–0.24, $I^2 = 0$) and 0.30% (95% CI 0.09–0.51, $I^2 = 0$). The 14- and 30-day incidences of adverse events were 0.56% (95% CI 0.28–0.84, $I^2 = 0$) and 1.2% (95% CI 0.79–1.6, $I^2 = 0$). Cancer was associated with increased 30-day mortality [RR 4.9; 95% prediction interval (PI) 2.7–9.1; $I^2 = 0$]. Pre-existing cardiopulmonary disease, abnormal troponin, and abnormal (N-terminal pro–)B-type natriuretic peptide [(NT-pro)BNP] at presentation were associated with an increased incidence of 14-day adverse events [RR 3.5 (95% PI 1.5–7.9, $I^2 = 0$), 2.5 (95% PI 1.3–4.9, $I^2 = 0$), and 3.9 (95% PI 1.6–9.8, $I^2 = 0$), respectively], but not mortality. At 30 days, cancer, abnormal troponin, and abnormal (NT-pro)BNP were associated with an increased incidence of adverse events [RR 2.7 (95% PI 1.4–5.2, $I^2 = 0$), 2.9 (95% PI 1.5–5.7, $I^2 = 0$), and 3.3 (95% PI 1.6–7.1, $I^2 = 0$), respectively].

Conclusions: The incidence of adverse events in home-treated PE patients, selected by a validated triage tool, was very low. Patients with cancer had a three- to five-fold higher incidence of adverse events and death. Patients with increased troponin or (NT-pro)BNP had a three-fold higher risk of adverse events, driven by recurrent venous thromboembolism and bleeding.

GRAPHICAL ABSTRACT



Abbreviations: IPDMA individual patient data meta-analysis; (NT-pro)BNP (N-terminal pro–)B-type natriuretic peptide; PE pulmonary embolism; VTE venous thromboembolism.

INTRODUCTION

Acute pulmonary embolism (PE) has a broad spectrum of clinical presentations.[1, 2] Haemodynamically unstable patients as well as stable patients with an elevated risk of deterioration due to obstructive shock or respiratory failure should be hospitalized and closely monitored, while others might be eligible for immediate discharge and home treatment. As home treatment is associated with high patient satisfaction and lower healthcare costs, identification of acute PE patients with no medical contraindication to home treatment is relevant for both individuals, local hospital governance, and society.[3-5]

The PE Severity Index (PESI) and the simplified PESI (sPESI) are clinical prognostic models estimating the absolute 30-day mortality.[6-8] The Hestia rule consists of a checklist of 11 indications to hospitalize PE patients (**Table 1).**[9, 10] Strategies based on either of these triage tools have proven safe to select PE patients eligible for home treatment, with low rates of adverse events.[8-11]

However, most studies evaluating the safety of home treatment included relatively low numbers of patients and were conducted in single centres, resulting in broad confidence intervals (CIs) around the incidences of adverse outcomes. Moreover, specific patient subgroups, e.g., those with cancer, serious comorbidities or intermediate-risk PE were underrepresented or even excluded, fuelling discussion on the applicability of the trial results to these groups.[12-14]

We performed a systematic review and individual patient-data meta-analysis (IPDMA) to estimate the overall incidence of adverse events in patients with acute PE who received home treatment and were selected using validated triage tools. We aimed to estimate incidences of adverse events in predefined clinically relevant patient subgroups.

METHODS

Search strategy and selection criteria

We conducted a systematic literature search up to January 2024 for all relevant publications in PubMed, Embase, Web of Science, Cochrane Library, Emcare, Academic Search Premier, the WHO COVID-19 database and Google scholar (see **Supplementary data online, Appendix A**). Relevant publications were independently assessed for eligibility in duplicate by four individual authors (D.L., D.D., C.T. and F.A.K.). Discrepancies were resolved by discussion. Study designs

eligible for inclusion were (I) prospective cohort studies or randomized controlled trials investigating different algorithms to assess eligibility for home treatment, with (II) established acute symptomatic or incidental acute PE patients involving subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiogram (CTPA) or a high-probability ventilation/perfusion (VQ) imaging, (III) who were managed according to a predefined algorithm determining initiation of initial treatment as in- or outpatient, (IV) with a minimum follow-up duration of one month, (V) reporting at least one of the predefined outcomes, and (VI) including a minimum of 50 patients treated at home.

Lead investigators of the included studies were invited to provide de-identified individual patient data (IPD) of patients who received home treatment upon diagnosis. Patients with a PE diagnosis during hospitalization (>48 h) were excluded from this study. Individual patient information was collected, including demographics, risk factors for venous thromboembolism (VTE), comorbidities, items for evaluation of PE severity (e.g., vital signs, laboratory results, presence of right ventricular (RV) overload and/or dysfunction) and time until discharge from the hospital **(Appendix B**). All available data on the occurrence of recurrent VTE, bleeding complications, mortality, and loss to follow up according to the pre-specified definitions from the protocol were collected. Data from the original studies were converted to a universal database either by the primary researcher of the original study or by the lead investigator of this IPDMA. Correctness of conversion was performed by repeating analysis of the original studies in the new data set to identify nonmatching results.

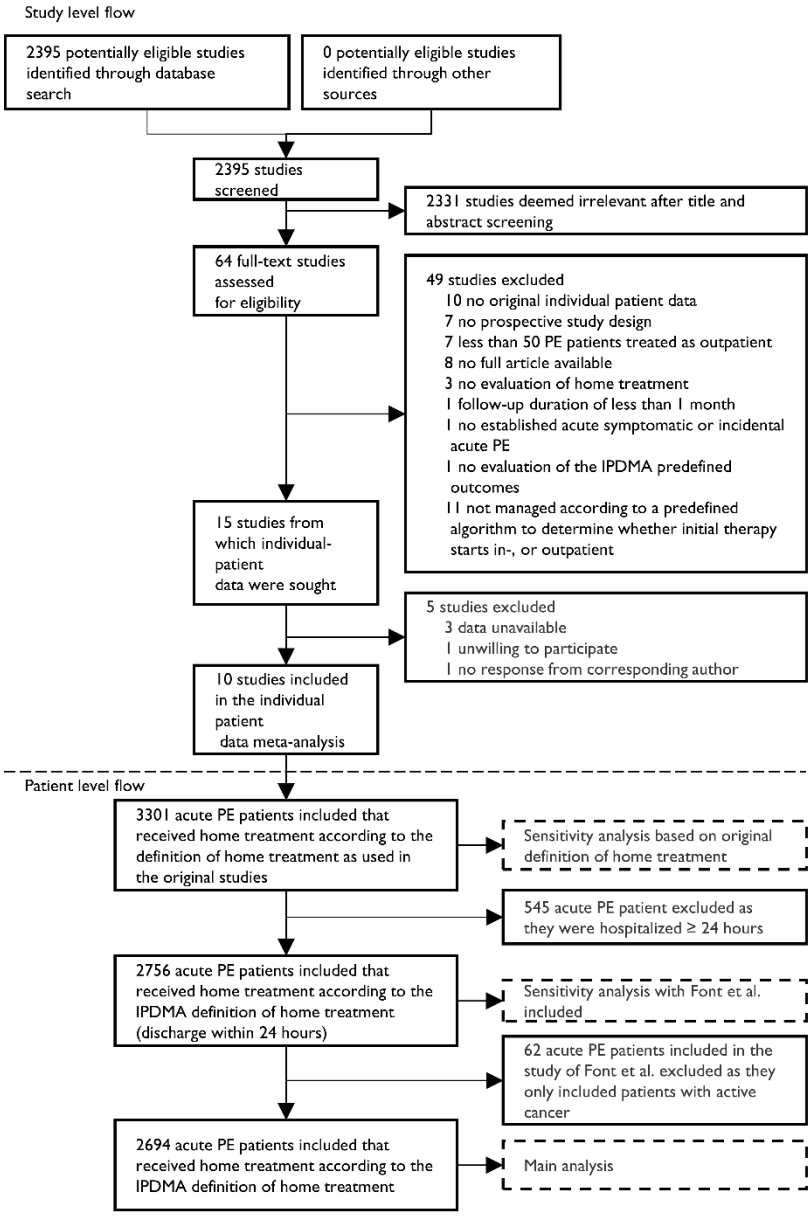
Risk of bias was evaluated using a modified version of the Newcastle Ottawa Scale (NOS) for observational studies.[15] For the risk of bias analysis, each arm of a randomized trial was considered as an independent observational cohort. Studies were eligible to be awarded a maximum of three stars for quality of patient selection, as well as for outcome assessment. A study was considered at low risk of bias when achieving three stars in selection and two or three stars in outcome, at moderate risk of bias with two stars in selection and two or three stars in outcome, and at high risk of bias with zero or one star in selection or zero or one star in outcome. The evaluation of the risk of bias was independently performed by two researchers (D.D. and D.L.) and disagreements were resolved by discussion or by consultation of a third researcher (F.A.K.) if the two researchers could not agree.

Table 1: Hestia rule, PESI and sPESI

Hestia	Answer	PESI	Points	sPESI	Points
Is the patient hemodynamically unstable? [a]	Yes /No	Age	Years	Age >80 years	1
Is thrombolysis or embolectomy necessary?	Yes /No	Male sex	+ 10	History of cancer	1
Active bleeding or high risk of bleeding?[b]	Yes /No	History of cancer	+ 30	Chronic cardiopulmonary disease	1
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?	Yes /No	History of heart failure	+ 10	Systolic blood pressure <100mmHg	1
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes /No	History of chronic lung disease	+ 10	Heart rate ≥110 b.p.m.	1
Severe pain needing intravenous pain medication for more than 24 h?	Yes /No	Heart rate ≥110 b.p.m.	+ 20	Arterial oxygen saturation <90%	1
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)[c]?	Yes /No	Systolic blood pressure <100mmHg	+ 30		
Does the patient have a creatinine clearance of < 30 mL/min?[d]	Yes /No	Respiratory rate ≥30	+ 20		
Does the patient have severe liver impairment?[e]	Yes /No	Temperature <36°C/96.8°F	+ 20		
Is the patient pregnant?	Yes /No	Altered mental status (disorientation, lethargy, stupor, or coma)	+ 60		
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes /No	Arterial oxygen saturation <90%	+ 20		
If all questions can be answered with 'No' the patient has a negative Hestia rule and is eligible for home treatment		If the PESI class is I (total score of 0-65) or II (total score of 66-85) a patient is eligible for home treatment		If the sPESI = 0, a patient is eligible for home treatment.	

a Include the following criteria but leave these to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats min–1; condition requiring admission to an intensive care unit. b Gastrointestinal bleeding in the preceding 14 days, recent stroke (< 4 weeks ago), recent operation (< 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 . 109 L-1), uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg). c This subjective item allows to hospitalize patients based on medical or social reasons needing hospitalization. However, since it is a subjective item, interpretation on when a patients required hospitalization based on this item can very. For example, not all patients with active cancer were assessed to require hospitalization based on their malignancy and thus received home treatment in the original studies. d Calculated creatinine clearance according to the Cockcroft–Gault formula. e Left to the discretion of the physician. Abbreviations: b.p.m. beats per minute; h hour; PESI pulmonary embolism severity index; sPESI simplified pulmonary embolism index

Figure 1 Flowchart of included studies.



Above the dashed line is the study flowchart on study level. We included 10 studies in our IPDMA. Below the dashed line is the study flowchart on patient-level data. The main analysis was performed only with patients who were discharged within 24 h. IPDMA, individual patient data meta-analysis; PE, pulmonary embolism.

Outcomes

Our primary aim was to evaluate the safety of home treatment in the overall population by calculating the 14-day incidence of all-cause mortality and adverse events (i.e. a combined endpoint of recurrent VTE, major bleeding and all-cause mortality). We defined home treatment as discharge from the hospital within 24 h after diagnosis of PE, randomization, or emergency department registration; this meant that patients who were hospitalized for >24 h were excluded from our main analysis (**Figure 1b**). We also evaluated other adverse outcomes: (I) 30-day incidences of all-cause mortality and of adverse events, (II) 14- and 30-day incidences of recurrent VTE and (III) 14- and 30-day incidence of major bleeding[16].

The secondary aims of this study were to evaluate all-cause mortality and adverse outcomes in relevant patient subgroups. The following pre-defined subgroups were evaluated based on the presence or absence of the following characteristics: symptomatic vs. incidental PE, cancer, decreased kidney function, pre-existing cardiopulmonary disease, abnormal (N-terminal pro–)B-type natriuretic peptide ((NT-pro)BNP), abnormal troponin, RV overload, RV dysfunction and the applied triage tool (i.e. Hestia or sPESI/PESI). Definitions of these subgroups are described in appendix C. Cancer was considered active if meeting at least one of the following criteria: (I) current diagnosis of cancer, (II) receiving treatment for cancer or (III) not receiving treatment for cancer and not in complete remission (e.g. palliative patients).[17]

Statistical analysis

Baseline characteristics were described using median and interquartile range (IQR) or mean and standard deviation (SD) for continuous variables and counts and proportions for categorical variables.

Data included in our analysis were missing with proportions ranging from 1 to 62% (**Appendix D, Table S1**)**.** Values non-completely missing were handled using multiple imputations by chained equations with a fixed-effect approach, taking study into account as a cluster variable using the mice package (**Appendix E**).[18, 19] Using fully conditional specifications, we defined an imputation model containing all subgroup variables and the outcomes at 14 days for imputation and added auxiliary variables to improve imputation. The number of imputed data sets was 75 and the number of iterations per imputation was 50. When values were completely missing in a study (i.e. a variable was 100% missing within a certain

study), missing variables were not handled using imputations; these variables remained missing for all individuals derived from that study (**Appendix B, Table S1**). Individuals with missing subgroup or outcome data were excluded from the corresponding analysis after imputation.[20, 21]

Overall and for each subgroup, the incidence of each safety measure was calculated as a proportion at the corresponding prediction time point averaged over the included studies (i.e. using a fixed effects approach). Proportion and standard error were calculated across imputed data sets using Rubin's rules and 95% CI were computed by a Wald interval.[22]

We calculated the relative risk (RR) for adverse events when a subgroup characteristic was present vs. absent. Relative risks were estimated in each study using a penalized log-binomial model with the subgroup variable as the only independent variable and calculated over imputed data sets using Rubin's rules to arrive at an estimate of the RR for each study.[22] Single value studies (e.g., subgroup characteristic was present in all patients or absent in all patients; **Appendix B, Table S1**) were excluded from this analysis. Due to very low event fractions across studies and even zero events in some cases, a Firth's correction was applied using the brglm2 package.[23, 24] To arrive at an overall RR across studies, we subsequently used a random effects model with restricted maximum likelihood estimation to derive prediction intervals (PIs).

For the evaluation of specific triage tools to assess eligibility for home treatment, studies were only included in the subgroup strategy of the tool that was originally used in the study to assess eligibility. Subsequently incidence of adverse events was calculated with a corresponding 95% CI for each tool. No direct statistical comparison across different tools was performed due to the methodological challenge of comparing outcomes across distinct study designs and populations, emphasizing the descriptive nature of this sub-analysis.

We performed three sensitivity analyses. First, the definition of home treatment in the studies, e.g., Barco et al[25] (discharge within 48 h) and Otero et al[26] (discharge within 72-120 h), varied from our IPDMA definition of home treatment. We performed a sensitivity analysis that included all patients who did not meet the IPDMA definition of home treatment of discharge within 24 h (excluded from main analysis) but were treated at home according to the definition of home treatment of the original study (**Figure 1b**). Second, as Font et al.[27] included only patients with cancer, this study may not be an accurate representation of low-risk acute PE patients who received home treatment and was therefore excluded from

the main analysis. However, to maximize the utilization of available data and ensure that the valuable information that these patients hold contributed to a comprehensive assessment of home treatment safety across different patient profiles, we performed a sensitivity analysis for the overall safety by including the study by Font et al.[27] Finally, as we used multiple imputations to handle missing data, but as we did not have exact information on how each variable was collected in a data set, we cannot guarantee that missing values were truly missing at random, potentially influencing the imputation model. We therefore performed a sensitivity analysis of the overall safety based on the non-imputed complete case data. The sensitivity analyses were performed to explore robustness of our results and not to establish statistical significance compared with the main analysis. Therefore, no significance tests were performed as part of this analysis.

All analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

RESULTS

Included studies

The literature search resulted in 2395 studies, of which 64 full texts were screened for eligibility. Fifteen studies met the predefined inclusion and none for the exclusion criteria. Their corresponding authors were contacted with a request to share de-identified IPD. Data of 10 studies were shared and included in our study (**Figure 1**). Nine studies had a low risk of bias and one study a moderate risk of bias[27]: potential selection bias as only patients with cancer were included; Appendix D, Table S2). As Font et al.[27] included only patients with cancer, this study may not be an accurate representation of low-risk acute PE patients who received home treatment and was therefore excluded from the main analysis, characteristics of the included studies are summarized in **Table 2**. There were no important issues when checking the IPD.

Outcomes

Patients

A total of 3301 acute PE patients received home treatment, according to the definition of home treatment in the original studies. Of these, 2756 (83%) were discharged within 24 h. Excluding Font et al. resulted in a total of 2694 acute PE patients discharged within 24 h (**Figure 1**). The following triage tools were used in the studies to assess eligibility for home treatment: I) Hestia rule (none of the 11 items present; with/without RV overload/dysfunction), II) sPESI (0 points) or PESI (class I-II) in combination with clinical judgement (with/without RV overload/dysfunction), or III) a list of inclusion and exclusion criteria predefined to select eligible patients for home treatment not based on Hestia/sPESI. The characteristics after imputation of patients discharged within 24 h are depicted in **Table 3**.

All-cause mortality

Table 4 presents the overall incidence of safety outcomes at 14- and 30 days in patients discharged within 24 h. At 14 days, three patients had died, corresponding to a pooled 14-day mortality of 0.11% (95%CI 0.0-0.24). One had a PE-related death, one had a major bleeding-related death, one died due to a cause other than PE or major bleeding. The 14-day incidence of combined adverse events was 0.56% (95%CI 0.28-0.84), 0.34% (95%CI 0.12-0.56) for recurrent VTE, and 0.19% (95%CI 0.03-0.35) for major bleeding.

At 30 days, eight patients had died, corresponding to a pooled 30-day mortality of 0.30% (95%CI 0.09-0.51). Two out of eight had a PE-related death, one had a major bleeding-related death, and five died due to a cause other than PE or major bleeding. The 30-day incidence of all adverse events was 1.2% (95%CI 0.79-1.6), 0.57% (95%CI 0.28-0.86) for recurrent VTE and 0.45% (95%CI 0.19-171) for major bleeding.

Age and sex were not associated with an increased 14- or 30-day mortality (**Figure 2**, **Table 5 and 6**). In terms of cardiopulmonary comorbidities and signs of RV dysfunction (i.e. RV/LV ratio>0.9, elevated cardiac biomarkers), no subgroup was associated with an increased 14- or 30-day mortality. Only patients with cancer had an increased 30-day mortality (RR 4.9; 95% PI 2.7-9.1; **Table 6**).

Table 2: characteristics of included studies

Study	Primary study goal	Study period	Selection of low risk patients	Follow-up time (in days)	Outcome ad-judication	PE patients treated at home according to the	
						study definition, n (% of total study population)	IPDMA definition of home treatment, n (% of previous column)
Barco et al.[25] [HoT-PE]	Evaluate the efficacy and safety of home treatment in low risk acute PE patient treated with rivaroxaban	05-2014 – 06-2018	Negative Hestia rule and no RV dysfunction or intracardiac thrombi	90	Yes	520 (100)§	170 (32)β
Bledsoe et al.[3]	Evaluate the efficacy and safety outpatient treatment in low risk acute PE patients	01-2013 10-2016	PESI class I or II with a list of exclusion criteria including RV dysfunction on echocardiography	90	No	200 (100)π	192 (96) β
Exter et al.[28] [Vesta]	Evaluate the utility and safety of the Hestia rule versus Hestia rule in combination with NT-proBNP testing for selection of outpatient PE treatment	12-2010 – 02-2014	Negative Hestia rule with/without negative NT-proBNP testing	90	Yes	513 (93) ¥	513 (100)×
Font et al.[27]	Evaluate the feasibility of outpatient treatment in patients with cancer and PE	05-2006 – 12-2009	Negative Hestia-like criteria: systolic blood pressure < 100 mm Hg, arterial oxygen pressure < 60 mm Hg or pulse oximetry <90%, active bleeding, platelet count ≥50,000 /mm3, renal failure, lack of social support, poor treatment compliance, or the presence of other admission criteria according to treating physicians.	90	Yes	62 (45)α	62 (100)α
Kabrhel et al. [29]	Determine whether a protocol combining risk stratification, treatment with rivaroxaban, and defined follow-up is associated with a greater proportion of patients with VTE treated as outpatients	09-2015 - unknown	Negative: social of psychological barrier, abnormal vital signs, coronary artery disease or congestive heart failure, elevated troponin, high risk of bleeding, large PE, intermediate PE with RV dysfunction, high risk DVT	28±	No	164 (25)#	122 (74)∞

Kline et al.[30] [MATH-VTE]	Evaluate the safety and efficacy of home treatment with a DOAC in low risk acute PE patient presented at the emergency department	04-2016 – 03-2019	Negative modified Hestia rule or sPESI of 0 plus physician judgement	30	No	604 (100) £	604 (100)£
Otero et al.[26]	Evaluate efficacy and safety of early discharge in patients with low risk according to a clinical prediction rule	02-2005 – 04-2007	≤2 points on a clinical prediction score, hemodynamic instability, troponin >= 0.1 ng/mL, saturation <93%, need for hospitalization for comorbidities, severe COPD, severe asthma, active or high risk of bleeding, pregnancy, morbid obesity or RV dysfunction	30	No	72 (55)Ω	0 (0) ×
Roy et al.[11] [HOME-PE]	Evaluate safety and efficacy of Hestia versus sPESI in the selection of outpatient PE treatment	01-2017 – 07-2019	Negative Hestia rule or sPESI of 0 (overruling by clinician possible)	30	Yes	739 (38)†	681 (92)∞
Vinson et al.[31] [eSPEED]	Evaluate the effect of an integrated electronic clinical decision support system to facilitate risk stratification and decision for selection of outpatient PE treatment	01-2014 – 04-2015	PESI class I or II with a broad list of relative contraindications from variables from the Ottawa and Hestia exclusion criteria (including absence of RV dysfunction)	30	No	130 (19)¥	116 (89)∞
Zondag et al.[9, 10] [Hestia]	Evaluate the efficacy and safety of outpatient treatment according to the Hestia rule in patients with acute PE	05-2008 – 04-2010	Negative Hestia rule	90	Yes	297 (100)¥	296 (100)×

Since follow-up was only 28 days we used 28 days as a surrogate measurement for incidence within 30 days for Kabhrel et al. § Discharge from the hospital within 48h of presentation; π observation or hospitalization for >12 to <24 hours; ¥ discharge from the hospital within 24 hours of PE diagnosis; α discharge within 12 hours after PE diagnosis; † discharge within 24 hours of presentation or randomization; £ discharge within 24 hours after triage; Ω discharge at 72 or 120 hours (61 and 39% respectively); β within 24 hours after randomization/inclusion; × within 24 hours after acute PE diagnosis; ∞ within 24 hours after ED presentation; # discharged directly from the ED or admitted to the ED observation unit with a plan for discharge; ± Abbreviations: DOAC direct oral anticoagulant; DVT deep vein thrombosis; N-terminal pro–B-type natriuretic peptide NTproBNP; PE pulmonary embolism; PESI pulmonary embolism severity index; RV right ventricle; sPESI simplified pulmonary embolism index; VTE venous thromboembolism

Table 3: characteristics patients that received home treatment (defined as discharge within 24 hours)

Study, year (reference)	Overall	Zondag et al., 2011[9, 10]	Exter et al., 2016[28]	Roy et al., 2021[11]	Kline et al., 2021[30]	Barco et al., 2020[25]	Kabrhel et al., 2019[29]	Font et al., 2014[27]	Vinson et al., 2018[31]	Bledsoe et al., 2018[3]
Patients, n	2756	296	513	681	604	170	122	62	116	192
Mean age (SD)	54.0 (16.0)	54.5 (15.4)	53.5 (14.7)	56.4 (16.2)	52.0 (16.6)	54.5 (16.0)	55.4 (16.4)	62.5 (10.3)	60.3 (15.1)	44.4 (14.3)
Female, n (%)	1307 (47%)	124 (42%)	235 (46%)	314 (46%)	301 (50%)	80 (47%)	64 (52%)	25 (40%)	61 (53%)	103 (54%)
Triage tool applied, n (%)										
Negative Hestia (or Hestia like) rule	1685 (61%)	296 (100%)	513 (100%)	351 (51%)	463 (77%)	0 (0%)	0 (0%)	62 (100%)	0 (0%)	0 (0%)
sPESI 0 or PESI I/IIα	471 (17%)	0 (0%)	0 (0%)	330 (49%)	141 (23%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
sPESI 0 or PESI I/II and absence of RVDα	308 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	116 (100%)	192 (100%)
Negative Hestia (or Hestia like) criteria and absence of RVD	170 (6.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	170 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other tool	122 (4.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	122 (100%)	0 (0%)	0 (0%)	0 (0%)
Treatment with a DOAC, n (%)	1550 (59%)	0 (0%)	3 (1%)	565 (83%)	604 (100%)	170 (100%)	43 (35%)	0 (0%)	*	165 (86%)
Risk factors, n (%)										
Recent immobilization or surgery	300 (12%)	27 (9%)	69 (13%)	68 (10%)	54 (9%)	26 (15%)	17 (14%)	39 (63%)	*	*
Estrogen use	297 (12%)	47 (16%)	91 (18%)	64 (9%)	41 (7%)	31 (18%)	8 (7%)	8 (13%)	8 (7%)	*
Symptomatic PE, n (%)	1659 (96%)	296 (100%)	513 (100%)	681 (100%)	*	155 (91%)	*	14 (23%)	*	*
Vital signs at presentation[€], n (%)										
Heart rate ≥110/min	223 (8%)	27 (9%)	35 (7%)	63 (9%)	62 (10%)	3 (2%)	*	0 (0%)	15 (13%)	18 (9%)
Respiratory rate of ≥ 30/min	13 (1%)	*	*	*	5 (1%)	2 (1%)	*	*	4 (3%)	2 (1%)

Oxygen saturation <90% or need for oxygen	54 (2%)	19 (6%)	4 (1%)	23 (3%)	2 (0%)	1 (1%)	*	0 (0%)	5 (4%)	0 (0%)
Comorbidities, n (%)										
Cancer#	289 (10%)	28 (9%)	34 (7%)	50 (7%)	24 (4%)	19 (11%)	55 (45%)	62 (100%)	16 (14%)	2 (1%)
Previous VTE	846 (32%)	74 (25%)	120 (23%)	169 (25%)	375 (62%)	34 (20%)	34 (28%)	4 (6%)	*	37 (19%)
Decreased kidney function^	210 (8%)	12 (4%)	22 (4%)	66 (10%)	67 (11%)	12 (7%)	11 (9%)	2 (3%)	11 (9%)	6 (3%)
Preexisting cardio-pulmonary disease¥	504 (18%)	12 (4%)	25 (5%)	161 (24%)	186 (31%)	12 (7%)	30 (25%)	17 (27%)	28 (24%)	32 (17%)
Laboratory/imaging results, n (%)										
Abnormal troponinΩ	251 (11%)	*	67 (13%)	117 (17%)	53 (9%)	*	4 (3%)	*	9 (8%)	1 (1%)
Abnormal (NT-pro)BNP±	234 (10%)	*	27 (5%)	78 (11%)	80 (13%)	10 (6%)	11 (9%)	*	21 (18%)	6 (3%)
RV overload§	351 (26%)	201 (68%)	*	106 (16%)	*	9 (5%)	15 (12%)	21 (34%)	*	*
RVD on echocardiography	31 (3%)	*	*	*	20 (3%)	0 (0%)	6 (5%)	*	3 (3%)	2 (1%)

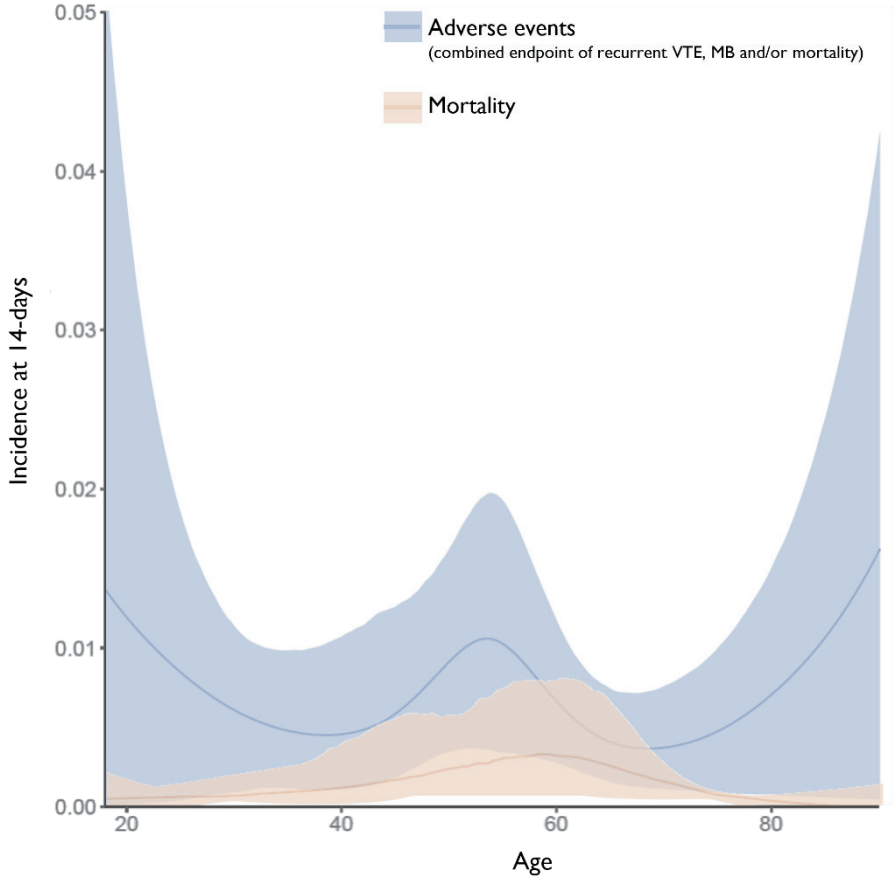
* Variable systematically missing within a study. α in combination with a negative clinical judgement € Vinson et al. reported the worst vital signs throughout the hole of the patients' ED stay # cancer was defined as (1) a current diagnosis of cancer, (2) receiving treatment for cancer or (3) not receiving treatment for cancer and not in complete response; ^Estimated Glomerular Filtration Rate < 60 ml/min; ¥Preexisting pulmonary disease was defined as a history of chronic obstructive pulmonary disease, asthma, or lung fibrosis, a preexisting cardiovascular disease, defined as any of coronary artery disease, heart failure, congenital heart disease, cardiomyopathy or rheumatic heart disease ; ΩAbnormal troponin was defined as a troponin level >99th percentile according to local technique; ± NT-proBNP > 500 ng/L or BNP level >100 ng/L ; §Right ventricle/ left ventricle ratio >0.9 on computed tomography pulmonary angiogram or echocardiogram. Abbreviation: DOAC direct oral anticoagulant; PE pulmonary embolism; RV right ventricular; RVD right ventricle dysfunction SD standard deviation; VTE venous thromboembolism; RV/LV right ventricle/left ventricle

Table 4: overall incidence of safety

outcomes	14-day	30-day
All-cause mortality, %, (95%CI)		
All patients discharged within 24 hours	0.11 (0.0 to 0.24)	0.30 (0.09 to 0.51)
Including Font et al.	0.18 (0.02 to 0.34)	0.37 (0.14 to 0.60)
Triage tool: Hestia (or Hestia-like) rule	0.19 (0.0 to 0.40)	0.31 (0.04 to 0.58)
Triage tool: PESI or sPESI*	0.0 (0.0 to 0.0)	0.21 (0.0 to 0.63)
All patients discharged within 120 hours	0.25 (0.08 to 0.42)	0.40 (0.18 to 0.62)
Recurrent VTE, %, (95%CI)		
All patients discharged within 24 hours	0.34 (0.12 to 0.56)	0.57 (0.28 to 0.86)
Including Font et al.	0.37 (0.14 to 0.60)	0.59 (0.30 to 0.88)
Triage tool: Hestia (or Hestia like) rule	0.52 (0.17 to 0.87)	0.80 (0.36 to 1.2)
Triage tool: PESI or sPESI*	0.11 (0.0 to 0.41)	0.43 (0.0 to 1.0)
All patients discharged within 120 hours	0.43 (0.20 to 0.66)	0.65 (0.37 to 0.93)
Major bleeding, %, (95%CI)		
All patients discharged within 24 hours	0.19 (0.03 to 0.35)	0.45 (0.19 to 0.71)
Including Font et al.	0.22 (0.04 to 0.40)	0.52 (0.25 to 0.79)
Triage tool: Hestia (or Hestia like) rule	0.35 (0.06 to 0.64)	0.62 (0.24 to 1)
Triage tool: PESI or sPESI*	0.0 (0.0 to 0.0)	0.43 (0.0 to 1.0)
All patients discharged within 120 hours	0.28 (0.10 to 0.46)	0.53 (0.28 to 0.78)
Combined endpoint, %, (95%CI)		
All patients discharged within 24 hours	0.56 (0.28 to 0.84)	1.2 (0.79 to 1.6)
Including Font et al.	0.66 (0.36 to 0.96)	1.3 (0.90 to 1.8)
Triage tool: Hestia (or Hestia like) rule	0.86 (0.41 to 1.31)	1.5 (0.94 to 2.1)
Triage tool: PESI or sPESI*	0.21 (0.0 to 0.63)	1.1 (0.13 to 2.0)
All patients discharged within 120 hours	0.77 (0.47 to 1.1)	1.4 (0.96 to 1.8)

***** in combination with a negative clinical judgement Abbreviations: PESI pulmonary embolism severity index; sPESI simplified pulmonary embolism index

Figure 2 Incidence (%) of 14-day adverse events and mortality with 95% prediction intervals vs. age (in years) as a continuous variable.



For distribution of age, see Supplementary data online, Appendix D; Figure S2. MB, major bleeding; VTE, venous thromboembolism

Table 5: Combined endpoint and mortality at 14 days of all patients that were discharged withing 24 hours

		Combined endpoint of VTE MB or all-cause morality					
		Events (n)	Patients (n)	%	(95%CI)	RR	(95%PI)
Overall		15	2660	0.56	(0.28 to 0.84)		
Age	18-40*	3	580	0.52	(0.0 to 1.1)		
	41-60	8	1086	0.74	(0.23 to 1.3)	1.10	(0.66 to 1.8)
	61-80	4	894	0.45	(0.01 to 0.8)	0.96	(0.48 to 1.4)
	>81	0	99	0.00	(0.0 to 0.0)	0.77	(0.52 to 1.2)
Sex	Female	6	1264	0.47	(0.09 to 0.85)	1.1	(0.48 to 2.4)
	Male*	9	1396	0.64	(0.22 to 1.1)		
Symptoms	Incidental	0	15	0.00	(0.0 to 0.0)	1.0	(0.0 to 1005)
	Symptomatic*	10	1641	0.61	(0.23 to 0.99)		
Treatment	LMWH or VKA	7	1012	0.69	(0.18 to 1.2)	1.3	(0.78 to 2.3)
	DOAC*	8	1532	0.52	(0.16 to 0.88)		
Cancer[#]	Yes	1	217	0.46	(0.0 to 1.4)	1.7	(0.7 to 3.9)
	No*	14	2443	0.57	(0.27 to 0.87)		
Previous VTE	Yes	7	830	0.81	(0.2 to 1.4)	1.3	(0.55 to 3.3)
	No*	8	1714	0.48	(0.15 to 0.81)		
Decreased kidney function^	Yes	1	203	0.25	(0.0 to 0.94)	0.47	(0.22 to 1)
	No*	14	2457	0.59	(0.29 to 0.89)		
Preexisting cardio-pulmonary disease[¥]	Yes	6	479	1.30	(0.29 to 2.3)	3.5	(1.5 to 7.9)
	No*	9	2181	0.40	(0.13 to 0.67)		
Abnormal troponin[Ω]	Yes	3	249	1.23	(0.0 to 2.6)	2.5	(1.3 to 4.9)
	No*	8	1946	0.41	(0.13 to 0.69)		
Abnormal (NT-pro) BNP[±]	Yes	3	210	1.60	(0.0 to 3.3)	3.9	(1.6 to 9.8)
	No*	8	2154	0.35	(0.1 to 0.6)		
Signs of RV overload§	Yes	5	326	1.69	(0.29 to 3.1)	2.7	(0.62 to 11)
	No*	3	910	0.28	(0.0 to 0.62)		

This table presents the 14-day incidence of the combined endpoint of VTE, MB or all-cause mortality and the 14-day incidence of all-cause mortality. I2 were all 0% for all analysis, except for: a I2= 0.68% * RR presents the ratio of the risk for an event for the exposure group to the risk for the non-exposure/reference group; non-exposure/reference group is marked with an asterisk # (1) Current diagnosis of cancer, (2) receiving treatment for cancer or (3) not receiving treatment for cancer and not in complete response;

Table 5 continued

		All-cause morality					
		Events (n)	Patients (n)	%	(95%CI)	RR	(95%PI)
Overall		3	2664	0.11	(0.0 to 0.24)		
Age	18-40*	0	582	0.00	(0.0 to 0.0)		
	41-60	2	1086	0.18	(0.0 to 0.44)	1.28	(0.9 to 1.82)
	61-80	1	896	0.11	(0.0 to 0.33)	1.14	(0.86 to 1.5)
	>81	0	99	0.00	(0.0 to 0)	NA	NA
Sex	Female	2	1266	0.16	(0.0 to 0.38)	1.3	(0.65 to 2.5)
	Male*	1	1398	0.07	(0.0 to 0.21)		
Symptoms	Incidental	0	15	0.00	(0.0 to 0.0)	1.0	(0.0 to 1005)
	Sympto-matic*	3	1641	0.18	(0.0 to 0.39)		
Treatment	LMWH or VKA	3	1014	0.30	(0.0 to 0.63)	3.1	(0.17 to 56)
	DOAC*	0	1534	0.00	(0.0 to 0)		
Cancer[#]	Yes	1	219	0.46	(0.0 to 1.4)	2.9	(0.8 to 10)
	No*	2	2445	0.08	(0.0 to 0.19)		
Previous VTE	Yes	1	831	0.12	(0.0 to 0.36)	1.3	(0.49 to 3.4)
	No*	2	1717	0.12	(0.0 to 0.28)		
Decreased kidney function^	Yes	0	203	0.00	(0.0 to 0.0)	0.78	(0.58 to 1.1)
	No*	3	2461	0.12	(0.0 to 0.26)		
Preexisting cardio-pulmonary disease[¥]	Yes	1	480	0.28	(0.0 to 0.75)	2. 70[a]	(0.68 to 11)
	No*	2	2184	0.08	(0.0 to 0.2)		
Abnormal troponin[Ω]	Yes	0	249	0.14	(0.0 to 0.6)	0.86	(0.56 to 1.3)
	No*	2	1950	0.08	(0.0 to 0.21)		
Abnormal (NT-pro)BNP[±]	Yes	3	2664	0.11	(0.0 to 0.24)		
	No*	0	582	0.00	(0.0 to 0.0)		
Signs of RV overload[§]	Yes	2	1086	0.18	(0.0 to 0.44)	1.28	(0.9 to 1.82)
	No*	1	896	0.11	(0.0 to 0.33)	1.14	(0.86 to 1.5)

^Estimated Glomerular Filtration Rate < 60 ml/min; ¥Preexisting pulmonary disease was defined as a history of chronic obstructive pulmonary disease, asthma, or lung fibrosis, a preexisting cardiovascular disease, defined as any of coronary artery disease, heart failure, congenital heart disease, cardiomyopathy or rheumatic heart disease; ΩAbnormal troponin was defined as a troponin level >99th percentile according to local technique; ± NT-proBNP > 500 ng/L or BNP level >100 ng/L ; §Right ventricle/ left ventricle ratio >0.9 on computed tomography pulmonary angiogram or echocardiogram; Abbreviations: CI, confidence interval; DOAC direct oral anticoagulant; LMWH low molecular weight heparin; MB, major bleeding; NA not applicable; RR relative risk; RV right ventricle; TTE trans thoracic echocardiography; VKA vitamin K antagonist; VTE, venous thromboembolism.

Table 6: Combined endpoint and mortality at 30 days of all patients that were discharged withing 24 hours

		Combined endpoint of VTE MB or all-cause morality					
		Events (n)	Patients (n)	%	(95%CI)	RR	(95%PI)
Overall		32	2653	1.2	(0.79 to 1.6)		
Age	18-40*	8	580	1.4	(0.43 to 2.3)		
	41-60	12	1084	1.1	(0.49 to 1.7)	0.82	(0.45 to 1.5)
	61-80	12	889	1.4	(0.59 to 2.1)	0.91	(0.61 to 1.4)
	>81	0	99	0.0	(0.0 to 0.0)	0.49	(0.31 to 0.77)
Sex	Female	18	1260	1.4	(0.77 to 2.1)	1.4[a]	(0.57 to 3.4)
	Male*	14	1393	1.0	(0.49 to 1.5)		
Symptoms	Incidental	0	15	0.0	(0.0 to 0.0)	1	(0.0 to 986)
	Symptomatic*	20	1640	1.2	(0.69 to 1.8)		
Treatment	LMWH or VKA	14	1007	1.4	(0.67 to 2.1)	1.4	(0.72 to 2.9)
	DOAC*	17	1530	1.1	(0.58 to 1.6)		
Cancer[#]	Yes	5	211	2.4	(0.31 to 4.4)	2.7	(1.4 to 5.2)
	No*	27	2442	1.1	(0.7 to 1.5)		
Previous VTE	Yes	13	829	1.6	(0.73 to 2.4)	1.3	(0.65 to 2.6)
	No*	18	1708	1.1	(0.57 to 1.5)		
Decreased kidney function[^]	Yes	1	202	0.49	(0.0 to 1.5)	0.35	(0.14 to 0.88)
	No*	31	2451	1.3	(0.82 to 1.7)		
Preexisting cardio-pulmonary disease[¥]	Yes	8	476	1.8	(0.57 to 2.9)	1.9	(0.9 to 3.8)
	No*	24	2177	1.1	(0.65 to 1.5)		
Abnormal troponin[Ω]	Yes	6	248	2.6	(0.59 to 4.5)	2.9	(1.5 to 5.7)
	No*	19	1941	1.0	(0.53 to 1.4)		
Abnormal (NT-pro)BNP[±]	Yes	6	208	2.7	(0.47 to 4.9)	3.3	(1.6 to 7.1)
	No*	19	2149	0.91	(0.51 to 1.3)		
Signs of RV overload[§]	Yes	9	325	2.7	(0.96 to 4.5)	2.0[b]	(0.68 to 6)
	No*	8	905	0.9	(0.29 to 1.5)		

This table presents the 30-day incidence of the combined endpoint of VTE, MB or all-cause mortality and the 30-day incidence of all-cause mortality. I2 were all 0% for all analysis, except for: a I2=7.3; bI2=0.32; c I2= 4.2%; * RR presents the ratio of the risk for an event for the exposure group to the risk for the non-exposure/reference group; non-exposure/reference group is marked with an asterisk # (1) Current diagnosis of cancer, (2) receiving treatment for cancer or (3) not receiving treatment for cancer and not in complete response;

Table 6 continued

		All-cause morality					
		Events (n)	Patients (n)	%	(95%CI)	RR	(95%PI)
Overall		8	2660	0.30	(0.09 to 0.51)		
Age	18-40*	1	582	0.17	(0.0 to 0.51)		
	41-60	2	1085	0.18	(0.0 to 0.44)	0.93	(0.47 to 1.8)
	61-80	5	893	0.56	(0.07 to 1.1)	1.3	(0.54 to 2.9)
	>81	0	99	0.0	(0.0 to 0.0)	0.84	(0.62 to 1.1)
Sex	Female	6	1264	0.47	(0.09 to 0.85)	1.7	(0.98 to 2.9)
	Male*	2	1396	0.14	(0.0 to 0.34)		
Symptoms	Incidental	0	15	0.0	(0.0 to 0.0)	1.0	(0.0 to 986)
	Sympto-matic*	6	1640	0.37	(0.08 to 0.66)		
Treatment	LMWH or VKA	6	1011	0.59	(0.12 to 1.1)	2.6	(0.91 to 7.5)
	DOAC*	1	1533	0.07	(0.0 to 0.2)		
Cancer[#]	Yes	4	215	1.9	(0.06 to 3.7)	4.9	(2.7 to 9.1)
	No*	4	2445	0.16	(0.0 to 0.32)		
Previous VTE	Yes	3	831	0.36	(0.0 to 0.77)	1.8	(0.57 to 5.7)
	No*	4	1713	0.23	(0.0 to 0.46)		
Decreased kidney function[^]	Yes	0	203	0.18	(0.0 to 0.76)	0.66	(0.39 to 1.1)
	No*	8	2457	0.31	(0.09 to 0.53)		
Preexisting cardio-pulmonary disease[¥]	Yes	2	478	0.34	(0.0 to 0.86)	1.8[c]	(0.36 to 9.5)
	No*	6	2182	0.29	(0.06 to 0.52)		
Abnormal troponin[Ω]	Yes	1	249	0.6	(0.0 to 1.6)	2.2	(0.59 to 8.1)
	No*	5	1947	0.23	(0.02 to 0.44)		
Abnormal (NT-pro)BNP[±]	Yes	1	210	0.4	(0.0 to 1.3)	0.84	(0.52 to 1.4)
	No*	5	2154	0.24	(0.03 to 0.45)		
Signs of RV overload[§]	Yes	2	327	0.55	(0.0 to 1.4)	0.70	(0.4 to 1.2)
	No*	3	909	0.35	(0.0 to 0.74)		

^Estimated Glomerular Filtration Rate < 60 ml/min; ¥Preexisting pulmonary disease was defined as a history of chronic obstructive pulmonary disease, asthma, or lung fibrosis, a preexisting cardiovascular disease, defined as any of coronary artery disease, heart failure, congenital heart disease, cardiomyopathy or rheumatic heart disease; ΩAbnormal troponin was defined as a troponin level >99th percentile according to local technique; ± NT-proBNP > 500 ng/L or BNP level >100 ng/L ; §Right ventricle/ left ventricle ratio >0.9 on computed tomography pulmonary angiogram or echocardiogram; Abbreviations: CI, confidence interval; DOAC direct oral anticoagulant; LMWH low molecular weight heparin; MB, major bleeding; NA not applicable; RR relative risk; RV right ventricle; TTE trans thoracic echocardiography; VKA vitamin K antagonist; VTE, venous thromboembolism.

Adverse events (combined endpoint of all-cause mortality, recurrent venous thromboembolism and major bleeding)

Pre-existing cardiopulmonary comorbidity, and an abnormal troponin or an abnormal (NT-pro)BNP were all associated with an increased incidence of 14-day adverse events (RR 3.5 (95%PI 1.5-7.9), 2.5 (95%PI 1.3-4.9) and 3.9 (95%PI 1.6-9.8), respectively; Table 5). At 30 days, an abnormal troponin, an abnormal (NT-pro)BNP or cancer were associated with an increased incidence of adverse events (RR 2.9 (95%PI 1.5-5.7), 3.3 (95%PI 1.6-7.1), and 2.7 (95%PI 1.4-5.2), respectively; Table 6). Decreased kidney function was associated with a lower risk of 14- and 30-day adverse events (0.47 (95%PI 0.22-1.0) and 0.35 (95%PI 0.14-0.88), respectively; **Tables 5 and 6**). Subgroup analysis for recurrent VTE and major bleeding are presented in **Appendix D, Tables S3 and S4**.

Hestia or sPESI

There was no clear difference in all-cause mortality between patients selected by Hestia or (s)PESI plus clinical judgment (**Table 4**). Patients selected using Hestia had a higher incidence of recurrent VTE than patients selected using (s)PESI (14 days: 0.52% (95%CI 0.17 to 0.87) vs. 0.11% (95%CI 0.0 to 0.41); 30 days: 0.80% (95%CI 0.36 to 1.2) vs. 0.43% (95%CI 0.0 to 1.0), respectively), and a higher incidence of major bleeding (14 days: 0.35% (95%CI 0.06 to 0.64) vs. 0.0% (95%CI 0.00 to 0.0); 30 days: 0.62% (95%CI 0.24 to 1.0) vs. 0.43% (95%CI 0.0 to 1.0), respectively).

Sensitivity analysis

According to the definition of home treatment from the original studies (discharge within 120 h at most), 3301 patients received home treatment. Of these patients, 83% were discharged <24 h, 12% within 24-48 h, 1.4% within 48-72 h, 0.9% within 72-120 h and in 2% information on time to discharge was unknown. The baseline characteristics of all 3301 patients are demonstrated in appendix D, Table S5. All sensitivity analyses, including those based on the definition of home treatment in the original studies (**Table S6-S9**), the inclusion of Font et al. (**Table S11-S14**), and the analysis based on the non-imputed data (**Table S15-S18**), revealed no substantial differences in the incidence of adverse outcomes or subgroup analyses compared to the main analysis.

DISCUSSION

In this IPDMA, home-treated PE patients, who were selected using predefined validated triage tools (e.g., Hestia rule or (s)PESI in combination with a negative clinical judgement), had low 14-day mortality (0.18%) and incidence of adverse events (0.66%). As expected, patients with cancer showed a higher (three-to five-fold) all-cause mortality and incidence of adverse events. Patients with increased troponin or (NT-pro)BNP had a an approximately three-fold higher incidence of adverse events, but not of mortality.

The ESC guideline risk stratification model suggests that the sPESI score or Hestia rule should be used to select patients eligible for home treatment.[2] By default, according to sPESI, all patients with cancer, with chronic cardiopulmonary disease or older than 80 years should be hospitalized.[7] In line with previous studies and this recommendation, our study confirmed a higher incidence of death and adverse events in cancer patients treated at home.[7, 13] However, the absolute risk was low, and mortality was partially due to the underlying cancer. Out of the six patients with cancer that died within 30 days, only one patient had a PE-related death after 10 days and one patient died of major bleeding after 5 days. Notably, we found no increased mortality in patients older than 80 years who were selected for home treatment. Patients with pre-existing cardiopulmonary comorbidity had a higher incidence of adverse events at 14 days but not at 30 days, which was mainly driven by a higher incidence of recurrent VTE as there was no higher incidence of mortality.

According to ESC guidelines, PE patients with RV overload on CTPA or with increased troponin levels require hospitalization. Elevation of other laboratory biomarkers, such as (NT-pro)BNP, may provide additional prognostic information.[2, 32] This recommendation is based on a meta-analysis that showed that otherwise 'low-risk' patients (i.e. sPESI of 0 or negative Hestia rule) with RV overload, abnormal troponin or abnormal (NP-pro)BNP have an increased risk of 30-day mortality (RR 3.37, 5.14 and 3.63 respectively).[12] The current study did not show an association between 30-day mortality and RV overload or abnormal biomarkers. The observed difference between the two studies is likely due to the inclusion of hospitalized patients in the other meta-analysis, while the current meta-analysis focused on patients selected for home treatment by fulfilling low-risk criteria based on the individual triage tools. On the other hand, RV overload represented a formal exclusion criterion in some trials, whereas it was part of the

broader clinical judgement in most of the other trials adopting either the sPESI or Hestia rule, possibly resulting in an underestimation of the association. Clinical judgement on top of triage tools nonetheless seems to add additional safety in selecting low-risk patients eligible for home treatment, partly diluting the additional value of cardiac markers or RV overload.[14, 33] Echocardiographic assessed RV dysfunction had the highest proportion of missing data across the included studies, was found in a low number of patients, and its definition was not homogeneous across studies. We could therefore not provide a solid conclusion on the safety of home treatment in patients with RV dysfunction on echocardiography and decided to show only this data in **appendix D** table S19-S20.

Patients with renal impairment appeared to have a better outcome of care than those with normal renal function. This seems contradictory and could be explained by I) the exclusion of patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min) from most studies and II) the low number of patients in this category in our database. Our interpretation is that patients with mild to moderate renal insufficiency who do not meet any of the Hestia criteria or are considered at low risk of death by the sPESI, at least do not face a clearly higher incidence of adverse outcomes.

The interpretation of absolute risks is clinically more relevant than that of RRs in patients with (vs. without) a subgroup variable. When considering the safety of home treatment of acute PE, it can be debated what absolute threshold for early mortality rate is acceptable. In the original sPESI study, a 30-day all-cause mortality of 1.1% among patients is identified as low-risk.[7] Adding additional criteria to sPESI or Hestia for assessing home treatment eligibility would most likely result in a lower risk of mortality, although at the cost of a lower number of patients eligible for home treatment, as was shown in the HoT-PE trial.[25] Patients with signs of cardiopulmonary impairment, including those with elevated troponin or (NT-pro)BNP, and/or signs of RV dysfunction or RV overload, had an absolute 30-day risk of adverse events exceeding 2.5%, although 30-day mortality was only 0.40-0.60%. These absolute risks should inform clinicians and patients concerning the safety of early discharge and home treatment. From a healthcare resource perspective, if all deaths in our study were considered to be PE-related and preventable by hospitalization, 58-263 additional acute PE patients with cancer, or 500 additional acute PE patients with RV overload would need to be hospitalized to prevent one death. Clearly, it remains questionable whether hospitalization

would have actually prevented these deaths, in particular in the case of cancer-related death, or other complications as recurrent VTE or bleeding as there is no comparison between hospitalized and home-treated patients. Therefore, when looking at preventing PE-related complications in our study, the added value of hospitalization remains debatable. As hospitalization is more expensive than home treatment, healthcare costs associated with hospitalizations must also be considered.[4]

When considering eligibility for home treatment, clinical judgement and individualized treatment decisions remain important. This was highlighted by the HOME-PE trial: after shared decision-making, 0.5%-3.3% of the patients deemed ineligible for home treatment by the Hestia rule or sPESI ultimately received home treatment and 3.4% (by the Hestia rule) and 28.5% (by the sPESI) of the patients deemed eligible for home treatment were ultimately hospitalized.[11] Studies within this IPDMA that utilized the (s)PESI score for home treatment eligibility also incorporated clinical judgment. Only patients with an PESI II/III or sPESI of 0 in combination with a negative clinical judgement actually receive home treatment. Therefore, the application of risk classification scores used in this IPDMA in daily practice should always be combined with a clinical judgment. Clinical judgement is not only important for overruling home treatment, but hospitalization might also be overruled in certain patients based on clinical judgement and individualized decision making. For patients with a limited life expectancy, such as patients with cancer, focusing on other outcomes such as patient satisfaction or quality of life, might be more important than the risk of death. Home treatment has been associated with high patient satisfaction, although this has only been investigated by two studies, without a comparison with comparable hospitalized patients.[3, 34]

The feasibility of home treatment has increased in recent years with the introduction of direct oral anticoagulants (DOACs), as these are safer and easier to use than conventional treatment. Up to 40% of the patients included in this IPDMA were treated with a vitamin K antagonist, which has been associated with a higher bleeding risk compared with DOACs.[35] This was also confirmed in our study, where patients treated with a vitamin K antagonist had an incidence of major bleeding at 14 days of 0.30% compared with 0.13% for those treated with a DOAC. Ultimately, implementation of home treatment strategies, including specific selection criteria, depends on local healthcare systems and infrastructure, and therefore may vary across different geographical, social, and cultural contexts.

Our study has strengths and limitations. Its main strength lies in its large number of patients and the state-of-the-art statistical methods. This enabled evaluation of the safety of home treatment with more accuracy and narrower 95% CIs than reported previously. This is also the first study to investigate specific subgroups of interest suspected to be at higher risk for adverse events when receiving home treatment.

As a first limitation, the calculation of RRs is difficult within subgroups with few events, resulting in RRs with a higher level of uncertainty, reflected in broad 95%PIs. Even so, we used Firth's correction to handle small-sample bias. Some subgroups may exhibit a non-significant RR for adverse outcomes due to a lack of statistical power. However, this is because overall absolute risks in these subgroups were low. Therefore, the emphasis should be on considering absolute risks rather than solely detecting differences in risks, especially when comparing incidence rates that potentially fall within a range considered safe from a clinical perspective. Second, we have performed multiple imputations of variables with a high level of missingness. For data sets where variables are missing (completely) at random, this approach is reliable and will reduce bias.[36] We assumed that missing (completely) at random was mostly applicable for our data set. However, we did not have exact information on how each variable was collected in a data set, so we cannot guarantee that missing values were truly missing at random, as abnormal values might have been more frequently reported than normal ones. Imputed values may, therefore, not accurately reflect true (unobserved) values. We have reported all percentages of missingness in appendix D, Table S1, aiming for transparency when interpretating the data. Third, the subgroup definitions applied in this IPDMA were not fully standardized. Forth, our data include only adverse event rates but do not contain other relevant outcomes such as unscheduled visits, patient satisfaction, quality of life or cost effectiveness. Such outcomes therefore were not included in this IPDMA, nor were data of patients that were hospitalized for comparison. Finally, some studies included in our IPDMA excluded patients with certain subgroup characteristics (e.g., cancer, RV overload), which may have resulted in an underestimation of the prognostic impact of these characteristics in our analysis. The current study did not show an association between troponin, (NTpro)BNP, RV overload and mortality in patients selected for home treatment but this association might have been underestimated due to this limitation, and these findings should thus be interpreted with caution. Clinicians should focus on the absolute incidences, while keeping in mind the

uncertainty due to the small number with the reflecting 95%CI, when discussing the risk of home treatment and assessing home treatment as a potential treatment option.

CONCLUSION

Validated triage tools such as Hestia or sPESI in combination with a negative clinical judgement can be used in the emergency department to select acute PE patients for home treatment, as the rate of adverse events and death in our cohort was very low. Patients with cancer had a three-to five-fold higher incidence of 30-day mortality or adverse events. Patients with increased troponin or (NT-pro)BNP had a three-fold higher risk of adverse events, driven by recurrent VTE and bleeding complications. The point estimates of the absolute risk of adverse events provide important evidence to inform clinical shared decision-making in daily practice.

REFERENCES

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
2. Konstantinides SV, Meyer G, Becattini C, 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: 41(4): 543-603.
3. Bledsoe JR, Woller SC, Stevens SM, et al. Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. Chest 2018: 154(2): 249-256.
4. Hendriks SV, van den Hout WB, van Bemmel T, et al. Home Treatment Compared to Initial Hospitalization in Normotensive Patients with Acute Pulmonary Embolism in the Netherlands: A Cost Analysis. Thromb Haemost 2022: 122(3): 427-433.
5. Klok FAandHuisman MV. When I treat a patient with acute pulmonary embolism at home. Hematology American Society of Hematology Education Program 2020: 2020(1): 190-194.
6. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005: 172(8): 1041-1046.
7. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010: 170(15): 1383-1389.
8. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011: 378(9785): 41-48.
9. Zondag W, Hiddinga BI, Crobach MJT, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 2013: 41(3): 588-592.
10. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011: 9(8): 1500-1507.
11. Roy PM, Penaloza A, Hugli O, et al. Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. Eur Heart J 2021: 42(33): 3146-3157.
12. Barco S, Mahmoudpour SH, Planquette B, et al. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2019: 40(11): 902-910.
13. Hendriks SV, Huisman MV, Eikenboom JCJ, et al. Home treatment of patients with cancer-associated venous thromboembolism - An evaluation of daily practice. Thromb Res 2019: 184: 122-128.
14. Hendriks SV, Klok FA, den Exter PL, et al. Right Ventricle-to-Left Ventricle Diameter Ratio Measurement Seems to Have No Role in Low-Risk Patients with Pulmonary Embolism Treated at Home Triaged by Hestia Criteria. Am J Respir Crit Care Med 2020: 202(1): 138-141.
15. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000 [cited 2023 26/10]; Available from: Available at http://www.ohri.ca/programs/clinical_epidemiology/oxfordasp
16. Schulman SandKearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005: 3(4): 692-694.
17. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC Subcommittee on official Communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis 2021: 19(1): 297-303.

18. Jolani S, Debray TPA, Koffijberg H, et al. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. Statistics in Medicine 2015: 34(11): 1841-1863.
19. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009: 338: b2393.
20. White IR, Royston PandWood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 2011: 30(4): 377-399.
21. Von Hippel PT. Regression with missing ys: an improved strategy for analyzing multiply imputed data. Sociological Methodology 2007: 37(1): 83-117.
22. Marshall A, Altman DG, Holder RL, et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Medical Research Methodology 2009: 9(1): 57.
23. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993: 80(1): 27-38.
24. Wang X. Firth logistic regression for rare variant association tests. Front Genet 2014: 5: 187.
25. Barco S, Schmidtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. Eur Heart J 2020: 41(4): 509-518.
26. Otero R, Uresandi F, Jiménez D, et al. Home treatment in pulmonary embolism. Thromb Res 2010: 126(1): e1-5.
27. Font C, Carmona-Bayonas A, Fernández-Martinez A, et al. Outpatient management of pulmonary embolism in cancer: data on a prospective cohort of 138 consecutive patients. J Natl Compr Canc Netw 2014: 12(3): 365-373.
28. den Exter PL, Zondag W, Klok FA, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial. Am J Respir Crit Care Med 2016: 194(8): 998-1006.
29. Kabrhel C, Rosovsky R, Baugh C, et al. Multicenter Implementation of a Novel Management Protocol Increases the Outpatient Treatment of Pulmonary Embolism and Deep Vein Thrombosis. Acad Emerg Med 2019: 26(6): 657-669.
30. Kline JA, Adler DH, Alanis N, et al. Monotherapy Anticoagulation to Expedite Home Treatment of Patients Diagnosed With Venous Thromboembolism in the Emergency Department: A Pragmatic Effectiveness Trial. Circ Cardiovasc Qual Outcomes 2021: 14(7): e007600.
31. Vinson DR, Mark DG, Chettipally UK, et al. Increasing Safe Outpatient Management of Emergency Department Patients With Pulmonary Embolism: A Controlled Pragmatic Trial. Ann Intern Med 2018: 169(12): 855-865.
32. Klok FA, Mos ICandHuisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008: 178(4): 425-430.
33. Hendriks SV, den Exter PL, Zondag W, et al. Reasons for Hospitalization of Patients with Acute Pulmonary Embolism Based on the Hestia Decision Rule. Thromb Haemost 2020: 120(8): 1217-1220.
34. Simon LE, Iskin HR, Vemula R, et al. Emergency Department Patient Satisfaction with Treatment of Low-risk Pulmonary Embolism. West J Emerg Med 2018: 19(6): 938-946.
35. van der Hulle T, Kooiman J, den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014: 12(3): 320-328.
36. Madley-Dowd P, Hughes R, Tilling K, et al. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol 2019: 110: 63-73.

Supplementary file

4

Risk assessment and management strategies in older patients with acute pulmonary embolism

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J Thromb Haemost. 2025 Feb;23(2):588-599

ABSTRACT

Background: Managing older patients with acute pulmonary embolism (PE) is challenging due to their underrepresentation in clinical trials, comorbidities, and increased complication risk.

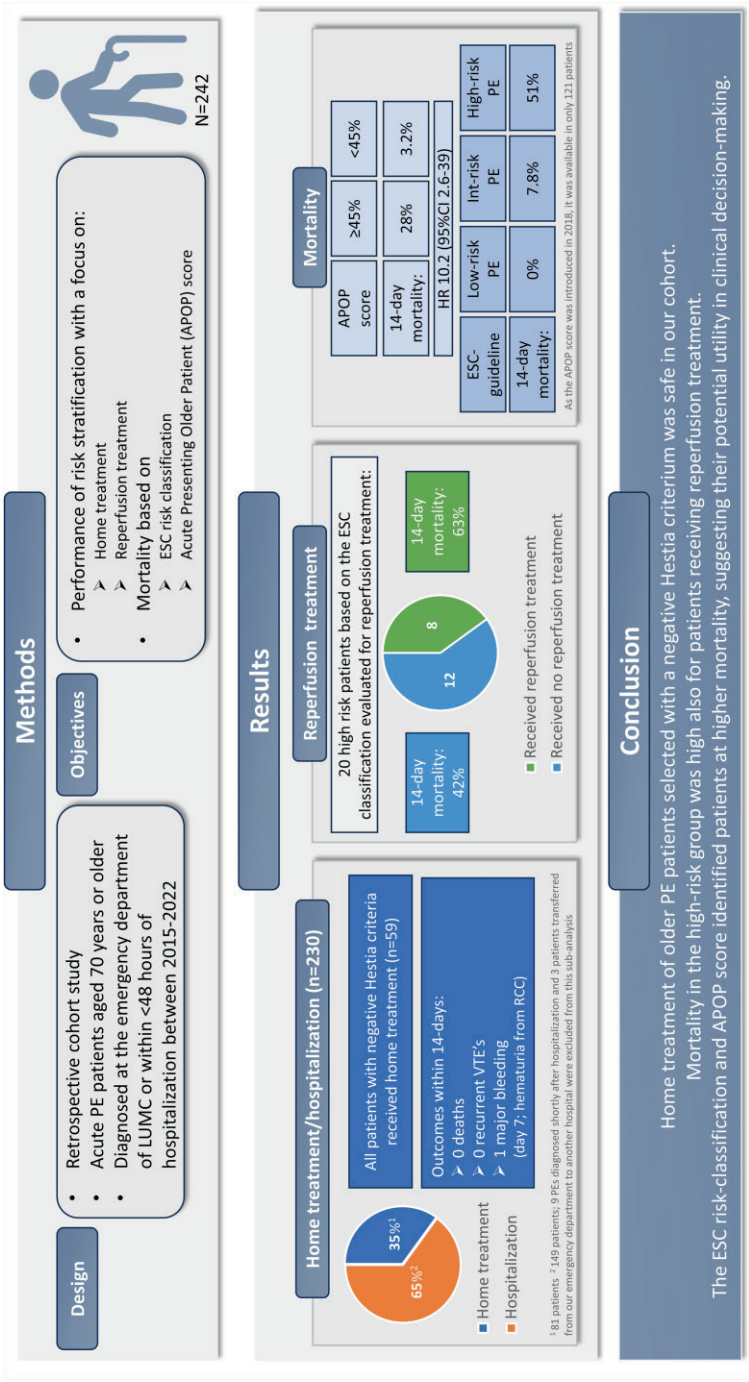
Objectives: To evaluate risk assessment and management outcomes in older patients with PE focusing on home and reperfusion treatment.

Methods: A retrospective analysis was conducted on patients aged 70 years or older diagnosed with acute PE at an academic medical center (2015-2022).

Results: In total, 242 patients with a mean age of 77 years were included. All 59 patients with negative Hestia criteria were discharged ≤24 hours, and in total 81 patients (35%) received home treatment. Among these 14-day mortality and recurrent venous-thromboembolism were 0% and major bleeding occurred in 1.3% (1 patient, 95%CI 0.11-6.1). European Society of Cardiology risk-classification showed 9 low-risk PE (3.9%), 199 intermediate-risk (87%), and 20 high-risk (8.8) patients with PE. In 5 of the 20 high-risk patients, hypotension was mainly caused by another condition, that is, sepsis. Eight high-risk patients received reperfusion therapy. The 14-day mortality rate was 51% in high-risk patients (95%CI 27-71); 5 of 8 patients receiving reperfusion treatment died within 5 days. Patients with an Acute Presenting Older Patient score of ≥45% had higher 14-day mortality (28%; 95%CI 12-46) compared to <45% (3.2%; 95%CI 0.85-8.3; HR 10.2; 95%CI 2.6-39).

Conclusion: Selecting for home treatment using Hestia was safe for older PE patients in our cohort. Mortality in the high-risk group was high also when receiving reperfusion treatment. The European Society of Cardiology risk-classification and Acute Presenting Older Patient score identified patients at higher mortality risk, suggesting their potential utility in clinical decision-making.

GRAPHICAL ABSTRACT



INTRODUCTION

Treating older patients (aged 70 years or higher) with acute pulmonary embolism (PE) comes with challenges.[1] First, older patients are often not adequately represented in clinical trials, complicating the interpretation of risk stratification models and outcomes of management strategies for this patient category. Second, older patients often present at the hospital with multiple medical problems that might interfere with routine acute PE treatment (e.g., high risk of bleeding due to head trauma, decreased kidney function). Third, older patients are more at risk for developing complications when being hospitalized, such as delirium, pneumonia or urinary tract infection, which makes home treatment particularly relevant for this patient category. Additionally, when applying the risk stratification advised by the European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guideline using the simplified PE Severity Index (sPESI) score to assess clinical PE severity, all patients aged above 80 years old are classified as non-low risk of death excluding them from home treatment.[2-4] However, frailty is not taken into account in this risk stratification, and a risk-classification model developed specifically for older patients might be more applicable to triage older patients with acute PE. Lastly, older patients often have altered (patho)physiology, such as prevalent hypertension, making vital sign cut-offs defined for younger cohorts potentially inadequate for assessing disease severity in older adults.

In this study we aimed to evaluate the presentation and treatment outcomes of acute PE in older patients. In more detail, we evaluated how risk assessment was performed and what outcomes were of subsequent management decisions in older patients with acute PE focussing on home and reperfusion treatment. Furthermore, we aimed to evaluate the association between mortality and risk-classification according to the ESC guideline and according to the Acute Presenting Older Patient (APOP) score, a risk assessment tool that predicts mortality or functional decline in older (not PE specific) patients presenting to the emergency ward.

METHODS

Study design and patients

This was a retrospective cohort study of patients with acute PE aged 70 years or older, diagnosed between December 1st 2015 and September 1st 2022 at the

Leiden University Medical Center, a Dutch academic hospital. Patients were excluded if they had a hospital acquired PE (defined as PE diagnosis >48 hours after admission) or when the PE was not diagnosed at the emergency department or within 48 hours after admission (i.e., [incidental] PE diagnosed at the outpatient visit). We collected all data on presentation, risk-classification, treatment and outcomes (see **appendix A** for used definitions). As the study involved the use of routinely collected deidentified data, the need for consent was waived by the Medical Ethics Review Committee and no informed consent was obtained from the patients. Patients had the option to record in their medical records if they do not wish for their data to be used for research purposes (optout policy of our hospital).

Data extraction was performed individually by three researchers (D.L., D.A., L.T.). For the risk stratification to select eligible patients for home treatment, different strategies are available. The first strategy uses the Hestia criteria, a 12-item checklist. Patients negative for all items are eligible for home treatment.[5, 6] The second strategy follows the ESC guidelines, classifying patients as low-risk if they have a hemodynamically stable PE, a sPESI score of 0, negative Hestia criteria, no signs of right ventricular dysfunction, and normal troponin levels if measured (Appendix B, Table S1). In our hospital, the local protocol recommends using the Hestia criteria. Patients negative for all Hestia items are discharged directly from the emergency department, while those with any positive Hestia criteria are hospitalized. Adherence to this protocol and patient outcomes were evaluated. The subjective item medical or social reason for hospital treatment was scored if any non-Hestia reason for hospitalization was noted in the patient's electronic record, such as the need for intravenous medication. To check correct classification and further characterization of this item 1 researcher (D.L.) adjudicated all patients with a medical or social reason for hospital treatment.

As the ESC risk classification is not routinely used in our hospital, patients were assigned post-hoc to the following 4 risk categories low risk, intermediate-low risk, intermediate-high risk, and high risk.

For patients with acute PE with an indication for reperfusion treatment, ESC guidelines are followed.[7] High-risk or those judged to be at risk of imminent decompensation with severe PE are discussed in a multidisciplinary team, for reperfusion treatment consideration. We evaluated the frequency of patients receiving reperfusion treatment, the reasons for refraining from reperfusion treatment, and the subsequent outcomes.

Moreover, since 2018, the APOP score was calculated in patients upon emergency department arrival. The APOP score is a risk assessment tool introduced in 2018 that predicts mortality or functional decline in older patients presenting to the emergency department. Items within this score are whether a patient 1) arrives with an ambulance, 2) needed help before emergency department visit (e.g. with cooking, doing groceries), 3) needed help bathing or showering, 4) was hospitalized in the past 6 months, and 5) had an impaired cognition. The outcome of the APOP score predicts the individual risk (%) of a patient for functional decline or mortality within 3 months. It categorizes patients with scores ≥45% as high-risk.[8, 9]

Outcomes

Home treatment was defined as immediate discharge from the emergency department or within 24 hours after arrival. Adverse event outcomes that were evaluated were as follows: 1) recurrent venous thromboembolism (VTE), 2) major bleeding, and 3) all-cause mortality. Recurrent VTE was defined as symptomatic, objectively confirmed proximal DVT, or nonfatal or fatal PE.[10] Major bleeding was defined according to the criteria proposed by the International Society on Thrombosis and Haemostasis.[10] Causes of death were defined according to a modified version of the ISTH death classification i.e. PE-related death (category A), unknown cause of death (B), major bleeding related death (category C) or cause of death other than PE or major bleeding (category D).[11] All clinical events were adjudicated by 2 investigators (D.L. and F.A.K.).

Statistical analysis

Characteristics were described using median and IQR or mean and SD for continuous variables and counts and proportions for categorical variables. Missing data were not imputed. The 14-, 30-, and 90-day events rates were calculated and presented in a Kaplan-Meier curve, and adjusted for death as a competing risk. We chose to focus on 14-day outcomes as they reflect more accurately the potential impact of treatment decisions made during the acute phase, such as home care, hospitalization, or reperfusion treatment. However, we also report 30- and 90-day outcomes, as they are commonly used in the literature. Patients in our study were followed up at the outpatient clinic for at least 3 months. Recurrent VTE or major

bleeding events were evaluated until the scheduled follow-up appointment. Patients who were lost to follow-up before the scheduled appointment were censored at the last documented encounter with their treating physician at the hospital, and patients who died before the scheduled appointment were censored at the day they died. Mortality was evaluated until the date of data collection. We reviewed electronic patient files to identify registered dates of death at the time of data collection beyond the outpatient clinic follow-up. Median follow-up was calculated using the reverse Kaplan Meier method. Hazard ratios (HRs) were estimated using a Cox proportional hazard model. All analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing; www.R-project.org).

RESULTS

Patients

Of the 456 patient with acute PE aged 70 years or older at diagnosis, 242 older patients with acute PE were enrolled, with a mean age of 77 years, 64 (26%) were aged older than 80 and 7 (2.9%) older than 90 years (**Figure S1, S2**). In addition, 50% were male, 47 patients had a history of VTE (19%), and 56 had an active malignancy, comprising 21 cases with localized disease, 30 with metastatic disease, and 5 with hematological cancer (8.7%, 12%, and 2.1% of all patients, respectively; **Table 1**). Additionally, 41 patients had previous cardiovascular disease (17%), 28 had pre-existing pulmonary comorbidities (12%), and 9 had confirmed dementia (3.7%). Of the 242 patients, 9 PEs were diagnosed during hospitalization. The majority of patients presented with unprovoked PE (135; 56%) and experienced dyspnea as presenting symptom (187; 79%). The first vital signs when presenting to the emergency department indicated that 37 had a heart rate ≥110 beats/min (15%), 11 had a systolic blood pressure <100 mmHg (4.6%), and 112 had an oxygen saturation of <90% or required oxygen supplementation (47%). Additionally, 110 exhibited signs of right ventricular overload on CTPA (46%; defined as RV/LV ratio >1 or presence of backflow into the inferior vena cava). Post-hoc risk classification revealed that 50 patients had a sPESI score of 0 (21%), while in 59 patients, all Hestia criteria were negative (25%).

Table 1: baseline characteristics of the included patients.

Characteristics	Overall (n=242)
Age (mean, SD)	77 (5.8)
Male sex	120 (50)
Comorbidities (n, [%])	
Previous VTE	47 (19)
Previous DVT	21 (45)
Previous PE	30 (64)
Localized active malignancy	21 (8.7)
Metastatic active malignancy	30 (12)
Not solid active malignancy	5 (2.1)
Cardiovascular disease	41 (17)
Hypertension	106 (44)
Diabetes mellitus	52 (22)
(paroxysmal) Atrial fibrillation	20 (8.3)
Preexisting pulmonary comorbidity	28 (12)
Chronic kidney disease	25 (10)
CVA or TIA	35 (15)
Dementia	9 (3.7)
APOP high risk for death or functional decline (>45%) (n, [%])	26 (22)*
Unprovoked PE (n, [%])	135 (56)
Duration of complaints (median [IQR])	2.00 [1.00, 7.00]
Dyspnea (n, [%])	187 (79)
Chest pain (n, [%])	96 (41)
Coughing (n, [%])	57 (24)
Hemoptysis (n, [%])	6 (2.5)
Syncope (n, [%])	29 (12)
DVT symptoms (n, [%])	23 (9.5)
Altered mental status (n, [%])	24 (10)
Vital signs (n, [%])	
Heartrate ≥110	37 (15)
Blood pressure <100 mmHg	11 (4.6)
Respiratory rate >30 breaths/min	25 (12)
Oxygen saturation <90% or need for oxygen suppletion	112 (47)
Temperature <36 °C	19 (8.5)
PE diagnosis at the ED (n, [%])	233 (96)
Referred to ED with suspicion PE (n, [%])	
No	50 (22)
Yes	80 (34)
Unknown/unclear	103 (44)
Imaging	
Most proximal location of PE (n, [%])	
Central / Lobar / Segmental / Subsegmental	85 (35) / 9 (3.7) / 107 (44) / 41 (17)
RV pressure overload on CTPA (n, [%])	110 (46)
Severity	
sPESI score ≥ 1 (n, [%])	50 (21)
Negative Hestia criteria (n, [%])	59 (25)

* missing in patients diagnosed with PE <2018; 50% missingness; 121 patients. Abbreviations: APOP: Acute Presenting Older Patient, CVA: Cerebrovascular Accident, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, SD: Standard Deviation, TIA: Transient Ischemic Attack, VTE: Venous Thromboembolism.

According to the ESC risk classification model, 9 patients had low-risk PE (3.9%); 199 had intermediate-risk PE (87%), of which 116 were intermediate-low-risk (51% of all patients) and 47 were intermediate-high-risk (21% of all patients); and 20 patients had high-risk PE (8.8%). Median follow-up for recurrent VTE or major bleeding was 94 days, and median follow-up for mortality was 812 days. Of the total patients, 43 (18%) had their last encounter with their treating physician less than 80 days after diagnosis. Of these, 27 patients (11%) were alive beyond 90 days. However, 16 patients (6.6%) were not evaluated at the Leiden University Medical Center beyond this encounter and are thus considered lost to follow-up.

Home treatment versus hospitalization

Among the 233 patients presenting with PE to the emergency department (9 PEs diagnosed shortly after hospitalization and 3 patients transferred from our emergency department to another hospital were excluded from this sub-analysis), 59 were negative for all Hestia criteria (25%) who all received home treatment (56 were immediately discharged from the emergency department and 3 hospitalized < 24 hours). 171 patients had ≥1 positive Hestia criteria (74%) of who 3 were transferred from the emergency department to another hospital (1.8%), 149 were hospitalized (87%) and 22 received home treatment (13%; 21 hospitalized <24 hours and 1 immediately discharged home). Thus, 57 were discharged home directly from the emergency department, 24 were hospitalized but discharged within 24 hours after emergency department registration (totalling 81 patients receiving home treatment; 35%) and 149 were hospitalised >24 hours (65%; **Table 2, Table S2, Figure 1**).

All patients who were negative for all Hestia criteria received home treatment (n=59). Twenty-two patients with ≥1 positive Hestia criteria also received home treatment, of which 1 was discharged directly from the emergency department and 21 were hospitalized for <24 hours (**Figure 1**). Reasons for a positive Hestia criteria were mostly because of temporary need for oxygen therapy, a perceived high risk of bleeding, considerable RV overload on imaging tests, or because low molecular weight heparin injections had to be administered (**Table S2**). Of the home treated patients 53 had a sPESI score ≥1 (65%) and 26 had presence of RV overload (32%).

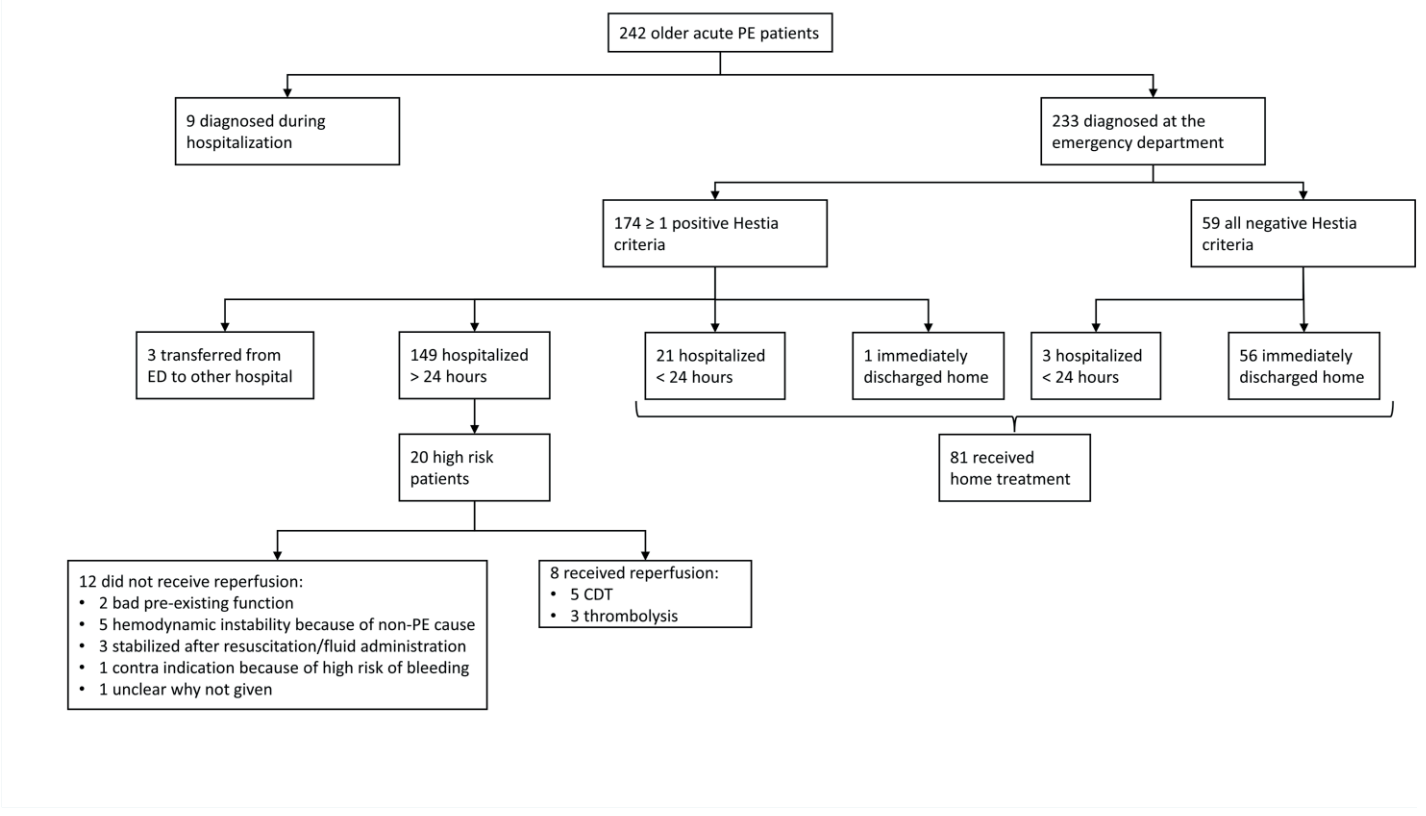
Table 2: home treatment vs hospitalization	Patients (n=242)	Home treatment (n=81)[α]	Hospitalisation (n=149)[α]
Presentation			
Severity			
sPESI ≥1 , n (%)	191 (79.3)	53 (65)	128 (85.9)
Aged ≥80 years	64 (26)	19 (23)	39 (26)
Preexisting cardiopulmonary comorbidity	62 (26)	16 (20)	41 (28)
Malignancy	89 (37)	33 (41)	51 (34)
Heart rate ≥110 bpm	37 (15)	5 (6.2)	31 (21)
Systolic blood pressure < 100 mmHg	11 (4.6)	0 (0)	10 (6.7)
Oxygen saturation <90% or need for oxygen suppletion[#]	112 (46.5)	8 (9.9)	96 (64)
Hestia ≥1, n (%)	174 (74.7)	22 (27)	149 (100)
Hemodynamic instability	20 (8.6)	0 (0)	20 (13)
Need for oxygen suppletion	123 (52.8)	6 (7.4)	115 (77.2)
PE diagnosis under anticoagulant treatment	3 (1.3)	0 (0)	3 (2)
Thrombolysis or embolectomy necessary	8 (3.4)	0 (0)	8 (5.4)
Active bleeding or high risk of bleeding	15 (6.4)	7 (8.6)	8 (5.4)
Severe pain needing IV pain medication	6 (2.6)	0 (0)	6 (4)
Creatinine clearance of <30mL/min	4 (1.7)	0 (0)	4 (2.7)
Severe liver impairment	4 (1.7)	0 (0)	4 (2.7)
Heparin-induced thrombocytopenia	0 (0)	0 (0)	0 (0)
Medical or social reason for hospitalization	97 (42)	14 (17)	81 (54)
Presence of RV overload, n (%)	110 (45.5)	26 (32)	79 (53)
ESC classification*			
Low risk PE , n (%)	9 (3.9)	9 (12)	0 (0)
Intermediate risk PE, n (%)	199 (87.3)	67 (88)	129 (86.6)
Intermediate-low risk PE, n (%)	116 (50.9)	47 (62)	67 (45)
Intermediate-high risk PE, n (%)	47 (21)	5 (6.6)	42 (28)
Intermediate-risk PE not further classified, n (%)	36 (16)	15 (20)	20 (13)
High risk PE, n (%)	20 (8.8)	0 (0)	20 (13)
Reperfusion treatment, n (%)	8 (40)	0 (0)	8 (40)
Fragile patients (APOP ≥45%), n (%)	26 (21)	6 (16)	17 (22)

	Patients (n=242)	Home treatment (n=81)[α]	Hospitalisation (n=149)[α]
Diagnosed during hospitalization, but within 48 hours after presentation, n (%)	9 (3.7)	0 (0)	0 (0)
Died during ER visit/hospitalization, n (%)	25 (10)	0 (0)	23 (15)
Home treatment, n (%)	81 (35)	81 (100)	0 (0)
Hospitalization, n (%)	149 (65)	0 (0)	149 (100)
ICU admission, n (%)	25 (14)		
Median duration of hospitalization (days)	3.0		
Outcomes			
Median survival (days)	1503	NA	1372
14-day mortality, % (95%CI)	11% (7.7%, 16%)	0.00% (0.0%, 4.6%)	17% (11%, 23%)
30-day mortality, % (95%CI)	15% (11%, 20%)	3.8% (1.0%, 9.8%)	20% (14%, 27%)
90-day mortality, % (95%CI)	18% (13%, 23%)	3.8% (1.0%, 9.8%)	25% (18%, 32%)
14-day recurrent VTE, % (95%CI)	0.00% (0.0%, 1.9%)	0.00% (0.0%, 4.6%)	0.00% (0.0%, 3.2%)
30-day recurrent VTE, % (95%CI)	0.46% (0.04%, 2.4%)	0.00% (0.0%, 4.7%)	0.74% (0.07%, 3.7%)
90-day recurrent VTE, % (95%CI)	0.46% (0.04%, 2.4%)	0.00% (0.0%, 6.4%)	0.74% (0.07%, 3.7%)
14-day major bleeding, % (95%CI)	2.2% (0.83%, 4.8%)	1.3% (0.11%, 6.1%)	2.8% (0.93%, 6.6%)
30--day major bleeding, % (95%CI)	2.2% (0.83%, 4.8%)	1.3% (0.11%, 6.1%)	2.8% (0.93%, 6.6%)
90--day major bleeding, % (95%CI)	4.3% (2.1%, 7.7%)	4.0% (1.1%, 10%)	4.6% (1.9%, 9.3%)

[α] 9 patients where the PE was diagnosed during hospitalization were excluded from these subgroups, 3 patients were transferred from ED to another hospital, hospitalization time unknown [#] first measurement when presenting to the ED * only including acute PE patients where the PE is diagnosed at the ER; missing in 5 patients due to missing sPESI score. Patients where the PE was diagnosed during hospitalization were excluded from this sub-analysis. Abbreviations: APOP: Acute Presenting Older Patient, CI: Confidence Interval, ER: Emergency Room, ESC: European Society of Cardiology, ICU: Intensive Care Unit, IV: Intravenous, NA: not applicable, n: Number, PE: Pulmonary Embolism, sPESI: simplified Pulmonary Embolism Severity Index, VTE: Venous Thromboembolism

Among hospitalized patients, 128 had a sPESI score ≥1 (86%), all patients had at least one positive Hestia criterium and 79 were diagnosed with RV overload (53%). Notably, the primary reason for hospitalization, as per Hestia criteria, was the need for oxygen supplementation (present in 115 patients (77%)). Reasons why the item "Medical or social reason for treatment in the hospital" was positive were mostly due to presence of another disease requiring hospitalization (**Figure S3** e.g. indication for intravenous antibiotic treatment).

Figure 1: flow chart of treatment decisions



CDT catheter directed therapy; ED emergency department; PE pulmonary embolism

All ESC classification low-risk patients received home treatment (n=9). Moreover, 67 out of 199 patients with intermediate-risk PE were treated at home (34% of all intermediate-risk PE patients). None of the patients who received home treatment died within 14 days or experienced recurrent VTE (95%CI 0-4.6), but one patient (1.3%; 95%CI 0.11-6.1) treated with apixaban had a non-fatal major bleeding event due to haematuria related to a renal cell carcinoma 7 days after PE diagnosis. Within 30-days, 3 patients receiving home treatment died, which were all considered to be cancer and not PE related (3.8%; 95%CI 1.0-9.8). Within 30-days no home treated patients had a recurrent VTE (0%; 95%CI 0.0-4.7) and there we no additional major bleedings beyond one patient previously described (1.3%; 95%CI 0.11-6.1). For hospitalized patients, 25 patients died within 14 days (17%; 95%CI 11-23), none had a recurrent VTE (0%; 95%CI 0.0-3.2), and 4 had a major bleeding rate (2.8%; 95%CI 0.93-6.6). Within 30-days this was 20%, 0.74% and 2.8% respectively (95%CI 14-27, 0.07-3.7, 0.93-6.6 respectively).

Reperfusion treatment

Details on high-risk patients and those admitted to the ICU are provided in **Table 3**. Among the 20 high-risk patients, 8 received reperfusion treatment (40%): three with full dose systematic thrombolysis and 5 with catheter-directed reperfusion therapies. Reasons for not administering reperfusion treatment to other high-risk patients were: 2 considered to be too frail to justify treatment escalation and admission to an ICU, five experienced hemodynamic instability due to non-PE conditions (e.g. sepsis), 3 had become stabilized after initial resuscitation or saline administration, 1 had a contraindication for systemic thrombolysis due to a high risk of bleeding while catheter directed therapies (CDT) were not yet available, and in 1 patient it was unclear why reperfusion treatment was not given. Among the 8 patients who received reperfusion treatment, 3 survived beyond 14 days; the remaining 5 died within 14 days due to PE-related causes despite reperfusion treatment (63%). All 3 patients who received thrombolysis died within 14-days due to a PE-related death; none of them suffered a bleeding complication. Of the 12 high-risk patients not receiving reperfusion treatment, 5 died within 14 days (42%), 3 due to PE-related causes. Within 30-days, similar numbers were seen: 30-day mortality was 63% among patients receiving reperfusion treatment and 42% among patients not receiving reperfusion treatment.

Table 3: details on high risk/ICU patients

	ESC	ICU	Reperfusion treatment	Reason no reperfusion treatment was given	Sort of reperfusion treatment	Died within 14 days	Cause of death; category
1.	High	No	Yes		CDT	Yes	PE-related; A
2.	High	No	Yes		CDT	No	
3.	High	No	Yes		CDT	No	
4.	High	Yes	Yes		CDT	No	
5.	High	Yes	Yes		CDT	Yes	PE-related; A
6.	High	Yes	Yes		Thrombolysis	Yes	PE-related; A
7.	High	Yes	Yes		Thrombolysis	Yes	PE-related; A
8.	High	Yes	Yes		Thrombolysis	Yes	PE-related; A
9.	High	No	No	Bad pre-existing functioning		Yes	PE-related; A
10.	High	No	No	Hemodynamic instability because of sepsis and pericardial tamponade		Yes	Other than PE or MB; D
11.	High	Yes	No	Hemodynamic instability because of sepsis		Yes	Other than PE or MB; D
12.	High	Yes	No	Hemodynamic instability because of distributive shock		Yes	PE-related; A
13.	High	Yes	No	Unclear why not given		Yes	PE-related; A
14.	High	No	No	Contra-indication because of high risk of bleeding		No	
15.	High	No	No	Hemodynamic instability because of sepsis		No	
16.	High	Yes	No	Hemodynamic instability because of cardiac infarction		No	
17.	High	Yes	No	Stabilized after initial resuscitation		No	
18.	High	Yes	No	Stabilized after fluid administration		No	
19.	High	Yes	No	Stabilized after fluid administration		No	
20.	High	No	No	Bad pre-existing functioning		LTFU	
21.	Int*	Yes	No	No hemodynamic instability		No	
22.	Int*	Yes	No	No hemodynamic instability- ICU admission because of covid-19 pneumonitis		No	
23.	Int-high	Yes	No	Contra-indication because of active bleeding- no hemodynamic instability		No	
24.	Int-high	Yes	No	No hemodynamic instability		No	
25.	Int-high	Yes	No	No hemodynamic instability		No	
26.	Int-high	Yes	No	No hemodynamic instability		No	
27.	Int-high	Yes	No	Stabilized at the emergency department without need for reperfusion treatment		No	

28.	Int-high	Yes	No	Stabilized after fluid administration - contra indication reperfusion	No
29.	Int-low	Yes	No	No hemodynamic instability	No
30.	Int-low	Yes	No	ICU admission because of respiratory insufficiency due to pneumocystis jiroveci pneumonia	No
31.	Int-low	Yes	No	No hemodynamic instability-ICU admission because of respiratory insufficiency due to organizing pneumonia	No
32.	Int-low	Yes	No	No hemodynamic instability-ICU admission because of compartment syndrome	No
33.	Int-low	Yes	No	No hemodynamic instability-ICU admission because of respiratory insufficiency due to interstitial lung disease	No

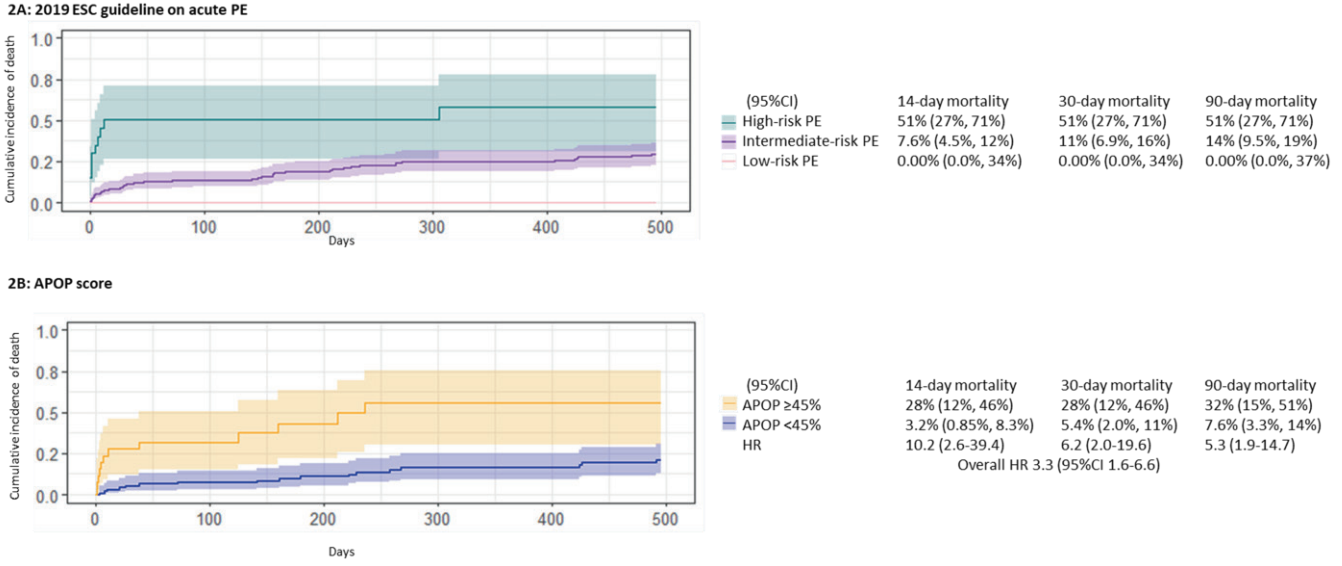
*intermediate risk not further specified. Abbreviations: CDT catheter directed therapies; ESC European Society of Cardiology; ICU intensive care unit; Int intermediate; LTFU lost to follow-up; MB major bleeding; PE pulmonary embolism

Outcomes according to the ESC risk classification and APOP score

Figure 2A illustrates the mortality rates according to ESC risk classification: none of the low-risk patients died within 14 days (0%; 95%CI 0-34), whereas 15 intermediate-risk patients died (7.6%; 95%CI 4.5-12) and 10high-risk patients (51%; 95%CI 27-71). There was no clear difference between intermediate-high and intermediate-low risk PE patients (14-day mortality 4.4% vs 7.9%, respectively; **Figure S4**). **Figure 3** depicts the distribution of patients based on ESC risk classification who received home treatment, reperfusion treatment, and survived the first 14 days after PE diagnosis. Within 30-days mortality was 0% for low risk patients (95%CI 0-34), 11% for intermediate risk (95%CI 6.9-16) and 51% for high risk (95%CI 27-71).

The APOP score was introduced as routine care in 2018 and available in 121 patients. Patients classified as high risk for functional decline or mortality based on the APOP score (>45%) exhibited an increased risk of death, with a HR of 3.3 (95%CI 1.5-7.1; **Figure 2B**). A high APOP score was not only associated with an increased risk of death shortly after diagnosis (14-day HR 10.1 [95%CI 2.7-38.9]), but also during longer follow-up (90-day HR 5.3 [95%CI 2.0-14.2]; **Figure 2B**).

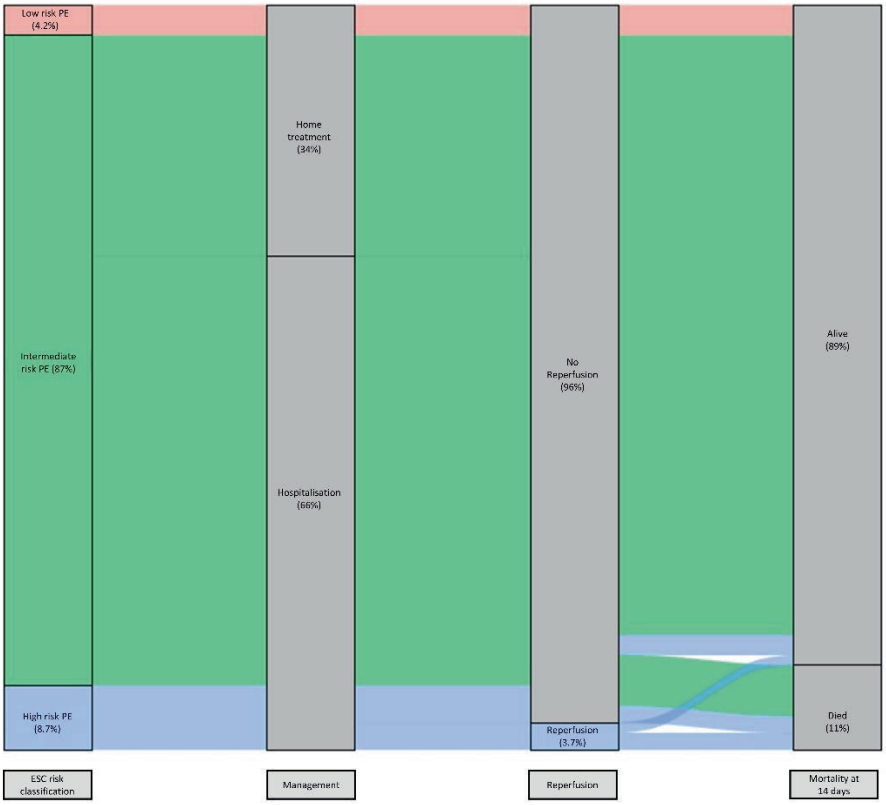
Figure 2: All-cause mortality according to different risk classification scores in older acute PE patients



Both graphs present the cumulative incidence (%) of death within days after acute PE diagnosis.
2A: mortality according to the 2019 ESC guideline on acute pulmonary embolism. This score is not specific for older patients. No 95%CI could be calculated for the low-risk event group as no events occurred
2B: The Acute Presenting Older Patient (APOP) score is a risk classification score that identifies older patients at higher risk for mortality or functional decline. A score of 45% means that the patient had a 45% risk on mortality or functional decline. This score is not PE specific. Patients with an APOP score ≥45% are classified as 'high risk'.
Supplementary file, figure S6 showed the risk tables for both figures.
Abbreviations: APOP Acute Presenting Older Patient, CI confidence interval, ESC European Society of Cardiology, HR hazard ratio, NA not applicable, PE pulmonary embolism

Specifically, 7 patients with a high APOP score died within 14 days (28%; 95%CI 12-46), compared to 3 patients with a low APOP score (3.2%; 95%CI 0.85-8.3). Within the ESC-defined intermediate-risk group, patients with an APOP ≥45% had a 28% mortality within 14-days, while this was 3.5% for APOP of <45% (**Table S3;** HR 2.95, 95%CI 1.27-6.87). Within 30-days the same numbers were seen: 30-day mortality was 5.4% for APOP<45% and 28% for APOP≥45% (HR 6.2, 95%CI 2.0-20).

Figure 3: Alluvial plot for risk-classification, management and outcomes



Low risk PE patients according to the ESC risk classification are noted red, intermediate-risk PE as green and high-risk as blue. As all patients who received reperfusion treatment are high-risk PE patient, the reperfusion block is also coloured blue. There are slight differences in the reported frequencies in this figure compared to the tables as only patients in whom none of the variables were missing could be included in this figure. Abbreviations: ESC European Society of Cardiology; PE pulmonary embolism.

DISCUSSION

In this study we evaluated the clinical presentation and management of older patients with acute PE with a special focus on risk classification, home treatment and reperfusion treatment. In our cohort, all patients negative to all Hestia criteria received home treatment, which resulted in a safe treatment option as no deaths or recurrent VTE events occurred in home treated patients within the first 14-days. Within the high risk group, based on the ESC guideline risk classification, mortality within 14-days was high (51%) also for those patients receiving reperfusion treatment (mortality of 63%), with comorbidities contributing largely to the hemodynamic instability in almost half of such patients. The ESC risk classification identified patients at increasing risk of death. The APOP score is a potentially alternative strategy to predict mortality in older patients with acute PE, as a high APOP score correlated with increased mortality too (HR 3.3).

Current ESC guidelines recommendations advice classifying patients in low, intermediate and high risk categories. Low risk patients are eligible for home treatment.[7] However, in our hospital the Hestia criteria are utilized as the sole triaging tool to determine eligibility for home treatment, regardless of sPESI score or ESC risk classification. Evaluation of this cohort showed that older patients with acute PE who met none of the Hestia criteria were safely managed at home, confirming the findings of the HOME-PE study that showed that for triaging PE patients, the strategy based on the Hestia rule or based on sPESI are both safe and effective.[12] Indeed, a recent individual patients data meta-analysis also showed that patients with acute PE aged >80 years had no increased risk of adverse outcomes compared with younger patients when receiving home treatment. [13] It is important to note that 1 patient had a major bleeding 7 days after the index PE diagnosis. However, hospitalized patients had a median hospitalization duration of 3 days, while this bleeding occurred 7 days after the index PE; therefore it can be debated if this event would have be prevented with hospitalization.

When using the ESC guidelines recommendation to select patients eligible for home treatment, patients with a sPESI score of > 0 cannot be classified as low risk, meaning that individuals over 80 years old, by definition, are excluded from home treatment.[3] Indeed, the PESI score correlates with increased 6-month all-cause mortality, even in older patients, but it can be debated whether this mortality risk is preventable by hospitalization. [14] Moreover, with the ESC risk classification only a small fraction of patients in our cohort (3.9%) would have been deemed eligible

for home treatment, contrasting with the 25% of older acute patients with acute PE safely selected for home treatment using the Hestia criteria (n=59). As home treatment is associated with higher patient satisfaction and lower health-care costs, increasing the number of patients that can safely receive home treatment is relevant for individuals, local hospital governance, and society.[15-17] Therefore, selecting older patient with acute PE for home treatment based on the Hestia criteria instead of the ESC-risk classification or sPESI score seems to be a safe alternative. Overall, when choosing which triaging tool for home treatment (e.g. based on the ESC classification or Hestia criteria) to implement in a certain hospital, local healthcare systems and infrastructure need to be taken into account, and different strategies may be preferred across different geographical, social, and cultural contexts.

Another focus of our study was the administration of reperfusion treatment in older patients with acute PE. Eight of the 20 older high-risk patients eventually received reperfusion treatment (40%). The most frequent reason for not giving reperfusion treatment was that the hemodynamic instability was not PE-related, raising questions about their high-risk classification and the applicability of the usual definition of high-risk PE in an elderly population: comorbidities appear to play a significant role when evaluating hemodynamically unstable older patients with acute PE. Despite receiving reperfusion treatment, outcomes in the high risk population were poor as over half of the patients died within 14-days. Remarkably, all three patients receiving thrombolysis died within 14-days due to a PE-related death, but these patients all presented after out-of-hospital cardiac arrest or had a cardiac arrest upon presentation for which resuscitation was needed during their emergency department stay. In such catastrophic PE cases, mortality is high even in younger patients (21% in hospital mortality for patients with high-risk PE and 42% in high-risk patients with hemodynamic collapse).[18] A recent study showed that usage of catheter directed reperfusion therapies in older frail patients was associated with reduced major bleeding and in hospital mortality compared with systemic thrombolysis, suggesting that CDTs might be more appropriate in older patients with high-risk PE.[19] However, randomized controlled trials evaluating different reperfusion treatments and in specific subpopulations such as older or frail patients are currently lacking (and perhaps will remain unavailable), as for example the HI-PEITHO trial (randomizing patients with intermediate-high risk PE between CDT plus anticoagulation vs anticoagulation alone) specifically excludes patients with acute PE aged older than 80 years.[20]

The ESC risk classification successfully identified patients at higher risk for death across the 3 risk classes: mortality within 14-days was 0% for low-risk patients, 7.6% for intermediate-risk patients and 51% for high-risk patients (no HR was calculated due to 0 events in the low-risk group). Notably, there was no clear difference in 14-day mortality between intermediate-high-risk or intermediate-low-risk patients. The APOP score also identified patients at higher risk for mortality (HR 3.3). Moreover, within the intermediate risk group, the APOP seemed to further differentiate the risk of death: intermediate risk patients with an APOP <45% had a 3.5% mortality within 14-days, while this was 28% for APOP≥45% (HR 2.95, 95%CI 1.27-6.87). The APOP score is a score designed to identify older patients at increased risk for mortality or functional decline irrespective of the underlying disease for which they come to the emergency department. Older patients form a special group of patients. Based on our results we hypothesize that implementing a risk-classification designed for older patients might help in better risk stratification and appropriate management decisions.

Our study has strengths and limitations. Strengths are the novelty of investigating risk stratification and management in this special population in a relatively large cohort. Limitations are that this was a retrospective cohort study, implicating that important data that has not been recorded in patient files, might have been missed. Also, data was collected from a single centre, which limits generalizability to other centres regarding the outcomes of our practice patterns. Second, we had no comparative cohort with younger patients with acute PE. However, it was not our aim to make a comparison but to describe current practice patterns for older patients with acute PE. Also, the APOP score has been administered to patients presenting to the emergency department since 2018. However, it was missing in 25% of the patients who presented after 2018. It is likely that this score was not recorded for patients with more severe diseases or comorbidities, as emergency department nurses may have been too busy to administer the score in these cases. This omission could have resulted in selection bias, particularly among high-risk patients. Therefore, we chose not to further evaluate the performance of the APOP score exclusively in this patient category. Finally, evaluation of risk classification cannot be separated from subsequent treatment. As patients were not managed according to the ESC risk classification, it remains unclear what outcomes of different treatment options would have been.

In conclusion, in our study older acute PE patients were safely selected for home treatment when none of the Hestia criteria were present. High-risk patients on the other hand had an unfavourable outcome, even if adequate reperfusion treatment is given. Risk-classification scores specifically designed for older patients might improve prognostication and management decisions in older acute PE patients.

REFERENCES

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
2. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005: 172(8): 1041-1046.
3. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010: 170(15): 1383-1389.
4. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011: 378(9785): 41-48.
5. Zondag W, Hiddinga BI, Crobach MJT, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 2013: 41(3): 588-592.
6. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011: 9(8): 1500-1507.
7. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) 2019: 1901647.
8. de Gelder J, Lucke JA, Blomaard LC, et al. Optimization of the APOP screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. Experimental Gerontology 2018: 110: 253-259.
9. de Gelder J, Lucke JA, de Groot B, et al. Predicting adverse health outcomes in older emergency department patients: the APOP study. Neth J Med 2016: 74(8): 342-352.
10. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC Subcommittee on official Communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis 2021: 19(1): 297-303.
11. Tritschler T, Kraaijpoel N, Girard P, et al. Definition of pulmonary embolism-related death and classification of the cause of death in venous thromboembolism studies: Communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis 2020: 18(6): 1495-1500.
12. Roy PM, Penaloza A, Hugli O, et al. Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. European heart journal 2021: 42(33): 3146-3157.
13. Luijten D, Douillet D, Luijken K, et al. Safety of treating acute pulmonary embolism at home: an individual patient data meta-analysis. European Heart Journal 2024.
14. Klingenberg R, Schlager O, Limacher A, et al. Risk stratification of elderly patients with acute pulmonary embolism. Eur J Clin Invest 2019: 49(9): e13154.
15. Bledsoe JR, Woller SC, Stevens SM, et al. Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. Chest 2018: 154(2): 249-256.
16. Hendriks SV, van den Hout WB, van Bemmel T, et al. Home Treatment Compared to Initial Hospitalization in Normotensive Patients with Acute Pulmonary Embolism in the Netherlands: A Cost Analysis. Thromb Haemost 2022: 122(3): 427-433.
17. Klok FAandHuisman MV. When I treat a patient with acute pulmonary embolism at home. Hematology American Society of Hematology Education Program 2020: 2020(1): 190-194.
18. Kobayashi T, Pugliese S, Sethi SS, et al. Contemporary Management and Outcomes of Patients With High-Risk Pulmonary Embolism. J Am Coll Cardiol 2024: 83(1): 35-43.

19. Farmakis IT, Barco S, Giannakoulas G, et al. A nationwide analysis of reperfusion therapies for pulmonary embolism in older patients with frailty. EuroIntervention 2023: 19(9): 772-781.
20. Klok FA, Piazza G, Sharp ASP, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study. American heart journal 2022: 251: 43-53.

5

Post pulmonary embolism syndrome and functional outcomes after acute pulmonary embolism

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Semin Thromb Hemost. 2023 Nov;49(8):848-860

ABSTRACT

Survivors of acute pulmonary embolism (PE) are at risk of developing persistent, sometimes disabling symptoms of dyspnea and/or functional limitations despite adequate anticoagulant treatment, fulfilling the criteria of the post-PE syndrome (PPES). PPES includes chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic pulmonary disease, post-PE cardiac impairment (characterized as persistent right ventricle [RV] impairment after PE), and post-PE functional impairment. To improve the overall health outcomes of patients with acute PE, adequate measures to diagnose PPES and strategies to prevent and treat PPES are essential. Patient-reported outcome measures (PROMS) are very helpful to identify patients with persistent symptoms and functional impairment. The primary concern is to identify and adequately treat patients with CTEPH as early as possible. After CTEPH is ruled out, additional diagnostic tests including cardiopulmonary exercise tests (CPET), echocardiography, and imaging of the pulmonary vasculature may be helpful to rule out non-PE-related comorbidities and confirm the ultimate diagnosis. Most PPES patients will show signs of physical deconditioning as main explanation for their clinical presentation. Therefore, cardiopulmonary rehabilitation provides a good potential treatment option for this patient category, which warrants testing in adequately designed and executed randomized trials. In this review, we describe the definition and characteristics of PPES and its diagnosis and management.

INTRODUCTION

Acute pulmonary embolism (PE) remains a frequently occurring disease. Improved treatment options and identification of less severe cases of PE using sensitive diagnostic tools have resulted in lower PE-related mortality rates in recent years.[1, 2] PE survivors are faced with a wide range of complications and long-term sequelae, such as recurrent PE, anticoagulation-associated major bleeding, and/or arterial cardiovascular complications.[3-6] Follow-up after acute PE therefore usually largely focuses on determining the optimal duration of anticoagulant therapy and the prevention of both recurrent PE and anticoagulation-associated bleeding[7].

In recent years, a lot of attention has been given to patient-reported outcomes such as quality of life (QoL) that complement the perspective from the above-mentioned traditional outcomes.[5, 8-13] Remarkably, up to half of the PE patients report persistent dyspnea, exercise intolerance, and/or functional limitations despite adequate anticoagulant treatment 3 to 6 months after the acute PE event.[8, 11, 14-17] Functional limitations include all adaptations in level of intensity or structural modifications in the ability of carrying out duties and/or activities at home or at work, due to physical, cognitive, and/or mental complaints after acute PE. These patients qualify for the post-PE syndrome (PPES).[18-20] A patient can be diagnosed with PPES after at least 3 months of adequate anticoagulant treatment. PPES is defined as the presence of any of the following: chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (PH), i.e., chronic thromboembolic pulmonary hypertension (CTEPH) or CTEPD without PH, post-PE cardiac dysfunction (characterized as persistent right ventricle [RV] impairment after PE) or post-PE functional impairment.[5, 21] In this review, we discuss the definition and characteristics of PPES, and what is currently known about its diagnosis and management.

CASE SCENARIO

A 50-year-old woman visits the outpatient clinic for a follow-up consultation 3 months after being diagnosed with an uncomplicated, unprovoked acute PE, which has been treated with a direct oral anticoagulant. Her medical history shows hypertension, for which she receives an angiotensin-converting enzyme inhibitor. She reports persistent dyspnea and functional limitations: she has not resumed her work, needs assistance from her neighbour in shopping for groceries, and is

unable to attend social activities due to fatigue. The treating physician wonders how these symptoms may be objectified, what diagnostic tests should be done, and how the patient should be treated.

THE POST-PE SYNDROME

The first category of PPES is caused by persisting thrombus after acute PE. In CTEPH, the acute thromboemboli fail to resolve adequately, causing fibrotic obstruction of the pulmonary artery tree, increased pulmonary vasculature resistance, and ultimately RV pressure overload and RV failure.[22, 23] The detailed pathophysiology of CTEPH and the reason for incomplete thrombus resolution remain unknown, although a proinflammatory state, abnormal fibrinolysis, and small vessel disease likely play a role.[22, 24-26] CTEPH is associated with poor QoL and is the most feared subgroup of PPES since untreated CTEPH is often fatal.[27-29] CTEPH is diagnosed by mismatched perfusion defects on ventilation/perfusion (V/Q) scan in combination with a mean pulmonary artery pressure (PAP) of ≥25 mm Hg and pulmonary capillary wedge pressure of ≤15 mm Hg measured with right heart catheterization (RHC).[7, 30] However, recent data from non-PH patients showed a normal mean PAP of 14.0 ± 3.3 mm Hg, suggesting an alternative definition of PH with a mean PAP of 21 instead of 25 mm Hg (two standard deviations above the mean PAP for non-PH patients), and a change in the definition of precapillary PH with a lower threshold of pulmonary vascular resistance of 2 instead of 3 Wood units has been proposed, although this definition has not yet been incorporated into the current guidelines.[23, 31]

Similar to CTEPH, CTEPD without PH is also characterized by unresolved thrombi, functional impairment, and abnormal cardiopulmonary exercise test (CPET) results, but the mean PAP at rest is normal.[32] When comparing CPET and RHC outcomes during exercise between CTEPD patients without PH and a healthy control group, CTEPD patients without PH have an increased mean PAP, inadequate increase of RV ejection fraction, and a decreased ventilatory efficiency (i.e., increased ventilation [VE]/CO2 output [VCO_2] ratio). This means that VE is increased during exercise without an accompanying increase in VCO_2, which is suggestive of an increase of dead space ventilation.[32-34] Complicating the identification and possible treatment of CTEPD patients without PH is the debatable definition of CTEPD without PH, since clear thresholds of CPET outcomes to diagnose CTEPD patients without PH remain open for discussion.

However, identifying potential CTEPD without PH is important because targeted treatment in CTEPH expertise centers could improve QoL and functional outcomes.[35, 36] The International Society on Thrombosis and Haemostasis (ISTH) suggests a definition of CTEPD without PH when the following four criteria are present: (1) exertional dyspnea of the New York Heart Association (NYHA) class ≥II, (2) persistent thromboembolic material in the pulmonary artery tree despite 3 months of adequate anticoagulant therapy, (3) normal mean PAP at rest, and (4) dead space ventilation as determined by CPET and/or PH during exercise. Currently, it is unknown whether CTEPD without PH may progress to CTEPH, and if so, how often this occurs.[23]

The second category of PPES comprises post-PE cardiac impairment. Post-PE cardiac impairment is defined by the ISTH as presence of intermediate/high echocardiographic probability of PH according to the European Society of Cardiology (ESC) criteria, RV hypokinesis, or RV dilatation, in combination with exertional dyspnea (NYHA II-IV).[21] At diagnosis of acute PE, 20 to 50% of the patients have RV dysfunction to some extent.[11, 16, 17, 37-39] Due to the initial ischemic and structural injury during the acute PE in combination with an inflammatory response in the RV, RV dysfunction can persist in a portion of the acute PE survivors possibly because of myocardial fibrosis.[16, 40-42] For 4 to 25% of the PE patients, RV dysfunction persists after several months.[11, 16, 17, 37, 39] However, in these studies no universal definition of RV dysfunction has been used, complicating the interpretation of these results. The use of the previously described definition of the ISTH of post-PE cardiac impairment could improve comparability between studies.

In most patients with post–acute PE, persisting dyspnea and functional impairment cannot be explained by the categories described earlier. Post-PE functional impairment is defined as persistent dyspnea, exercise intolerance, and/or diminished functional status after an acute PE with no apparent non-PE – related alternative explanation.[21] Decreased daily physical activity after a PE diagnosis with resulting physical deconditioning is one of the main explanations for post-PE functional impairment.[11, 18-20, 43, 44] In addition, persistent thoracic pain, anxiety, and post thrombotic panic syndrome, as well as fear for recurrences or complications, contribute largely to functional limitations, on both the social and professional level.[45-47] Post-PE functional impairment is associated with reduced QoL and higher prevalence of depression and permanent work-related disability.[10, 13, 43, 48-51]

Figure 1: Flow chart for patient self-report of the Post-VTE Functional Status scale.

PVFS scale grade		Description
0	No functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1	Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations	Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4	Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death	Death occurred before the scheduled assessment.

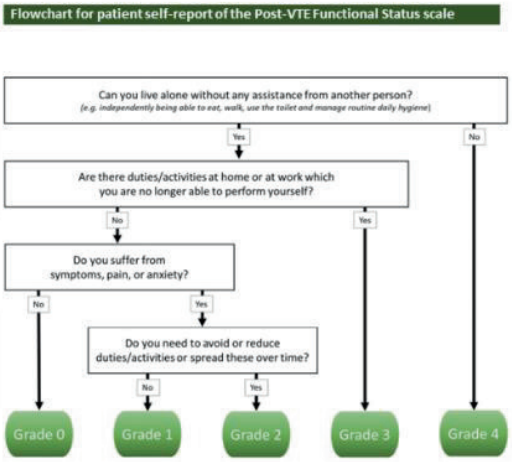


Image courtesy: Boon et al.[62]

ASSESSING LONG-TERM SYMPTOMS IN PE SURVIVORS

Validated patient-reported outcome measures (PROMS) are excellent tools to reproducibly assess the presence of persisting symptoms. By using PROMS, specific symptoms such as dyspnea, pain, fatigue, and psychological complaints and the impact on QoL can be assessed. For standardized evaluation of the severity of dyspnea, the Medical Research Council (MRC) dyspnea scale has been applied in PE patients.[7, 52] Alternative PROMS are PROMIS Short Form Dyspnea Severity, the (modified) Borg Dyspnea Scale, and the World Health Organization functional class.[7, 53-56] Disease-specific QoL can be assessed using the validated Pulmonary Embolism Quality in Life (PEmb-QoL) questionnaire, or alternatively, generic QoL PROMS can be applied.[9, 57-60] The Post-VTE Functional Status (PVFS) scale can be used to capture a general overview of the impact of persistent symptoms on functioning (**Figure 1**).[61]

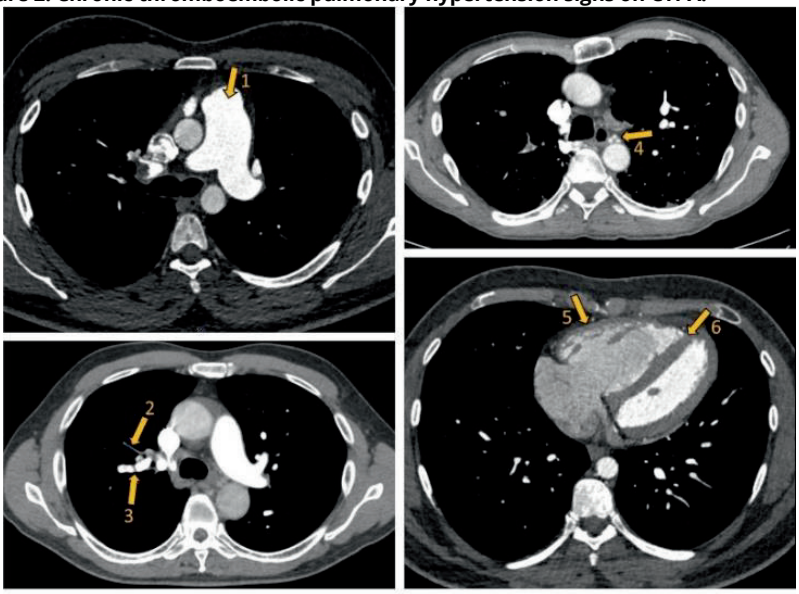
This scale was developed for assessment of overall functional status following an episode of venous thromboembolism (VTE) and refined guided by the input of VTE experts and patients.[62] The scale covers a broad spectrum of functional outcomes in six scale grades ranging from no symptoms and functional limitations to death, and captures both limitations in usual activities or duties and changes in

lifestyle. The PVFS scale can be administered through self-reported questionnaire by patients or with the use of a short structured interview, and can be applied to track functional status over time providing the ability to monitor the patients' functional recovery. As the PVFS scale was considered to be useful in the Coronavirus Disease 2019 (COVID-19) pandemic to measure functional status following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the Post-COVID-19 Functional Status (PCFS) scale was proposed after slight adaptation of the PVFS scale.[63] The construct validity of the scale has been demonstrated among adults with COVID-19 at 3 months after onset of symptoms, and the scale was able to discriminate between patients with varying degrees of fatigue, health-related QoL, and functional performance, confirming that the PCFS scale can be used to assess impact on functioning.[64, 65] In validation studies of translations of the PCFS scale into Turkish language, Mexican-Spanish, and Chilean-Spanish, and a cross-cultural adaptation study of the PCFS scale for the Chilean population, the scale had good psychometric properties in terms of reliability and was found to be a valid instrument.[66-69] To assess pain severity, PROMIS Short Forms for pain can be applied.[70] Psychological well-being can be assessed using the Patient Health Questionnaire-9 for depression and Generalized Anxiety Disorder-7 for anxiety, or the Hospital Anxiety and Depression Scale.[71-73] The Checklist Individual Strength with fatigue severity subscale is an adequate tool to measure fatigue.[74]

DIAGNOSTIC EVALUATION IN PATIENTS WITH PPES

In case patients have persisting symptoms and functional limitations that qualify for PPES, the first priority should be to rule out CTEPH: an early diagnosis will lead to improved survival and better QoL.[23, 75, 76] The presentation of CTEPH is rather nonspecific, which makes it difficult to identify patients based on the clinical presentation, unless they show (new) signs of overt right heart failure. Patients may, however, be identified by close assessment of the index computed tomography pulmonary angiography (CTPA) performed to confirm the PE. Certain CTPA characteristics have been shown to strongly predict a future CTEPH diagnosis: these signs of CTEPH can be reliably detected by both expert and nonexpert radiologists, and the presence of these should prompt additional diagnostic tests (**Figure 2**).[77-81]

Figure 2: Chronic thromboembolic pulmonary hypertension signs on CTPA.



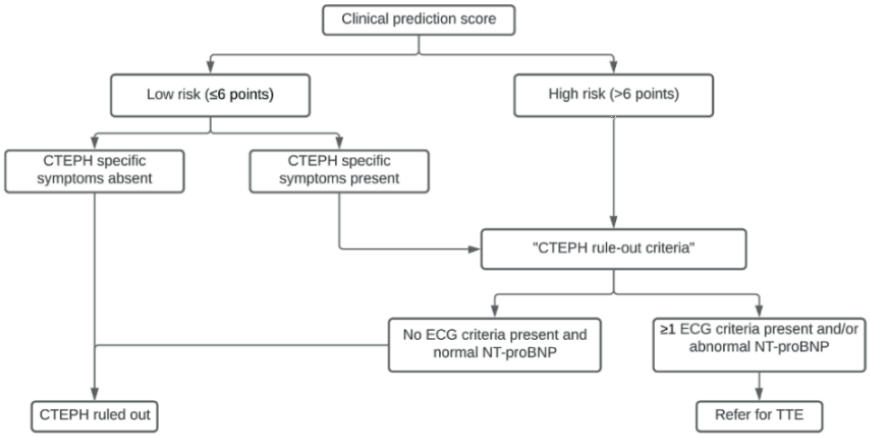
1. Dilated pulmonary trunk
2. Arterial retraction
3. Intravascular web
4. Dilated bronchial arteries
5. RV wall hypertrophy
6. Flattening of the interventricular septum

Image courtesy: Boon et al.[79]

While CTEPH can only be diagnosed through RHC, noninvasive tests can be used to rule out CTEPH. The diagnostic work-up of CTEPH starts with echocardiography.[7, 23, 82] A low probability of PH (peak tricuspid regurgitation of ≤2.8 m/s and no "PH signs") on transthoracic echocardiogram (TTE) rules out CTEPH.[7, 30] If the echocardiography indicates intermediate or high probability of PH, further evaluation should be performed with V/Q scanning and RHC in case of persistent perfusion defects.

A noninvasive screening algorithm consisting of a clinical prediction score and the so-called "CTEPH rule-out criteria" may also be used to rule out CTEPH.[83] The clinical prediction score can identify post-PE patients with a higher pretest probability of developing CTEPH.[84] The CTEPH rule-out criteria consist of a N-terminal-prohormone of brain natriuretic peptide (NT-proBNP; abnormal age- and gender-dependent level as defined by the assay's manufacturer) measurement and ECG reading (presence of three specific ECG characteristics of RV overload); if both are normal, CTEPH is considered ruled out (**Figure 3**).[85]

Figure 3: Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II algorithm.[87]



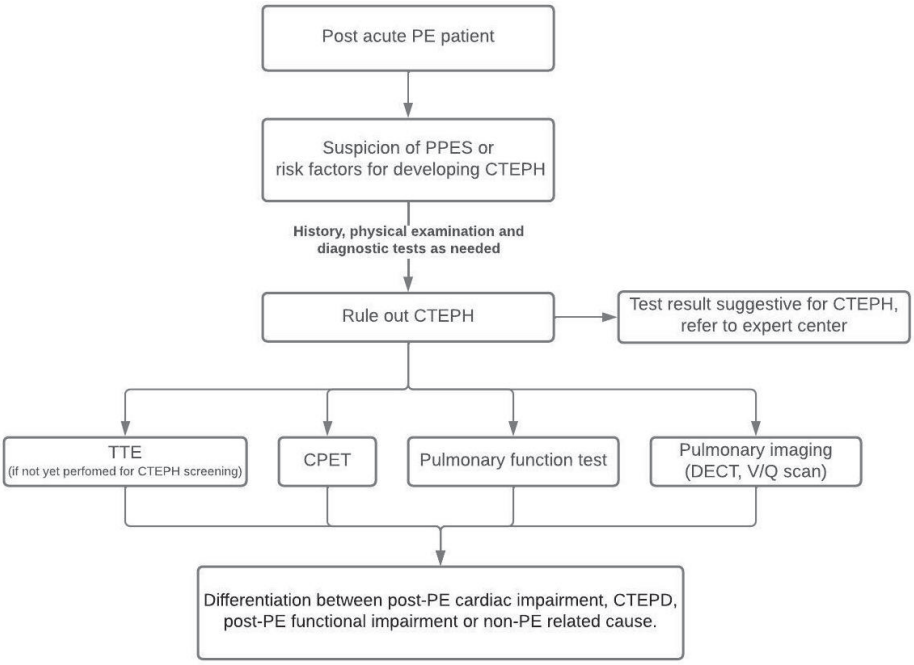
The ECG criteria of RV pressure overload: (1) rSR' or rSr' pattern in lead V1, (2) R:S > 1 in lead V1 with R > 0.5 mV, and (3) QRS axis > 90°. CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; NT-proBNP, N-terminal-prohormone of brain natriuretic peptide; TTE, transthoracic echocardiogram.

Application of the CTEPH rule-out criteria to rule out CTEPH without further testing was deemed safe in retrospective studies.[85, 86] The efficacy and safety of combining the clinical prediction score and CTEPH rule-out criteria in a noninvasive algorithm was prospectively evaluated in the Inshape II study.[87] CTEPH was considered ruled out in asymptomatic patients with a low risk of developing CTEPH according to the prediction score or in patients with normal NT-proBNP and no ECG characteristics for RV overload. Otherwise, standard evaluation with TTE as a first step was indicated. The algorithm resulted in a need for TTE in only 19% of the patients, with a low failure rate of 0.29%.[87]If CTEPH is ruled out, further diagnostic work-up depends on the characteristics of the individual patient. Potential useful diagnostic tests involve TTE (if not yet performed), CPET, pulmonary function tests, and imaging tests to evaluate the presence of persistent perfusion defects and residual clots (**Figure 4**).

The prevalence of post-PE cardiac impairment as well as other cardiological conditions such as systolic or diastolic dysfunction may be assessed with TTE. A recent follow-up study showed that left-sided diastolic dysfunction is the most frequent TTE abnormality in PE survivors, and out of all symptomatic subjects during follow -up, diastolic dysfunction was most frequently found to be the cause of functional limitations (34.2% of all symptomatic patients had diastolic

dysfunction).[88] Notably, in patients with a normal ECG and NT-proBNP level, the incidence of relevant abnormalities on echocardiography is low.

Figure 4: Flow chart for follow-up 3 months after an acute PE for the detection of PPES.



CPET, cardiopulmonary exercise test; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; DECT, dual-energy computed tomography; PE, pulmonary embolism; PPES, post–pulmonary embolism syndrome; TTE, transthoracic echocardiogram; V/Q, ventilation/perfusion.

A potential informative diagnostic test for patients with PPES without CTEPH can be CPET. CPET can be an excellent tool to further recognize pathological factors limiting exercise such as respiratory limitation, cardiovascular limitation, and peripheral muscle limitations.[89] With the recognition of the pathological limiting factor, potential therapeutic targets can be identified and prognostic information is provided.[89] Previous studies gave an interesting insight into the cardiopulmonary recovery after an acute PE. Overall, shortly after diagnosis, there is a decreased peak aerobic capacity (VO_2) which improves over time.[8, 43, 44, 90, 91] Also, increased physiological dead space proportion (the ratio of physiologic dead space over tidal volume [Vd/Vt]) and decreased stroke volume reserve are common among symptomatic post-PE patients with no residual pulmonary

vascular obstruction.[90] Mostly, CPET may play a role in detecting CTEPD without PH [92, 93] and post-PE functional impairment caused by deconditioning. Deconditioning (usually defined as low VO_2 at anaerobic threshold with normal cardiovascular, ventilatory, and gas exchange responses on CPET) is attributed to be the most frequent cause of post-PE persistent functional limitations and/or symptoms and no residual pulmonary vascular obstruction.[43, 44] Therefore, CPET might be useful for the selection of patients who will likely benefit from cardiopulmonary exercise training or rehabilitation as treatment of PPES. Moreover, CPET might also be useful after an intervention to evaluate improvement in cardiopulmonary response to exercise. Lastly, CPET, in combination with pulmonary function tests, can be useful for the evaluation of non-PE –related alternative causes of persistent symptoms.[23] Even though CPET can provide relevant information as explained earlier, it should be noted that interpretation of CPET can be difficult. There is no clear consensus on which parameters measured during CPET are essential in diagnosing PPES subgroups. Interpretation of CPET therefore relies on pattern recognition by physicians with knowledge and expertise regarding lung physiology. Interpretation can be difficult for those with fewer expertise. For detecting persistent perfusion defects, in particular in the diagnostic work-up for CTEPH, V/Q scanning remains the diagnostic standard.[7, 23] Single-Photon Emission Computed Tomography (SPECT) V/Q has shown to be superior to planar V/Q scanning.[23] Other pulmonary imaging strategies can also be used in the post-PE follow-up. Dual-Energy Computed Tomography (DECT), in which iodine maps represent areas with decreased lung perfusion, has an emerging role in the field.[23, 94] These pulmonary imaging techniques are adequate strategies to demonstrate persistent perfusion defects, but they should not be used as a routine screening test after acute PE. Perfusion defects may be associated with increased PAP and functional limitations, but 40% of patients with persistent perfusion defects do not report related symptoms.[95] Furthermore, the ELOPE study showed that the presence of persistent perfusion defects was equal in patients with a peak $VO_2 < 80\%$ of predicted compared with patients with a peak $VO_2 > 80\%$ of predicted, suggesting that persistent perfusion defects do not explain functional limitations in PPES.[43] Therefore, pulmonary imaging should only be performed in patients in whom CTEPH or CTEPD without PH is suspected based on the results of TTE and/or CPET.

TREATMENT

For CTEPH, pulmonary endarterectomy (PEA) is the treatment of choice (class I, level C recommendation).[7, 23, 30] PEA results in improved hemodynamic and exercise tolerance and is associated with low early mortality when performed in expert centers.[23, 96, 97] However, some patients are inoperable due to comorbidities or distal disease (even though which degree of distal disease is still operable is unknown). For these patients, potential treatment options are balloon pulmonary angioplasty (BPA), medical treatment, or a combination of both.[23, 30] Two large national BPA series from Germany and France showed that BPA is safe and suggest that it is effective in the treatment of CTEPH.[98, 99] Inoperable CTEPH patients were treated with BPA, after which they showed improvement of 6-minute walk test and reduction of mean PAP. The role of BPA in potential operable patients has not been evaluated and a randomized controlled trial comparing PEA with BPA is currently lacking. Based on clinical expertise, PEA remains the first choice of treatment for CTEPH.[23, 30]

Different PH-specific medications have been evaluated in randomized controlled trials for the treatment of technically inoperable CTEPH patients or patients with persistent PH after PEA (**Table 1**), showing beneficial value of treatment with PH-specific medication. However, the role of PH medication in relation to BPA or PEA remains unknown.[23] CTEPD patients without PH might also benefit from these treatments, but efficacy has only been evaluated in noncontrolled cohort studies with small patient populations.[35, 36] Since many remain unknown in the treatment of CTEPH or CTEPD without PH, it is recommended that all patients are referred to an expert center to be discussed in a multidisciplinary team.[23]

For post-PE, functional impairment deconditioning seems to be a major component. Therefore, it is suggested that exercise training or cardiopulmonary rehabilitation is an adequate treatment for this patient category. **Table 2** gives an overview of the studies that have investigated the effect of exercise training in post–acute PE patients. Overall, multiple studies have shown that exercise training in patients with PPES is safe.[100-107] Rehabilitation can be effective to improve outcomes of patients with persistent symptoms several months after the acute PE. Randomized controlled trials with large sample sizes investigating the effectiveness of a rehabilitation course in patients with PPES are currently lacking. However, several cohort studies have shown an improvement in QoL, dyspnea,

training intensity, and functional status after pulmonary rehabilitation.[105, 107] Therefore, for patients with post-PE functional impairment, rehabilitation should be considered as a possible treatment option.

To prevent deconditioning, negative spiraling, and PPES as a result, exercise training can also be initiated shortly after diagnosis. A randomized controlled trial showed significant improvement of estimated VO_2max, RV/left ventricle ratio, and health-related QoL in the high-intensity interval training group after 8 weeks of training started shortly after PE diagnosis, while no improvement was found in the control group.[106] A Danish trial randomized 140 patients between an 8-week home-based exercise program with nurse consultations starting 2 to 3 weeks after PE diagnosis and a control group. The exercise program resulted in a greater improvement of incremental Shuttle Walk Test and PE-specific QoL compared with the control group. However, between-group differences were small.[104] Since these two studies included unselected post-PE patients without considering persistent symptoms, the impact of an early exercise training program might be even larger in selected patients with persistent dyspnea and functional limitations, which should be evaluated in randomized controlled trials.

Table 1: PH medication studies for treatment of CTEPH

Study	Year	Study type	Patients	Intervention	Outcome
CHEST-1[108]	2013	RCT	Inoperable CTEPH of residual PH after PEA (n=261)	Riociguat	PVR mean difference of -226 dyn sec cm^{-5} for riociguat group and +23 dyn sec cm^{-5} for the control group (mean difference –246 dyn sec cm^{-5}; 95% CI –303 to –190) 6MWT mean difference of +39meter for riociguat group and -6 meter for placebo group (mean difference 46 m; 95% CI 25 to 67)
Reichenberger et al.[109]	2007	Open label uncontrolled	Inoperable CTEPH (n=104)	Silendafil	Decrease in PVR of 104 dyn sec cm^{-5} Increase in 6MWT of +51 meter
BENEFIT[110]	2008	RCT	Inoperable CTEPH of residual PH after PEA (n=157)	Bosentan	PVR mean difference of -146 dyn sec cm^{-5} for bosentan group and +30 dyn sec cm^{-5} for the control group (mean treatment effect -24.1%; 95% CI -31.5 to -16.0%) 6MWT mean difference of +2.9 meter for bosentan group and +0.8 meter for placebo group (mean difference 2.2 meter; 95% CI -22.5 to 26.8 meter)
MERIT-1[111]	2017	RCT	Inoperable CTEPH (n=80)	Macitentan	PVR mean difference of -206 dyn sec cm^{-5} for macitentan group and -86 dyn sec cm^{-5} for placebo group (geometric PVR ratio 0.84, 95% CI 0.70-0.99) 6MWT mean difference of +35 meter for macitentan group and +1 meter for placebo group (mean difference 34 meter; 95% CI 2.9 to 65.2)

6-minute walk test, 6MWT; chronic thromboembolic pulmonary hypertension, CTEPH; pulmonary hypertension, PH; pulmonary vascular resistance, PVR; randomized controlled trial, RCT.

Table 2: Summary of rehabilitation studies in post-acute PE patients

Author	Year	Study type	Patients and timing	Intervention	Control	Outcome
Lakoski et al.[100]	2015	RCT	VTE ≥6 weeks and <3 months before enrolment (n=17; 10 PE and 7 DVT)	3-month exercise and behavioral weight loss intervention	Usual care	No AE in either group; Mean difference of exercise per week of 133 minutes in favor of intervention group; VO_{2max} improved significantly for the intervention group (26.1 to 29.8 mL O^2 kg^{-1})
Noack et al.[101]	2015	Retrospective cohort study	Post-acute PE patients referred for rehabilitation; timing unknown (n=422)	3-week inpatient rehabilitation course	-	57 AEs occurred, all non-related to the rehabilitation course

Amoury et al. [102]	2018	Prospective cohort study	Post-acute PE patients; timing unknown (n=70)	3-week inpatient rehabilitation course	-	No patients died during rehabilitation; 4 patients (5.7%) died during the 12 months follow-up period 20 patients were hospitalized during the follow-up period (28.6%) of whom 1 patient due to newly diagnosed PE (1.4%) and 2 patients due to bleeding (2.8%)
Cires-Drouet et al.[103]	2020	Prospective cohort study	PE <28 days before enrolment (n=23)	3 months aerobic exercise training	-	No AE during the exercise period 1 death, 1 DVT and 5 readmissions due to non-exercise related reasons VO_{2max} improved significantly (+3.9 mL O^2 kg^{-1})
Rolving et al. [104]	2020	RCT	PE 2-3 weeks before enrolment (n=140)	8-week home based exercise program	Usual care with brief nurse consultation	The exercise program resulted in a greater improvement of incremental SWT and PE-specific QoL compared to the control group (mean difference 25 meter and 3.0 points on PEmb-QoL score respectively)
Nopp et al. [105]	2020	Retrospective cohort study	Acute PE median of 19 weeks before start rehabilitation (n=22)	6-week outpatient pulmonary rehabilitation	-	Mean improvement of 6MWT of 49.4 meter Improvement of self-reported health (78% of the patients reported much better or better health status)
Ghram et al. [106]	2021	RCT	Acute PE 3-4 weeks before baseline measurements (n=24)	8-week high-intensity interval training	Usual care	Improvement of estimated VO_2max (22.9 to 37.7 mL O^2 kg^{-1}; p<0.05), RV/LV ratio (1.1 to 0.8; p=0.005) and health-related QoL in the intervention group No significant improvement estimated VO_2max (28.6 to 33.3 mL O^2 kg^{-1}; p=0.08), RV/LV ratio (0.8 to 0.8 p=0.33) and health-related QoL for the control group
Boon et al.[107]	2021	Prospective cohort study	Patients with persistent moderate-to-severe dyspnea 3 months after acute PE (n=27)	12-week outpatient rehabilitation program	-	Significant improvement in training intensity (+20 Watt), PE-specific QoL (+3.9 points on PEmb-QoL score), fatigue (+16 points on Checklist Individual Strength scale) and functional status (67% of patients had improvement of ≥1 PVFS scale grade)

6-minute walk test, 6MWT; adverse event, AE; deep venous thromboembolism, DVT; Pulmonary embolism, PE; Post Venous-thromboembolism Functional Status, PVFS; Quality of life, QoL; randomized controlled trial, RCT; right ventricle/left ventricle, RV/LV; Shuttle Walk Test, SWT; venous thromboembolism, VTE.

PPES IN THE COVID-19 PANDEMIC

After a COVID-19 infection, 22 to 96% of the patients have persistent symptoms qualifying for "long Coronavirus disease" also known as "long-COVID". [112-120] It can be hypothesized that since the incidence of thromboembolic events in COVID-19 is high, patients qualifying for long-COVID might also qualify for PPES. Symptoms of long-COVID might mimic post-PE functional impairment due to reduced exercise capacity and deconditioning following COVID-19. There are several arguments to potentially expect a higher CTEPH and CTEPD without PH incidence in the COVID-19 pandemic. First, the increased number of patients with PE will result in a higher number of post-PE patients at risk for developing CTEPH or CTEPD without PH. [121-127] Second, it has been described that COVID-19 is associated with reduced fibrinolysis due to the inflammatory state. Elevated levels of plasminogen activator inhibitor-1 in COVID-19 have been shown, resulting in decreased fibrinolysis.[128-130] This hypofibrinolytic state could possibly facilitate incomplete thrombus resolution, which is part of the etiology of CTEPH and CTEPD without PH. Moreover, SARS-CoV-2 can invade endothelial cells directly or indirectly through an inflammatory effect.[128, 131] This can lead to endothelial dysfunction, which is one of the hallmarks of CTEPH.[22]

Third, one could argue that the presence of VTE may not have been evaluated properly in all COVID-19 patients. Most COVID-19–associated VTE events occur in patients during hospitalization or after hospitalization, and only a small proportion of the patients treated at home are tested for the presence of VTE.[132] Since they were never subjected to CTPA, a substantial number of these patients may have experienced undiagnosed VTE. Although long-term follow-up studies after COVID-19–associated PE are currently unavailable, the results of two studies may support a higher than expected incidence of CTEPH. TTE assessment in non–intensive care unit hospitalized COVID-19 patients showed a higher than expected prevalence of PH of 12% (24/200 patients), and COVID-19 survivors were found to have a 3-fold higher incidence of PH in the 4 months after the acute infection than non-COVID-19 patients (based on claims data).[133, 134] While any hypothesis on incidence of CTEPH in COVID-19 patients still should be regarded as speculation, ongoing studies are expected to provide relevant answers in the next year.[135] All in all, the possible higher incidence of CTEPH and CTEPD without PH underlines the need of adequate follow-up of patients with persistent symptoms after COVID-19 and awareness for chronic vascular COVID-19 complications.

CASE RESOLUTION

The patient reported a PVFS scale grade of 3, MRC grade of 2 (“I get short of breath when hurrying on the level or up a slight hill”), and a PEmb-QoL score of 16 points. She had a normal ECG but abnormal NT-proBNP of 192 ng/L (normal <125 ng/L). Follow-up TTE showed no abnormalities and a low probability of PH, and therefore CTEPH and post-PE cardiac impairment were considered excluded. The patient was subjected to CPET, which showed a decreased VO_2 at anaerobic threshold of 32% of predicted, Vd/Vt that appropriately decreased during exercise (until 0.25 at peak of exercise), VE/VCO_2 at anaerobic threshold of 31.2, and the patient reported a modified Borg score of perceived exertion of 7 (“very hard”) after exercise, indicating no dead space ventilation but potential deconditioning as cause of persistent symptoms. She was referred to a rehabilitation center for an 8-week outpatient rehabilitation course consisting of 60-minute endurance and strength exercise sessions, three times a week. After 8 weeks of exercise training, the patient reported increased functional status (PVFS scale grade of 1), only breathlessness with strenuous exercise (MRC grade 1), and improved QoL (PEmb-QoL score of 10, indicating a clinically relevant improvement). She was able to resume her usual professional and social activities.

CONCLUSION

Many patients suffer from persistent symptoms and functional limitations after acute PE. to manage these patients properly, awareness of PPES is of utmost importance. PROMS can help objectify complaints after acute PE and select patients in whom further evaluation is necessary. Since CTEPH is the most feared subgroup of PPES, evaluation of the presence of possible CTEPH has priority. Furthermore, since most PPES patients are ultimately diagnosed with post-PE functional impairment, treatment with exercise training programs could contribute to patients' functional recovery. Lastly, it is reasonable to consider and test for PPES in patients with long-COVID, even if they were not diagnosed with acute PE.

REFERENCES

1. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000–15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med 2020: 8(3): 277-287.
2. Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. Lancet Respir Med 2021: 9(1): 33-42.
3. Klok FA, Mos IC, Broek L, et al. Risk of arterial cardiovascular events in patients after pulmonary embolism. Blood 2009: 114(8): 1484-1488.
4. Klok FA, Zondag W, van Kralingen KW, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med 2010: 181(5): 501-506.
5. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2021: ehab816.
6. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
7. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). The European respiratory journal 2019: 54(3): 1901647.
8. Kahn SR, Akaberi A, Granton JT, 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 e999-990 e921.
9. Klok FA, Cohn DM, Middeldorp S, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. J Thromb Haemost 2010: 8(3): 523-532.
10. Klok FA, van Kralingen KW, van Dijk AP, et al. Quality of life in long-term survivors of acute pulmonary embolism. Chest 2010: 138(6): 1432-1440.
11. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
12. Tavoly M, Utne KK, Jelsness-Jørgensen LP, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. BMJ open 2016: 6(11): e013086.
13. Valerio L, Barco S, Jankowski M, et al. Quality of Life 3 and 12 Months Following Acute Pulmonary Embolism: Analysis From a Prospective Multicenter Cohort Study. Chest 2021: 159(6): 2428-2438.
14. Sista AKandKlok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. Thromb Res 2018: 164: 157-162.
15. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010: 104(11): 1744-1749.
16. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007: 28(20): 2517-2524.
17. Kline JA, Steuerwald MT, Marchick MR, et al. 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): 1202-1210.

18. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014: 28(6): 221-226.
19. Klok FAandBarco S. Follow-up after acute Pulmonary Embolism. Hamostaseologie 2018: 38(1): 22-32.
20. Boon GJAM, Huisman MVandKlok FA. Determinants and Management of the Post-Pulmonary Embolism Syndrome. Seminars in respiratory and critical care medicine 2021: 42(02): 299-307.
21. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research:Official Communication from the SSC of the ISTH. J Thromb Haemost 2021: 19: 297–303.
22. Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017: 26(143): 160112.
23. Delcroix M, Torbicki A, Gopalan D, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. The European respiratory journal 2020: 57(6): 2002828.
24. Lang IM, Dorfmuller PandVonk Noordegraaf A. The Pathobiology of Chronic Thromboembolic Pulmonary Hypertension. Ann Am Thorac Soc 2016: 13 Suppl 3: S215-221.
25. Quarck R, Wynants M, Verbeken E, et al. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. The European respiratory journal 2015: 46(2): 431-443.
26. Sharma S, Hofbauer TM, Ondracek AS, et al. Neutrophil extracellular traps promote fibrous vascular occlusions in chronic thrombosis. Blood 2021: 137(8): 1104-1116.
27. Mathai SC, Ghofrani HA, Mayer E, et al. Quality of life in patients with chronic thromboembolic pulmonary hypertension. The European respiratory journal 2016: 48(2): 526-537.
28. Roman A, Barbera JA, Castillo MJ, et al. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Arch Bronconeumol 2013: 49(5): 181-188.
29. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation 2016: 133(9): 859-871.
30. Galiè N, Humbert M, Vachiery J-L, 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 2015: 37(1): 67-119.
31. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. The European respiratory journal 2019: 53(1): 1801913.
32. Held M, Kolb P, Grün M, et al. Functional Characterization of Patients with Chronic Thromboembolic Disease. Respiration 2016: 91(6): 503-509.
33. Claeys M, Claessen G, La Gerche A, et al. Impaired Cardiac Reserve and Abnormal Vascular Load Limit Exercise Capacity in Chronic Thromboembolic Disease. JACC Cardiovasc Imaging 2019: 12(8 Pt 1): 1444-1456.
34. van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. J Thorac Cardiovasc Surg 2016: 152(3): 763-771.
35. Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. European Respiratory Journal 2014: 44(6): 1635-1645.

36. Coghlan JG. Balloon pulmonary angioplasty: does it have a role in CTED? Pulm Circ 2018: 8(1).
37. Ribeiro A, Lindmarker P, Johnsson H, et al. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. Circulation 1999: 99(10): 1325-1330.
38. Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic Pattern of Acute Pulmonary Embolism: Analysis of 511 Consecutive Patients. J Am Soc Echocardiogr 2016: 29(9): 907-913.
39. Golpe R, Testa-Fernández A, Pérez-de-Llano LA, et al. Long-term clinical outcome of patients with persistent right ventricle dysfunction or pulmonary hypertension after acute pulmonary embolism. European Journal of Echocardiography 2011: 12(10): 756-761.
40. Watts JA, Zagorski J, Gellar MA, et al. Cardiac inflammation contributes to right ventricular dysfunction following experimental pulmonary embolism in rats. J Mol Cell Cardiol 2006: 41(2): 296-307.
41. Iwadate K, Doi M, Tanno K, et al. Right ventricular damage due to pulmonary embolism: examination of the number of infiltrating macrophages. Forensic Sci Int 2003: 134(2-3): 147-153.
42. Gleditsch J, Jervan Ø, Tavoly M, et al. Association between myocardial fibrosis, as assessed with cardiac magnetic resonance T1 mapping, and persistent dyspnea after pulmonary embolism. Int J Cardiol Heart Vasc 2022: 38: 100935.
43. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest 2017: 151(5): 1058-1068.
44. Albaghdadi MS, Dudzinski DM, Giordano N, et al. Cardiopulmonary Exercise Testing in Patients Following Massive and Submassive Pulmonary Embolism. J Am Heart Assoc 2018: 7(5).
45. Hunter R, Noble S, Lewis S, et al. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. BMJ open 2019: 9(2): e024805.
46. Kirchberger I, Ruile S, Linseisen J, et al. The lived experience with pulmonary embolism: A qualitative study using focus groups. Respir Med 2020: 167: 105978.
47. Danielsbacka JS, Rostberg L, Olsén MF, et al. "Whole life changed" - Experiences of how symptoms derived from acute pulmonary embolism affects life. A qualitative interview study. Thromb Res 2021: 205: 56-62.
48. Keller K, Tesche C, Gerhold-Ay A, et al. Quality of life and functional limitations after pulmonary embolism and its prognostic relevance. J Thromb Haemost 2019: 17(11): 1923-1934.
49. Braekkan SK, Grosse SD, Okoroh EM, et al. Venous thromboembolism and subsequent permanent work-related disability. J Thromb Haemost 2016: 14(10): 1978-1987.
50. Willich SN, Chuang LH, van Hout B, et al. Pulmonary embolism in Europe - Burden of illness in relationship to healthcare resource utilization and return to work. Thromb Res 2018: 170: 181-191.
51. Jørgensen H, Horváth-Puhó E, Laugesen K, et al. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study. PLoS Med 2021: 18(8): e1003770.
52. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014: 112(3): 598-605.
53. Choi SW, Victorson DE, Yount S, et al. Development of a conceptual framework and calibrated item banks to measure patient-reported dyspnea severity and related functional limitations. Value Health 2011: 14(2): 291-306.
54. Crisafulli EandClini EM. Measures of dyspnea in pulmonary rehabilitation. Multidiscip Respir Med 2010: 5(3): 202-210.

55. Mador MJ, Rodis AandMagalang UJ. Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD. Chest 1995: 107(6): 1590-1597.
56. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004: 126(1 Suppl): 14s-34s.
57. Cohn DM, Nelis EA, Busweiler LA, et al. Quality of life after pulmonary embolism: the development of the PEmb-QoL questionnaire. J Thromb Haemost 2009: 7(6): 1044-1046.
58. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990: 16(3): 199-208.
59. Ware JE, Jr.andSherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992: 30(6): 473-483.
60. Hays RD, Bjorner JB, Revicki DA, et al. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 2009: 18(7): 873-880.
61. Klok FA, Barco SandSiegerink B. Measuring functional limitations after venous thromboembolism: A call to action. Thromb Res 2019: 178: 59-62.
62. Boon GJAM, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale. Thromb Res 2020: 190: 45-51.
63. Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. The European respiratory journal 2020: 56(1).
64. Machado FVC, Meys R, Delbressine JM, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Life Outcomes 2021: 19(1): 40.
65. Leite L, Carvalho L, de Queiroz D, et al. Can the Post-COVID-19 Functional Status scale discriminate between patients with different levels of fatigue, quality of life and functional performance? Pulmonology 2022.
66. Çalik Kütükcü E, Çakmak A, Kinaci E, et al. Reliability and Validity of the Turkish Version of Post-COVID-19 Functional Status Scale. Turk J Med Sci 2021: 51(5): 2304-2310.
67. Lorca LA, Torres-Castro R, Ribeiro IL, et al. Linguistic Validation and Cross-Cultural Adaptation of the Post-COVID-19 Functional Status Scale for the Chilean Population. Am J Phys Med Rehabil 2021: 100(4): 313-320.
68. Lorca LA, Ribeiro IL, Torres-Castro R, et al. Psychometric properties of the post-COVID-19 functional status scale for adult COVID-19 survivors. Rehabilitación 2021.
69. Moreno-Torres LAandVentura-Alfaro CE. Validation of the Post-Covid-19 Functional Status Scale into Mexican-Spanish. J Rehabil Med Clin Commun 2021: 4: 1000070.
70. Alonso J, Bartlett SJ, Rose M, et al. The case for an international patient-reported outcomes measurement information system (PROMIS®) initiative. Health Qual Life Outcomes 2013: 11: 210.
71. Kroenke K, Spitzer RLandWilliams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001: 16(9): 606-613.
72. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006: 166(10): 1092-1097.
73. Zigmond ASandSnaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983: 67(6): 361-370.
74. Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. J Psychosom Res 2017: 98: 40-46.
75. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. The European respiratory journal 2018: 52(6): 1801687.

76. Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Research 2021: 7(3): 00719-02020.
77. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
78. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021: 93: 64-70.
79. Boon GJAM, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2021.
80. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. AJR Am J Roentgenol 2020: 215(4): 800-806.
81. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. The European respiratory journal 2021: 58(6): 2100699.
82. de Perrot M, Gopalan D, Jenkins D, et al. Evaluation and management of patients with chronic thromboembolic pulmonary hypertension - consensus statement from the ISHLT. J Heart Lung Transplant 2021: 40(11): 1301-1326.
83. Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a Simple Noninvasive Screening Algorithm for Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism. TH Open 2018: 2(1): e89-e95.
84. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016: 14(1): 121-128.
85. Klok FA, Surie S, Kempf T, 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): 21-26.
86. Klok FA, Tesche C, Rappold L, 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.
87. Boon GJAM, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021: 76(10): 1002-1009.
88. Dzikowska-Diduch O, Kostrubiec M, Kurnicka K, et al. "The post-pulmonary syndrome - results of echocardiographic driven follow up after acute pulmonary embolism". Thromb Res 2020: 186: 30-35.
89. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir Rev 2019: 28(154): 180101.
90. Fernandes TM, Alotaibi M, Strozza DM, et al. Dyspnea Postpulmonary Embolism From Physiological Dead Space Proportion and Stroke Volume Defects During Exercise. Chest 2020: 157(4): 936-944.
91. Huang D, Guo J, Yang W, et al. Exercise Capacity and Ventilatory Efficiency in Patients With Pulmonary Embolism After Short Duration of Anticoagulation Therapy. Am J Med Sci 2020: 359(3): 140-146.
92. McCabe C, Deboeck G, Harvey I, et al. Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. Thromb Res 2013: 132(6): 659-665.

93. Held M, Hesse A, Gött F, et al. A symptom-related monitoring program following pulmonary embolism for the early detection of CTEPH: a prospective observational registry study. BMC Pulm Med 2014: 14: 141.
94. Fuld MK, Halaweish AF, Haynes SE, et al. Pulmonary perfused blood volume with dual-energy CT as surrogate for pulmonary perfusion assessed with dynamic multidetector CT. Radiology 2013: 267(3): 747-756.
95. Sanchez O, Helley D, Couchon S, et al. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemost 2010: 8(6): 1248-1255.
96. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. Circulation 2011: 123(16): 1788-1830.
97. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013: 62(25 Suppl): D92-99.
98. Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. The European respiratory journal 2019: 53(5).
99. Olsson KM, Wiedenroth CB, Kamp JC, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. The European respiratory journal 2017: 49(6).
100. Lakoski SG, Savage PD, Berkman AM, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. J Thromb Haemost 2015: 13(7): 1238-1244.
101. Noack F, Schmidt B, Amoury M, et al. Feasibility and safety of rehabilitation after venous thromboembolism. Vascular health and risk management 2015: 11: 397-401.
102. Amoury M, Noack F, Kleeberg K, et al. Prognosis of patients with pulmonary embolism after rehabilitation. Vascular health and risk management 2018: 14: 183-187.
103. Cires-Drouet RS, Mayorga-Carlin M, Toursavadkohi S, et al. Safety of exercise therapy after acute pulmonary embolism. Phlebology 2020: 35(10): 824-832.
104. Rolving N, Brocki BC, Bloch-Nielsen JR, et al. Effect of a Physiotherapist-Guided Home-Based Exercise Intervention on Physical Capacity and Patient-Reported Outcomes Among Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. JAMA network open 2020: 3(2): e200064.
105. Nopp S, Klok FA, Moik F, et al. Outpatient Pulmonary Rehabilitation in Patients with Persisting Symptoms after Pulmonary Embolism. Journal of clinical medicine 2020: 9(6): 1811.
106. Ghram A, Jenab Y, Soori R, et al. High-Intensity Interval Training in Patients with Pulmonary Embolism: A Randomized Controlled Trial. Med Sci Sports Exerc 2021: 53(10): 2037-2044. .
107. Boon GJAM, Janssen SMJ, Barco S, et al. Efficacy and safety of a 12-week outpatient pulmonary rehabilitation program in Post-PE Syndrome. Thromb Res 2021: 206: 66-75.
108. Ghofrani H-A, D'Armini AM, Grimminger F, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. New England Journal of Medicine 2013: 369(4): 319-329.
109. Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. European Respiratory Journal 2007: 30(5): 922-927.
110. Jaïs X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008: 52(25): 2127-2134.
111. Ghofrani HA, Simonneau G, D'Armini AM, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre,

phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med 2017: 5(10): 785-794.
112. Bliddal S, Banasik K, Pedersen OB, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep 2021: 11: 13153.
113. Carfì A, Bernabei RandLandi F. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020: 324(6): 603-605.
114. Chopra V, Flanders SA, O'Malley M, et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann Intern Med 2021: 174(4): 576-578.
115. Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. BMJ 2021: 374: n1648.
116. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021: 38: 101019.
117. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021: 397(10270): 220-232.
118. Naeije RandCaravita S. Phenotyping long COVID. The European respiratory journal 2021: 58(2): 2101763.
119. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021: 27: 601-615.
120. Vaes AW, Goërtz YMJ, Van Herck M, et al. Recovery from COVID-19: a sprint or marathon? 6-month follow-up data from online long COVID-19 support group members. ERJ Open Res 2021: 7(2): 00141-02021.
121. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020: 191: 145-147.
122. Kaptein FHJ, Stals MAM, Grootenboers M, et al. Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave. Thromb Res 2021: 199: 143-148.
123. Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Research and practice in thrombosis and haemostasis 2020: 4(7): 1178-1191.
124. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020: 18(7): 1743-1746.
125. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020: 46(6): 1089-1098.
126. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020: 191: 9-14.
127. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020: 191: 148-150.
128. Loo J, Spittle DAandNewnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax 2021: 76(4): 412-420.
129. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. J Am Coll Surg 2020: 231(2): 193-203.e191.
130. Whyte CS, Morrow GB, Mitchell JL, et al. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost 2020: 18(7): 1548-1555.
131. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020: 383(2): 120-128.
132. Pasha AK, McBane RD, Chaudhary R, et al. Timing of venous thromboembolism diagnosis in hospitalized and non-hospitalized patients with COVID-19. Thromb Res 2021: 207: 150-157.

133. Pagnesi M, Baldetti L, Beneduce A, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. Heart 2020: 106(17): 1324-1331.
134. Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. Bmj 2021: 373: n1098.
135. Kruip M, Cannegieter SC, Ten Cate H, et al. Caging the dragon: Research approach to COVID-19-related thrombosis. Research and practice in thrombosis and haemostasis 2021: 5(2): 278-290.

Supplementary file

6

Cardiopulmonary exercise testing in dyspnoeic persons with a recent acute pulmonary embolism

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Accepted for publication at Chest Pulmonary

ABSTRACT

Background: Cardiopulmonary exercise testing (CPET) may provide a helpful tool to assess underlying causes of dyspnea in acute pulmonary embolism (PE) patients. However, the response to exercise in the first weeks after diagnosis of an acute PE is currently unknown.

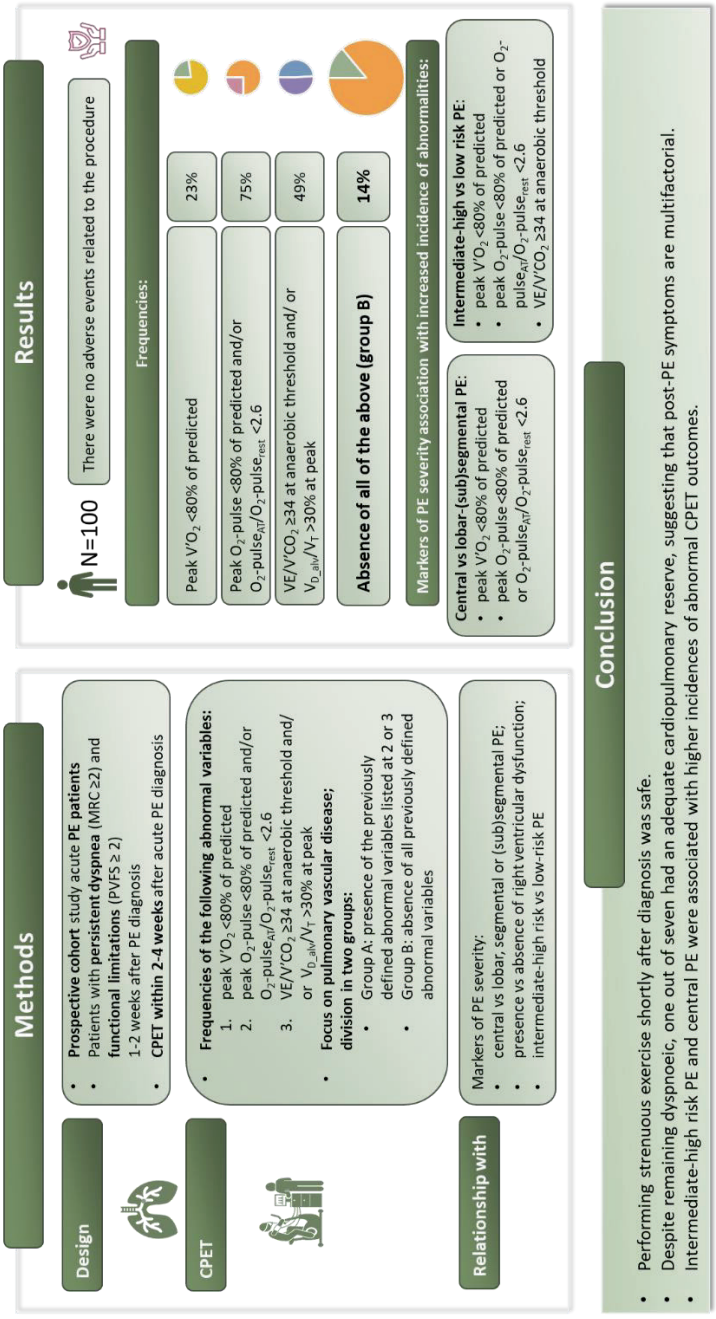
Research question: What are the cardiopulmonary responses to and safety of performing strenuous exercise within 2-4 weeks post-acute pulmonary embolism?

Study design and methods: 100 acute PE patients, without major comorbidities, experiencing dyspnea (Medical Research Council≥2) and functional limitations (Post VTE Functional status scale grade ≥2) 1-2 weeks after PE-diagnosis underwent CPET within 2-4 weeks after diagnosis. We evaluated the frequency of a peak $V'O_2$<80% of predicted, a peak O_2-pulse<80% of predicted or O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6 and a $V'E/V'CO_2$≥34 at anaerobic threshold (AT) or V_{D_alv}/V_T>30% at peak, and their association with markers of PE severity at diagnosis.

Results: There were no adverse events related to the procedure. CPET disclosed peak $V'O_2$<80% of predicted in 23% of the patients, O_2-pulse<80% of predicted or O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6 in 75% and $V'E/V'CO_2$ at AT≥34 or peak V_{D_alv}/V_T>30% in 49%. In one out of seven, none of the previously reported signs were present (14%). Intermediate-high risk PE and central PE were associated increased incidence of these abnormalities.

Interpretation: There were no complications when performing strenuous exercise in the first weeks after a PE diagnosis. Despite remaining dyspnoeic, one out of seven patients had adequate cardiopulmonary reserve, suggesting that post-PE symptoms are multifactorial. Intermediate-high risk and central PE were associated with higher incidences of abnormal CPET outcomes.

GRAPHICAL ABSTRACT



INTRODUCTION

In the acute phase of pulmonary embolism (PE), a thrombus causes ventilation-perfusion mismatch contributing to hypoxemia and increased pulmonary artery pressure potentially resulting in right ventricular failure, obstructive shock and death.[1-3] After initiation of anticoagulant treatment, there should be thrombus resolution and recovery of the cardiovascular system. However, up to 50% of acute PE survivors report persistent symptoms after 3 months, indicating post-PE syndrome.[4-10] There are three possible PE-related reasons why patients might remain symptomatic during follow-up: 1) incomplete thrombus resolution causing chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension (PH) in rest (i.e. thromboembolism with other physiological defects), 2) incomplete recovery of the right ventricle without residual pulmonary vascular obstruction and/or 3) post-PE functional impairment without physiological cardiopulmonary defects during exercise (e.g. exercise intolerance due to deconditioning).[11, 12] Post-PE patients might also have persistent symptoms unrelated to PE, such as pre-existing comorbidities and limitations.

Identification of factors limiting exercise tolerance in a particular patient might enhance outcomes.[11] Cardiopulmonary exercise testing (CPET) is a useful diagnostic test for this purpose.[13] A recent study showed a 50% prevalence of abnormal cardiopulmonary limitations (i.e. ventilatory inefficiency or insufficient cardiocirculatory reserve) 3-12 months post-PE.[14] However, the response to exercise and subsequent limitations in the first weeks after acute PE diagnosis are unknown. Given the suggested benefits of early exercise training programs to prevent post-PE functional impairment, there is a pressing need for a deeper understanding of the safety considerations and underlying pathophysiology associated with engaging in exercise shortly after PE diagnosis.[11, 15] In this study, we aimed to investigate the safety of performing CPET shortly after diagnosis, the cardiopulmonary response to exercise within the 2-4 week window following acute PE diagnosis, and correlate CPET outcomes with other markers of PE severity.

METHODS

Study population and procedures

This is a pre-planned sub-analysis of the ongoing PE@HOME study. The PE@HOME study is a prospective, multicentre, randomized controlled trial performed in the Netherlands that aimed to evaluate the effect of an exercise training program on exercise tolerance and prevention of the post-PE syndrome in acute PE patients. Patients were eligible for if they, were 18-years or older, had a CT pulmonary angiography (CTPA) confirmed PE and reported incomplete recovery at 1-2 weeks after acute PE (i.e. persistent dyspnoea assessed by a Medical Research Counsel [MRC] score of ≥ 2 and persistent function limitations assessed by a post-venous thromboembolism functional scale [PVFS] score of ≥2). Exclusion criteria were, a life expectancy <6 months, chronic dyspnoea from a known or suspected serious cardiopulmonary comorbidity (e.g. CTEPH, COPD > GOLD II, heart failure New York Heart Association Classification (NYHA) >2, or interstitial lung disease), covid-19 associated PE, presence of comorbidities requiring intensive treatment that would interfere with the study (e.g. planned surgery or malignancy requiring intense anti-cancer treatment), or incapability to follow study procedures or contra-indications for CPET.

Patients included in the study underwent a CPET within 2-4 weeks after the index PE. All CPETs were performed according to a prespecified cycle ergometer protocol including the following phases: resting, unloaded, testing and recovery phase.[16] Before starting the cycle ergometer protocol, spirometry was performed to calculate subsequent maximal voluntary ventilation (MVV; **table S1**). During the testing phase incremental exercise was performed with a ramp or minute-by-minute protocol. Exercise was continued until the point of subjective exhaustion was reached or one of the safety stopping criteria was met (**table S2**). At rest and peak capillary blood samples were obtained by finger puncture. Study procedures performed after the CPET, were outside of the scope of this sub-analysis. The study was approved by the medical ethics review committee MERC-LDD and written informed consent was obtained from all patients before enrolment.

Safety analysis

To evaluate the safety of CPET shortly after acute PE, we collected data on adverse events, which were defined as any undesirable event occurring during or after

CPET that was related to the index PE event or to the performance of the CPET and not caused by a pre-existing, non-PE related condition.

CPET analysis and definitions

Anaerobic threshold (AT) was determined using the V-slope method.[17] Participating sites reported outcomes of the following variables at rest, AT and peak exercise: load; oxygen uptake ($V'O_2$); carbon dioxide output ($V'CO_2$); minute ventilation (V'E); expiratory tidal volume (VTex; breathing frequency (BF); heart rate (HR); oxygen pulse (O_2-pulse; $V'O_2$/HR); expiratory carbon dioxide pressure ($PECO_2$); expiratory end-tidal carbon dioxide pressure ($PETCO_2$); ventilatory equivalent for carbon dioxide ($eqCO_2$; $V'E/V'CO_2$); transcutaneous oxygen saturation (SpO_2). Electrocardiograms (ECGs) and blood pressure levels were checked for abnormalities. From the capillary blood sample CO_2 tension (P_cCO_2), lactate levels and dead space ventilation (V_{D_alv}/V_T) were determined. Predicted values were used according to the Study of Health in Pomerania (SHIP; **Table S2**).[18]

Maximal exercise effort was achieved at the point when the patient discontinued exercise when ≥1 of the following was present at peak exercise: (1) $V'O_2$ >100% of predicted or a plateau in $V'O_2$ (defined by an increase in $V'O_2$ <2.0 mL/min/kg despite an increase in work rate by 5–10%[16]) (2) HR >100% predicted or HR reserve <15 beats/min (3) V'E ≥85% MVV (4) RER >1.05 (5) blood lactate ≥8 $mmol \cdot L^{-1}$ and/or (6) Borg score of ≥17 was achieved indicating severe leg discomfort or dyspnea.[19]

Abnormal findings were defined by consensus criteria such as a peak $V'O_2$<80% of predicted, a $\Delta V'O_2/\Delta$ load ≤ 8.4 mL/min/watt, a $V'E/V'CO_2$ at AT ≥34, a peak $P(c\text{-}ET)CO_2$ >0.3 kPa a V_{D_alv}/V_T>30%, peak HR<85% of predicted, a peak O_2-pulse<80% of the predicted value, a $V'O_2$ at AT < 40% of predicted at peak, a peak spO_2 <90% or >5% drop during exercise, a peak breathing frequency ≥60, and a breathing reserve (BR) < 15%.[19]

Stroke volume (SV) is not only defined by the O_2-pulse but also by the peripheral extraction of oxygen ($C_{a\text{-}v}O_2$; $SV=O_2\text{-pulse}/C_{a\text{-}v}O_2$). As the increase of $C_{a\text{-}v}O_2$ between rest and AT can be predicted, SV augmentation between rest and AT is reflected by the relative increase in O_2-pulse between rest and AT. [20] An $O_2\text{-pulse}_{AT}/O_2\text{-pulse}_{rest}$ <2.6 has a 92.6% sensitivity and 66.7% specificity for SV_{AT}/SV_{rest} which was 74% and 100% respectively for <2.2. [21] Thus an $O_2\text{-pulse}_{AT}/O_2\text{-pulse}_{rest}$ <2.2 and between 2.2–2.6 was also included.

Moreover, we looked in more detail at the presence or absence of signs more specific for pulmonary vascular disease.[22] Therefore, we divided patients in to two groups: group A are patients with presence of any of the following: 1) a peak O_2-pulse<80% of predicted, 2) an O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6, 3) V'E/V'CO_2 at AT≥34 or 4) a peak V_{D_alv}/V_T>30. Group B consisted of individuals with presence of all of the following: 1) VO_2 ≥80% of predicted, 2) peak O_2-pulse ≥80% of predicted, 3) O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ ≥ 2.6, 4) V'E/V'CO_2 at AT <34, and 5) peak V_{D_alv}/V_T ≤30%.

As SV augmentation is related to O_2-pulse and $C_{a\text{-}v}O_2$, O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ alone as a marker of poor SV augmentation might be more specific. Moreover, for ventilatory inefficiency V'E/V'CO_2 can also be caused by a low pCO_2 setpoint, and V_{D_alv}/V_T alone may be more specific. Therefore, we performed a sensitivity analysis where group A was defined as presence of any of the following: 1) an O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ <2.6, or 2) a peak V_{D_alv}/V_T>30. Group B was defined as presence of all of the following: 1) VO_2 ≥80% of predicted, 2) O_2-pulse$_{AT}$/O_2-pulse$_{rest}$≥2.6, and 3) peak V_{D_alv}/V_T ≤30%.

To correlate CPET outcomes with other markers of PE severity, the following markers of baseline PE severity were investigated: central, versus lobar, segmental or (sub)segmental PE; presence versus absence of right ventricular pressure overload; and intermediate-high risk versus low risk PE. We defined right ventricular (RV) pressure overload at index PE as a RV/left ventricle (LV) ratio on CTPA of ≥ 1 as echocardiography was not performed in most cases, however if echocardiography was performed, signs of RV dysfunction on echocardiography were also included (**Table S1**). PE risk was classified as low, intermediate-low, or intermediate-high according to the 2019 ESC guideline.[2] We correlated these subgroups to the following CPET outcomes: 1) a peak V'O_2<80% of predicted 2) V'E/V'CO_2 at AT ≥34, 3) a V_{D_alv}/V_T>30% at peak exercise,4) a peak O_2-pulse<80% of predicted, and 5) O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ <2.6.

Statistical analysis

Categorical variables are presented as frequency with percentages and continuous variables are presented as median with interquartile range (IQR). We calculated odds ratios for markers of PE severity on odds of having 1) a peak V'O_2<80% of predicted 2) V'E/V'CO_2 at AT ≥34, 3) a V_{D_alv}/V_T>30% at peak exercise,4) a peak O_2-pulse<80% of predicted, or 5) O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ <2.6. To visualize overlap of markers associated with pulmonary vascular disease we plotted these

in a Venn-diagram including. All analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing; www.R-project.org).

Table 1: baseline characteristics of all included patients (n=100)

Age (years, mean ±SD)	57.8 (12.5)
Male sex (n, %)	48 (48.0)
BMI (kg/m^2, mean ±SD)	29.2 (5.9)
Unprovoked (n, %)	68 (70.1)
Provoked by a transient risk factor (n, %)	22 (22.7)
Provoked by a permanent risk factor (n, %)	7 (7.2)
Comorbidities	
Previous VTE	32 (32.7)
COPD (GOLD I)	2 (2.0)
Heart failure	1 (1.0)
Hypertension	12 (12.2)
Stroke	3 (3.1)
Diabetes mellitus	5 (5.1)
Active malignancy	2 (2.0)
Anticoagulant treatment (n, %)	
Direct oral anticoagulant	93 (95.9)
Low molecular weight heparin	1 (1.0)
Vitamin K antagonist	3 (3.1)
Most proximal location of PE (n, %)	
Central; Lobar; Segmental; Subsegmental	35 (36.5); 12 (12.5); 37 (38.5); 12 (12.5)
RV pressure overload (n, %)*	33 (33.7)
Hospital admission at initial presentation (n, %)	61 (62.2)
sPESI of 0; ≥1 (n, %)	77 (81.1); 18 (18.9)
ESC intermediate-high risk (n, %)	5 (5.3)
ESC intermediate-low risk (n, %)	26 (27.4)
ESC intermediate not further classified (n, %)	22 (23.2)
ESC low risk (n, %)	42 (44.2)
MRC after 1-2 weeks of 2;3;4;5 (n, %)	56 (56.0); 36 (36.0); 5 (5.0); 3 (3.0)
PVFS after 1-2 weeks of 2;3;4 (n, %)	55 (55.0); 42 (42.0); 3 (3.0)

Percentages are over non-missing data *Right ventricular (RV) pressure overload at index PE was defined as a RV/left ventricle (LV) ratio on CTPA of ≥ 1 as echocardiography was not performed in most cases, however if echocardiography was performed, any of the following findings were also classified as having RV pressure overload: 1) RV/LV end-diastolic diameter ratio ≥ 0.9 (apical or subcostal 4-chamber view), 2) RV end-diastolic diameter > 30 mm (parasternal long-axis or short-axis view), 3) RV free wall hypokinesis (any view), 4) Tricuspid regurgitation velocity > 2.8 m/s (apical or subcostal 4-chamber view, or parasternal short-axis view), or 5) Inferior vena cava diameter > 21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration).Abbreviations: CWRT constant work rate cycle test, ESC European Society of Cardiology, MRC Medical Research Council, NT-proBNP N-terminal pro–B-type natriuretic peptide, PE pulmonary embolism, PVFS Post Venous Thromboembolism Functional Scale, RV right ventricular, SD standard deviation, sPESI simplified PESI.

RESULTS

Patient population

We included the first 100 acute PE patients who were included in the PE@HOME study and underwent CPET 2-4 weeks after their diagnosis (**Figure S1**). Mean age was 58 years and 48% was male. Of all patients, 12% had hypertension, 33% a previous venous thromboembolism, 2% COPD (GOLD stage I or II) and 2% an active malignancy (**Table 1**). All patients had a hemodynamically stable acute PE at presentation. The index PE presented in most patients as an unprovoked PE (70%). Approximately half of the patients had PE in segmental or subsegmental locations was segmental (38.5% and 12.5%, respectively). Most patients had no signs of RV pressure overload (66%).

CPET

CPET was performed after a median of 20 days (IQR 20-27). Six patients had a CPET >28 days post-PE due to logistical issues. In 22 of 100 patients, capillary blood gas analysis couldn't be performed due to staff shortages or equipment failure. Exercise was continued to exhaustion in 98 patients without incident.

In two patients CPET was stopped because of hypertension (systolic blood pressure > 250 mmHg); the hypertension was pre-existing and deemed non-PE related and therefore no adverse events occurred in these patients. In one other patient CPET was continued until subjective exhaustion was achieved, but retrospective evaluation of the ECG showed slight ST-elevations in V4-V6 during exercise without presence of chest pain, subsequent echocardiography showed no signs of PH and a non-dilated RV. Repeat CPET showed no ECG abnormalities and therefore this event was not counted as an adverse event.

Continuous and parameter CPET data are depicted in **Table 2**. No patients had a submaximal test. Generally, peak aerobic exercise capacity was preserved. Indeed, 77% of the patients had a peak $V'O_2 \geq 80\%$ predicted. In 28 patients $V'E/V'CO_2$ at AT was≥34 (28%), in 47 patients peak $P(c\text{-}ET)CO_2$>0.3 kPa (56%) and in 27 patients peak V_{D_alv}/V_T was>30% (35%). Fifteen patients had a peak heart rate<85% of predicted (15%), 27 had a peak O_2-pulse<80% of predicted (27%), 46 had a $O_2\text{-pulse}_{AT}/O_2\text{-pulse}_{rest}$ <2.2 (46%) and 27 had a $O_2\text{-pulse}_{AT}/O_2\text{-pulse}_{rest}$ ≥2.2 and <2.6 (27%). Ten patients had a $V'O_2$ at AT<40% of predicted (10%).

Table 2: CPET data 2-4 weeks after PE

Metabolic	Median (IQR)	Abnormal if	Frequency of abnormality (%)
Peak load [watt]	140 (104-182)		
Peak V'O_2 [mL/min]	1787 (1463-2173)	Peak V'O_2 < 80% of predicted	23 (23)
Δ V'O_2/Δ load [mL/min/watt]	10 (9.4-11)	Δ V'O_2/Δ load ≤ 8.4 mL/min/watt	10 (10)
Peak RER	1.12 (1.05-1.18)		
Cardiopulmonary			
Ventilatory inefficiency			
V'E/V'CO_2 at AT	31.1 (28.4-34.3)	V'E/V'CO_2 at AT ≥34	28 (28)
Peak P(c-ET)CO_2	0.4 (0.15-0.713)	P(c-ET)CO_2 at max >0.3 kPa	47 (56)
Peak V_{D_alv}/V_T [%]	27 (20.8-32.2)	Peak V_{D_alv}/V_T>30%	27 (35)
Cardiocirculatory			
Peak HR [beats/min]	146 (136-164)	Peak heart rate <85% of pred	15 (15)
Peak O_2-pulse (V'O_2/HR) [mL/beat]	11.8 (10.1-14)	Peak O_2-pulse<80% of pred	27 (35)
		O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ < 2.2	46 (46)
		O_2-pulse$_{AT}$/O_2-pulse$_{rest}$ ≥2.2 and ≤2.6	27 (27)
V'O_2 at AT [mL/min]	1050 (856-1281)	V'O_2 at AT < 40% of predicted at peak	10 (10)
Ventilatory			
Peak V'E [L/min]	73.4 (61.1-90)		
Peak oxygen saturation [%]	96 (94-98)	Peak spO_2 <90% or >5% drop during exercise	4 (4)
Peak breathing frequency [breaths/min]	37.2 (32.3-42.2)	Peak breathing frequency [breaths/min] ≥60	1 (1)
Peak breathing reserve ((MVV-V'E)/ MVV) [%]	36.3 (27.6-43.1)	BR < 15%	7 (7)

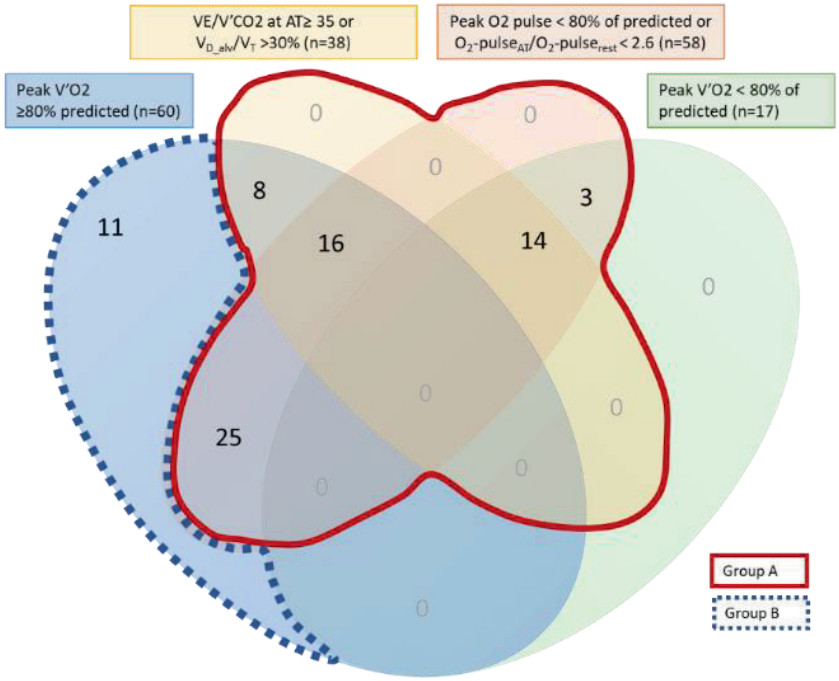
Continuous data is reported as median (IQR) and parameter data is reported as a frequency (%) Abbreviations: CPET: Cardiopulmonary Exercise Test, IQR: Interquartile Range, PE: Pulmonary Embolism, V'E: Minute Ventilation, V'O_2 : Oxygen Consumption (mL/min), V'CO_2: Carbon Dioxide Production (mL/min), HR: Heart Rate (beats/min), MVV: Maximal Voluntary Ventilation (L/min), p(c-ET)CO_2: Partial Pressure of Carbon Dioxide in the End-Tidal Gas (kPa), VD_alv/VT: Dead Space to Tidal Volume Ratio

Only four patients had a peak SpO_2<90% or >5% drop during exercise (4%), one patients had a peak breathing frequency≥60 (1%) and 7 patients had a BR<15% (7%).

Figure 1 presents the overlap of variables more specific for pulmonary vascular disease. In more detail out of the 77 patients included in this sub-analysis, 66 were classified as group A (86%) and 11 were classified as group B (14%). **Table S6** shows the mean variables and frequencies of other abnormalities in group B.

For the sensitivity analysis only including peak $V'O_2$<80% of predicted, O_2-$pulse_{AT}/O_2$-$pulse_{rest}$ <2.6 and a peak V_{D_alv}/V_T>30%, similar numbers were seen: group A included 65 patients (84%) and group B included 11 patients (14%). In one patient there was presence of a peak $V'O_2$<80% of predicted but no signs of a O_2-$pulse_{AT}/O_2$-$pulse_{rest}$ <2.6 or peak V_{D_alv}/V_T>30%.

Figure 1: Overview overlap patterns of limitation



This Venn diagram presents the absolute number per category. Patients in the blue circle had a peak $V'O_2$ ≥80% of predicted. Patients in yellow had a $V'E/V'CO_{2\geq34}$ at AT or a peak V_{D_alv}/V_T>30%. Patients in red had a peak O_2-pulse < 80% of predicted or an O_2-$pulse_{AT}/O_2$-$pulse_{rest}$ <2.6. Patients in green had a peak $V'O_2$<80% of predicted. Patients outside of these circles do not have these characteristics. Overlap of circles means multiple characteristics are present. Group A is circles with a red solid line and group B is circled with a blue dashed line.

Markers of PE severity

Table 3 presents the association between markers of PE severity and CPET outcomes. Presence of RV pressure overload was not associated with increased incidence of abnormal CPET outcomes. Central PE was associated with an increased incidence of a peak V'O_2<80% of predicted and a peak O_2-pulse<80% of predicted compared to a lobar or (sub)segmental PE (OR 3.4 [95%CI 1.1-10] and 3.4 [95CI 1.2-9.7], respectively).

Patients with an intermediate-high risk PE had an increased incidence of a peak V'O_2<80% of predicted, a peak O_2-pulse <80%, a O_2-pulse$_{AT}$/O_2-pulse$_{rest}$< 2.6 and a V'E/V'CO_2 at AT ≥34, (OR 10 [95%CI 0.94-150], 14 [95%CI 1.2-740], 4.6 [95%CI1.5 to 15]18 [95%CI 1.5-980], respectively) compared to patients with a low risk PE.

Table 3: OR of markers of PE severity

		RV pressure overload (n=33)	No RV pressure overload (n=65) *	Central (n=35)	Lobar-(sub)segmental (n=61)*	Intermediate-high (n=5)	Low risk (n=42)*
Peak V'O_2 <80% pred	n (%)	9 (27)	14 (22)	13 (37)	9 (15)	3 (60)	5 (12)
	OR (95%CI)	1.4 (0.45 to 4)		3.4 (1.1 to 10)		10 (0.94 to 150)	
Peak O_2-pulse<80% pred	n (%)	10 (30)	17 (26)	15 (43)	11 (18)	4 (80)	9 (21)
	OR (95%CI)	1.2 (0.43 to 3.4)		3.4 (1.2 to 9.7)		14 (1.17 to 740)	
O2-pulseAT/O2-pulserest < 2.6	n (%)	28 (85)	43 (66)	28 (80)	41 (67)	5 (100)	24 (57)
	OR (95%CI)	2.7 (0.86 to 10)		1.8 (0.63 to 5.9)		4.6 (1.5 to 15)	
V'E/V'CO_2 at AT ≥34	n (%)	11 (33)	16 (25)	10 (29)	16 (26)	4 (80)	7 (17)
	OR (95%CI)	1.5 (0.53 to 4.1)		1.1 (0.38 to 3)		18 (1.5 to 980)	
Peak V_{D_alv}/V_T >30%	n (%)	7 (21)	19 (29)	10 (29)	15 (25)	0 (0)	7 (21)
	OR (95%CI)	0.79 (0.23 to 2.5)		1.1 (0.38 to 3.4)		0 (0 to 3.7)	

* reference subgroup. Abbreviations: AT: anaerobic threshold, PE: Pulmonary Embolism, OR: Odds Ratio, pred: Predicted, RV: Right Ventricular, V'E: Minute Ventilation, V'O_2 : Oxygen Consumption (mL/min), V'CO_2: Carbon Dioxide Production (mL/min), HR: Heart Rate (beats/min), MVV: Maximal Voluntary Ventilation (L/min), p(c-ET)CO_2: Partial Pressure of Carbon Dioxide in the End-Tidal Gas (kPa), V_{D_alv}/V_T: Dead Space to Tidal Volume Ratio

DISCUSSION

The principle finding of our study is that strenuous exercise as soon as 2-4 weeks after a hemodynamically stable PE is safe and well-tolerated. No adverse events related to PE or causing harm to the patients were observed among the 100 tests performed. Notably, despite reporting dyspnea, 77% of the patients had a normal exercise capacity (i.e. a normal peak $V'O_2$) and in 14% of the patients no signs for a reduced exercise capacity (VO_2<80% of predicted), no signs of ventilatory inefficiency ($V'E/V'CO_2$ at AT≥34 and peak V_{D_alv}/V_T>30%) and no signs of insufficient cardiocirculatory reserve (peak O_2-pulse<80% of predicted and O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6) were observed. The presentation of acute PE was only partially predictive of post-PE cardiopulmonary function during CPET. Patients diagnosed with anatomically central PE had an increased incidence of a peak $V'O_2$<80% predicted, a peak O_2-pulse<80% predicted and a O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6. Those with intermediate-high risk PE appeared to have a higher risk of a peak O_2-pulse<80% predicted, a O_2-pulse$_{AT}$/O_2-pulse$_{rest}$<2.6 or a $V'E/V'CO_2$ at AT≥34.

Up to half of acute PE patients experience persistent symptoms and limitations in daily life despite adequate anticoagulant treatment, which is one aspect of the post-PE syndrome.[5-10] One potential cause is “post-PE functional impairment” where fear of complications combined with cautious medical advice for resuming exercise results in inactivity and deconditioning.[11, 23-25] Early exercise training has been suggested as a method to reduce inactivity and prevent deconditioning, potentially mitigating post-PE syndrome. Our results demonstrated that performing exercise in selected acute PE patients 2-4 weeks after diagnosis was safe, with no PE-related adverse events. Since CPET involves higher intensity than typical exercise training, our study suggests the potential safety of initiation of exercise training in the first weeks after PE diagnosis, aligning with previous studies reporting no adverse events during such programs for PE patients.[11, 15, 26, 27] This is crucial, as excessive caution regarding exercise resumption may contribute to inactivity and potential deconditioning. However, our study focused on a selected group of hemodynamically stable patients and the safety of exercise at home and in patients with severe acute PE remains to be established.

Despite all patients still experiencing dyspnea and functional limitations at 1-2 weeks post diagnosis, one out of seven patients displayed no signs of inefficient ventilation or insufficient cardiocirculatory reserve of which we conclude had an adequate cardiopulmonary response during exercise. Out of the 66 patients with

signs of ventilatory inefficiency or signs of insufficient cardiocirculatory reserve, 49 were still able to achieve a normal peak $V'O_2$ (74%). This important finding has two implications; 1) peak $V'O_2$ alone is insensitive for ruling out cardiopulmonary limitations such as exercise-related ventilatory inefficiency and poor cardiac reserve post-PE; 2) similar to other pulmonary diseases, post-PE patients may safely exercise of the type experienced during CPET despite the presence of demonstrable physiological defects associated with dyspnea.

Previous studies have reported that at 3-12 months post-acute PE, 47-55% of patients exhibit abnormal exercise capacity and 50% display adequate cardiopulmonary reserve.[5, 14] Moreover, when only looking at patients with post-PE impairment, approximately 20% exhibit adequate cardiopulmonary response during follow-up. [14] When looking at persistent symptoms and persistent vascular obstruction on imaging, the same pattern is seen: there is an association between persistent symptoms post-PE and persistent vascular obstruction, but a large proportion of patients with persistent symptoms do not have persistent vascular obstruction. [28] Therefore, these result highlight that not all post-PE dyspnea and/or functional limitation can be explained by these abnormalities, as a considerable proportion of the patients with symptoms had an adequate cardiopulmonary response and/or no abnormal exercise capacity. In these patients the cause of their post-PE symptoms remains unclear. The sensation of dyspnea in post-PE patients is probably caused by a neuromechanical dissociation and influenced by persistent clots and ventilation perfusion mismatch.[29] Consequently, a given respiratory workload can result in a different perception of dyspnea in various individuals.[30] In addition, psychological factors such as anxiety may also be involved in the sensation of dyspnea.

On the other hand, in 86% of the patients with dyspnea and functional limitations we did observe an abnormal cardiopulmonary limitation when performing exercise and during acute PE follow-up similar number are reported.[5, 14] Patients with a central PE or intermediate high risk PE are at increased risk for such abnormalities. Notably, the association of intermediate-high risk with abnormal exercise capacity was nonsignificant, but this was likely due to statistical power limitations (as the relationship between intermediate risk and abnormal exercise capacity was significant; **Table S5**). Interestingly, presence of RV pressure overload at presentation did not seem to correlate with abnormalities on CPET, nor did V_{D_alv}/V_T correlated with any of the markers of PE severity. Moreover, we expected that RV pressure overload would be within the causal pathway of central

PE leading to RV pressure overload resulting in abnormalities on CPET as central PE is associated with increased clot burden, and increased clot burden is associated with increased RV/LV ratio on CTPA.[31] However, we observed no association between RV pressure overload and abnormalities on CPET, which could potentially be attributed to the omission of the degree of RV pressure overload from the analysis. Instead, we used the –commonly used- indirect classification of pressure overload by only measuring the RV/LV ratio rather than all functional outcomes of the cardiac ultrasound and therefore maybe overestimating the pressure overload, especially in case of a slightly increased RV/LV ratio. Overall, whether patients who have an abnormal cardiovascular limitation in our cohort are also the patients who remain with limitations and symptoms during follow-up and what the impact is of exercise training programs on post-PE syndrome remains uncertain. This is being investigated in the ongoing PE@HOME trial, of which our study was a pre-planned sub-analysis.

The study's multicenter prospective design and the novelty of performing CPET soon after PE diagnosis are key strengths. However, several limitations should be noted. First, as part of the ongoing PE@HOME trial, only a selected group of acute PE patients with dyspnea and functional limitations were included, excluding those unable to participate in an 8-week exercise program (e.g., those undergoing cancer treatment, pregnant, or discharged to rehab). Second, capillary blood samples, rather than arterial $PaCO_2$, were used to calculate V_{D_alv}/V_T, possibly overestimating abnormalities, though the bias (<1 mmHg) is unlikely to affect results.[32] Third, despite the inclusion of a relatively large number of patients, subgroup analyses may have been underpowered. Also, we exclusively enrolled patients experiencing dyspnea and functional limitation, confirmed during a follow-up telephone assessment 1-2 weeks post-diagnosis, acknowledging the possibility of slight condition improvement before performing CPET at 2-4 weeks post-PE. Finally, although a harmonized CPET protocol was implemented, small locoregional deviations may have occurred.

In conclusion, here were no complications when performing strenuous exercise in the first weeks after a PE diagnosis. Despite remaining dyspnoeic, one out of seven patients had adequate cardiopulmonary reserve, suggesting that post-PE symptoms are multifactorial. Central PE and intermediate to high-risk PE are associated with higher incidences of CPET abnormalities. Further research is needed to elucidate the underlying causes of post-PE symptoms and the potential impact of early exercise initiation on outcomes.

REFERENCES

1. Ruigrok DandNoordegraaf AV. Pathophysiology of acute pulmonary embolism. *In:* Camm AJ, Lüscher TF, Maurer G, Serruys PW, eds. The ESC Textbook of Cardiovascular Medicine. Oxford University Press, 2018; p. 0.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *European Heart Journal* 2019: 41(4): 543-603.
3. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. *Nature Reviews Disease Primers* 2018: 4(1): 18028.
4. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev* 2014: 28(6): 221-226.
5. Kahn SR, Akaberi A, Granton JT, 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 e999-990 e921.
6. Sista AKandKlok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. *Thromb Res* 2018: 164: 157-162.
7. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. *Vasc Med* 2017: 22(1): 37-43.
8. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. *Respir Med* 2010: 104(11): 1744-1749.
9. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J* 2007: 28(20): 2517-2524.
10. Kline JA, Steuerwald MT, Marchick MR, et al. 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): 1202-1210.
11. Luijten D, de Jong CMM, Ninaber MK, et al. Post-Pulmonary Embolism Syndrome and Functional Outcomes after Acute Pulmonary Embolism. *Semin Thromb Hemost* 2022.
12. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. *Eur Heart J* 2021: ehab816.
13. Fernandes TM, Alotaibi M, Strozza DM, et al. Dyspnea Postpulmonary Embolism From Physiological Dead Space Proportion and Stroke Volume Defects During Exercise. *Chest* 2020: 157(4): 936-944.
14. Farmakis IT, Valerio L, Barco S, et al. Cardiopulmonary exercise testing during follow-up after acute pulmonary embolism. *Eur Respir J* 2023: 61(6).
15. Rolving N, Brocki BC, Bloch-Nielsen JR, et al. Effect of a Physiotherapist-Guided Home-Based Exercise Intervention on Physical Capacity and Patient-Reported Outcomes Among Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. *JAMA network open* 2020: 3(2): e200064.
16. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *European Respiratory Review* 2019: 28(154): 180101.

17. Beaver WL, Wasserman KandWhipp BJ. A new method for detecting anaerobic threshold by gas exchange. *Journal of Applied Physiology* 1986: 60(6): 2020-2027.
18. Gläser S, Ittermann T, Schäper C, et al. [The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing]. *Pneumologie* 2013: 67(1): 58-63.
19. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev* 2019: 28(154): 180101.
20. Stringer WW, Hansen JEandWasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol (1985)* 1997: 82(3): 908-912.
21. Alotaibi M, Yang JZ, Papamatheakis DG, et al. Cardiopulmonary exercise test to detect cardiac dysfunction from pulmonary vascular disease. *Respiratory Research* 2024: 25(1): 121.
22. Morris TA, Fernandes TMandChannick RN. Evaluation of Dyspnea and Exercise Intolerance After Acute Pulmonary Embolism. *CHEST* 2023: 163(4): 933-941.
23. Hunter R, Noble S, Lewis S, et al. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. *BMJ open* 2019: 9(2): e024805.
24. Kirchberger I, Ruile S, Linseisen J, et al. The lived experience with pulmonary embolism: A qualitative study using focus groups. *Respir Med* 2020: 167: 105978.
25. Danielsbacka JS, Rostberg L, Olsén MF, et al. "Whole life changed" - Experiences of how symptoms derived from acute pulmonary embolism affects life. A qualitative interview study. *Thromb Res* 2021: 205: 56-62.
26. Lakoski SG, Savage PD, Berkman AM, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. *J Thromb Haemost* 2015: 13(7): 1238-1244.
27. Cires-Drouet RS, Mayorga-Carlin M, Toursavadkohi S, et al. Safety of exercise therapy after acute pulmonary embolism. *Phlebology* 2020: 35(10): 824-832.
28. Cimini LA, Luijten D, Barco S, et al. Pulmonary perfusion defects or residual vascular obstruction and persistent symptoms after pulmonary embolism: a systematic review and meta-analysis. *ERJ Open Research* 2024: 01010-02023.
29. Mendonca CT, Schaeffer MR, Riley P, et al. Physiological mechanisms of dyspnea during exercise with external thoracic restriction: role of increased neural respiratory drive. *J Appl Physiol (1985)* 2014: 116(5): 570-581.
30. Porter JC. Chapter 23 - Dyspnea. *In:* Albert RK, Spiro SG, Jett JR, eds. Clinical Respiratory Medicine (Third Edition). Mosby, Philadelphia, 2008; pp. 293-309.
31. Furlan A, Aghayev A, Chang C-CH, et al. Short-term Mortality in Acute Pulmonary Embolism: Clot Burden and Signs of Right Heart Dysfunction at CT Pulmonary Angiography. *Radiology* 2012: 265(1): 283-293.
32. Kongstad HK, Rosendal CAH, Rasmussen BS, et al. Agreement between arterial and non-arterialised fingertip capillary blood gas and acid-base values. *Eur Clin Respir J* 2019: 6(1): 1644892.

Supplementary file

7

Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis

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Eur Respir J. 2023 Jul 7;62(1):2300449.

TO THE EDITOR:

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe late complication of acute pulmonary embolism (PE).[1, 2] The earlier CTEPH is diagnosed, the better the prognosis for CTEPH patients, both in terms of survival and quality of life.[2-4] Even with this knowledge, the diagnostic delay of CTEPH still remains considerably long with a reported median duration of 14.1 months in Europe in 2007-2009, and 15 months in 2015-2018.[5, 6] Knowledge of the exact incidence of and risk factors for CTEPH are crucial for designing PE follow-up pathways. A systematic review and meta-analysis (SRMA) published in 2017 showed an incidence of 0.56% for all PE patients and a 2.8-3.2% incidence for PE survivors.[7] Since the publication of this paper several large studies reporting CTEPH incidence after PE have been published. We aimed to update the 2017 SRMA.

In brief, we performed a literature search until the 3rd of April 2023. More information on the search strategy can be found in the supplementary data file published on Open Science Framework https://osf.io/7z6xk/. Eligible studies were cohort studies that reported CTEPH incidence in PE patients, who were evaluated for the presence of CTEPH, and in which CTEPH was confirmed by right heart catheterisation.

The risk of bias was assessed in accordance with the Cochrane Collaboration's tool and the PRISMA statement. Only studies with a low risk of bias were included (**Table S1 and able S2**).

Our primary aim was to update the point estimate of the incidence of CTEPH after PE in the three previously defined cohort subtypes: 1) "all comers" (consecutive patients with symptomatic PE, no exclusion criteria), 2) "survivors" (consecutive patients with symptomatic PE alive after a 3-month follow-up period) and 3) "survivors without major comorbidity" (survivors without predefined significant cardiopulmonary, oncological or rheumatologic comorbidities).

The secondary aims were to perform a trend analysis of CTEPH incidence over time using the date of publication of the individual papers, and to study the prognostic impact of right ventricular (RV) dysfunction at the index PE diagnosis. RV dysfunction was defined as RV/left ventricle ratio >1 on computed tomographic pulmonary angiography (CTPA) or echocardiographic signs of RV dysfunction.

Moreover, we updated the meta-analysis on the association between CTEPH incidence and unprovoked PE or recurrent venous thromboembolism (VTE).[7]

The incidence was calculated by dividing the number of confirmed CTEPH cases by the number of patients in the cohort initially selected for screening. For the calculation of the pooled incidences of CTEPH, we applied a generalised linear mixed-effect model. To assess the association for unprovoked PE, recurrent VTE and RV dysfunction with CTEPH, we calculated the pooled odds ratio (OR) and 95% confidence intervals (CI) by applying the Mantel-Haenszel method using a random effects model according to Restricted Maximum Likelihood. To evaluate the trend analysis of CTEPH incidence over time the pooled incidence per publication year was plotted. We assessed heterogeneity by calculating the I^2 statistic. All analyses were performed in R (*metaprop, metabin*) (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

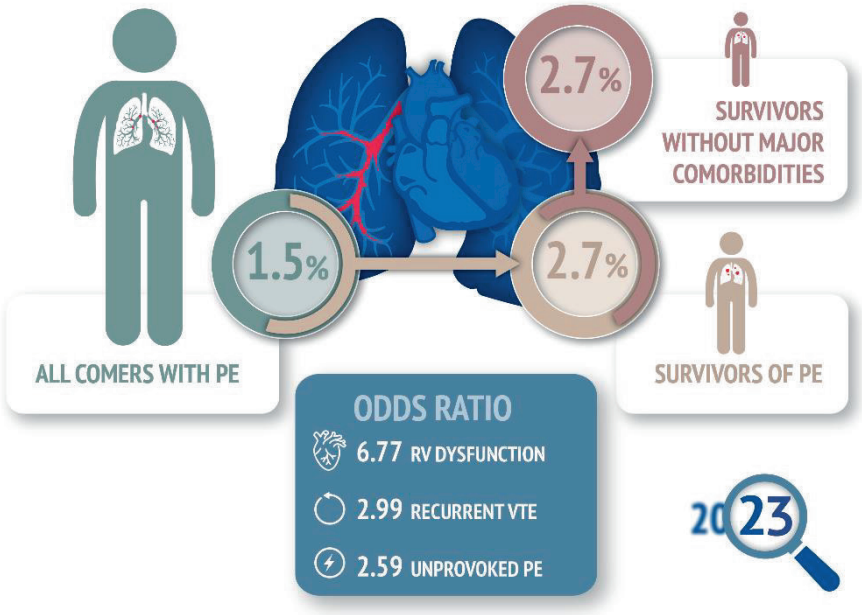
After reviewing 1707 publications, 15 additional studies were identified involving 6202 patients. Combined with the 15 studies identified in the 2017 SRMA, a total of 30 studies were included, for a total of 10249 PE patients (**Figure S1, table S2 and table S3**).

The overall weighted pooled incidence of CTEPH was 2.5% (95%CI 2.0-3.3; I^2=72%; **Figure 1**; figure S2) across all 30 studies. Four studies reported the incidence in 1820 all-comers who were followed for 6 months to 4 years. The weighted pooled incidence was 1.5% (95%CI 0.68-3.1; I^2=77%). Eight studies reported the CTEPH incidence in 3162 PE survivors. The weighted pooled incidence was 2.7% (95%CI 1.8-3.9; I^2=66%) after 3 months to 8 years of follow-up. Finally, 17 studies screened for CTEPH in survivors without major comorbidities: the weighted pooled incidence in these 5180 patients, followed for a period between 6 months and 8.8 years, was 2.7% (95%CI 1.9-3.8; I^2=72%). Funnel plot analysis showed partial asymmetry, most likely due to heterogeneity between studies (**Figure S3**).

We observed no clear trend over time (F**igure S4**). The weighted pooled OR of CTEPH diagnosis during follow-up time for RV dysfunction versus patients without RV dysfunction was 6.8 (95%CI 3.2-14.6; I^2=0.0%, τ^2=0; **Figure S5**). Two studies solely included patients with intermediate-high risk PE: the weighted pooled incidence in these 985 patients was 2.2% (95%CI 1.1-4.1; I^2=78%; **Figure S6**). The weighted pooled OR of CTEPH for unprovoked versus provoked PE was 2.6 (95%CI 1.0-6.5; I^2=57%; **Figure S7**) across nine studies. The weighted pooled OR of CTEPH for recurrent versus primary VTE was 3.0 (95%CI 1.6-5.5; I^2=0.0%, τ^2=1.0; figure S8).

CTEPH incidence seemed higher in studies performed in the Middle-East compared to Europe and/or Asia (6.1% [95%CI 4.7-8.0; I^2=0.0%, τ^2=0] versus 2.3% [95%CI 1.7-3.0; I^2=72%] versus 2.4% [95%CI 1.3-4.5; I^2=0.0%, τ^2=0] respectively; **Figure S9**).

Figure 1: Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism



RV right ventricular; VTE venous thromboembolism

This SRMA updated the existing literature on the incidence of CTEPH after PE. The incidence of CTEPH is 1.5% in PE all-comers and 2.7% in survivors with and without major comorbidities. Only one study applied the novel pulmonary hypertension definition, and reported a CTEPH incidence of 5.3%.[8, 9] Therefore, the pooled incidence from our analysis may be an underestimation according to the current diagnostic criteria. Surprisingly, CTEPH incidence seemed higher in studies performed in the Middle-East potentially due to patient selection or differences in PE treatment or follow-up. Both hypotheses remain to be studied.

For the all-comers cohort we observed a higher and more realistic CTEPH incidence compared to the 2017 SRMA: 1.5% versus 0.56%.[7] This is more realistic

as the gap between the 0.56% and the 3% in survivors reported in the 2017 SRMA could not be easily explained by mortality alone. We did not observe a relevant difference in the incidence in the two survivor cohorts with this SRMA update: 2.7% vs 2.8-3.2% in the 2017 study.[7] The precision of risk estimates however considerably improved in light of a 2.5-fold higher number of patients evaluated.

Current epidemiological analysis suggest a CTEPH incidence of 3-5 cases per 100 000 patients per year in USA and Europa.[10] Approximately 25-35% of these patients lack a history of PE.[5, 6] Considering this and a one-per-1000 annual rate of PE, the estimated CTEPH incidence after PE ranges between 2.0-3.8%, which aligns with our results.

In the current SRMA, we confirm earlier observations that PE patients with recurrent VTE and/or an unprovoked PE are at higher risk of receiving a CTEPH diagnosis during follow-up (ORs 3.0 and 2.6 respectively). Additionally, we showed that patients with RV dysfunction at index PE are at higher risk of developing CTEPH (OR 6.8). Actually, these associations may mostly point to the fact that CTEPH was already present when the PE was diagnosed, but was misclassified as acute PE. This hypothesis is supported by the fact that the two studies that focused on intermediate-high risk PE, i.e. patients who may be expected to be at an increased risk of developing CTEPH, did not show a higher CTEPH incidence, as well as by previous studies that observed a strong correlation between signs suggestive for chronicity on CTPA scans at the index PE event and a future CTEPH diagnosis.[11-15] Routine evaluation of these signs of chronicity by radiologists, with or without help from artificial intelligence, is a promising approach to minimalise the current diagnostic delay.[2-4]

In conclusion the pooled CTEPH incidence in PE survivors was 2.7%. This incidence provides the best estimation relevant for designing PE patient follow-up pathways. RV dysfunction at the moment of the PE, unprovoked PE and/or recurrent VTE are associated with an increased CTEPH incidence. Higher awareness of CTEPH in such patients is warranted.

REFERENCES

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
2. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
3. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. The European respiratory journal 2018: 52(6): 1801687.
4. Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Research 2021: 7(3): 00719-02020.
5. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011: 124(18): 1973-1981.
6. Guth S, D'Armini AM, Delcroix M, et al. Current strategies for managing chronic thromboembolic pulmonary hypertension: results of the worldwide prospective CTEPH Registry. ERJ Open Research 2021: 7(3): 00850-02020.
7. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. European Respiratory Journal 2017: 49(2): 1601792.
8. Held M, Pfeuffer-Jovic E, Wilkens H, et al. Frequency and characterization of CTEPH and CTEPD according to the mPAP threshold > 20 mm Hg: Retrospective analysis from data of a prospective PE aftercare program. Respir Med 2023: 210: 107177.
9. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by 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 for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). European Heart Journal 2022: 43(38): 3618-3731.
10. Gall H, Hoeper MM, Richter MJ, et al. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. European Respiratory Review 2017: 26(143): 160121.
11. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
12. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2021.
13. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021: 93: 64-70.
14. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. Eur Respir J 2021.
15. Barco S, Mavromanoli AC, Kreitner K-F, et al. Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism. CHEST.

Supplementary file

8

Diagnostic efficacy of ECG-derived ventricular gradient for the detection of chronic thromboembolic pulmonary hypertension in patients with acute pulmonary embolism

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J Electrocardiol. 2022 Sep-Oct;74:94-100

ABSTRACT

Introduction: Application of the chronic thromboembolic pulmonary hypertension (CTEPH) rule out criteria (manual electrocardiogram [ECG] reading and N-terminal pro-brain natriuretic peptide [NTproBNP] test) can rule out CTEPH in pulmonary embolism (PE) patients with persistent dyspnea (InShape II algorithm). Increased pulmonary artery pressure may also be identified using automated ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO).

Methods: A predefined analysis of the InShape II study was performed. The diagnostic performance of the VG-RVPO for the detection of CTEPH and the incremental diagnostic value of the VG-RVPO as new rule-out criteria in the InShape II algorithm were evaluated.

Results: 60 patients were included; 5 (8.3%) were ultimately diagnosed with CTEPH. The mean baseline VG-RVPO (at time of PE diagnosis) was -18.12 mV·ms for CTEPH patients and -21.57 mV·ms for non-CTEPH patients (mean difference 3.46 mV·ms [95%CI -29.03 to 35.94]). The VG-RVPO (after 3-6 months follow-up) normalized in patients with and without CTEPH, without a clear between-group difference (mean Δ VG-RVPO of -8.68 and -8.42 mV·ms respectively; mean difference of -0.25 mV·ms, [95%CI -12.94 to 12.44]). The overall predictive accuracy of baseline VG-RVPO, follow-up RVPO and Δ VG-RVPO for CTEPH was moderate to poor (ROC AUC 0.611, 0.514 and 0.539, respectively). Up to 76% of the required echocardiograms could have been avoided with VG-RVPO criteria replacing the InShape II rule-out criteria, however at cost of missing up to 80% of the CTEPH diagnoses.

Conclusion: We could not demonstrate (additional) diagnostic value of VG-RVPO as standalone test or as on top of the InShape II algorithm.

INTRODUCTION

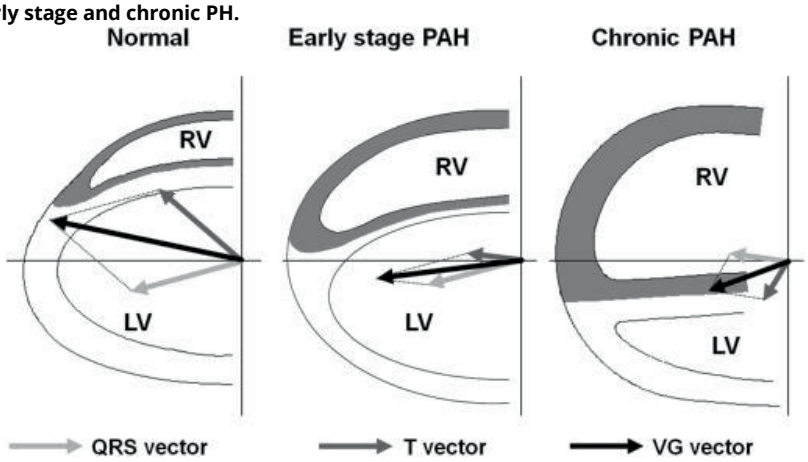
Chronic thromboembolic pulmonary hypertension(CTEPH) is the most feared long-term complication of acute pulmonary embolism (PE).[1-4] CTEPH can be fatal unless it is timely diagnosed and treated adequately.[1-3, 5, 6] Therefore, diagnosing CTEPH early after PE is key.[7] This latter remains a challenge with a diagnostic delays reported up to 24 months because of the non-specific clinical presentation of CTEPH, high frequency of post-pulmonary embolism functional limitations, low awareness among physicians and inefficient use of healthcare resources in the follow-up of PE patients.[8-11] Over the last years there has been no improvement of this diagnostic delay (median of 14.1 months from time of onset of symptoms till diagnosis in 2007-2009 vs 15 months in 2015-2018[8, 12]), underlining the need for dedicated, straightforward PE follow-up algorithms to detect CTEPH.

Currently there are multiple strategies for early CTEPH detection in PE patients. The European Society of Cardiology (ESC) Guideline on PE recommends echocardiography as a first step in patients with persisting dyspnea, functional limitations or risk factors for CTEPH.[13] For patients with high probability of pulmonary hypertension or intermediate probability of pulmonary hypertension on echocardiogram in combination with elevated N-terminal pro-brain natriuretic peptide (NTproBNP) levels or relevant risk factors, further diagnostic testing is indicated by ventilation/perfusion lung scintigraphy and right heart catheterization. A low probability of pulmonary hypertension on echocardiography rules out CTEPH. An alternative strategy involves sequential application of the CTEPH prediction score and CTEPH-rule out criteria to identify patients with an indication for echocardiography, i.e. the InShape II follow-up algorithm.[14-16] The CTEPH-rule out criteria involve manual electrocardiogram (ECG) reading and a NTproBNP blood test.[16-18] Normal NTproBNP and no ECG specific signs for right ventricle overload (defined as: [1] rSR' or rSr' pattern in lead V1, [2] R:S>1 in lead V1 with R>0.5 mV or [3] QRS axis >90°) rules out CTEPH, otherwise echocardiography is needed to further evaluate the presence of CTEPH. This algorithm has been proven safe and efficient with an indication for echocardiography in only 19% of patients, at cost of a diagnostic failure rate of 0.29%.[14]

Increased pulmonary pressure may also be identified using ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO).[19-21] In a normal heart the ventricular gradient points in a left direction,

therefore a normal VG-RVPO is negative. With increase of right ventricle pressure, the VG-RVPO becomes more positive and can therefore detect right ventricle pressure overload (**Figure 1**). Since the VG-RVPO is a numerical value that can be dichotomized to absent or present signs of right ventricle pressure overload with previous derived cut-off values, VG-RVPO might be more accurate than manual ECG reading for the assessment of increased right ventricle pressure on ECG. [22-25] Therefore, we hypothesized that replacing manual ECG reading with automated vector ECG assessment can be used to improve the accuracy of the InShape II follow-up algorithm. In a predefined analysis of the InShape II study, we investigated the diagnostic accuracy of the VG-RVPO for the detection of CTEPH and the incremental diagnostic value of the VG-RVPO to the InShape II algorithm.[14]

Figure 1: Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH.



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METHODS

Patients and study design

This was a predefined secondary outcome of the InShape II study which was a prospective international multicenter management study of patients diagnosed with an acute PE between February 2016 and October 2017. The study design, inclusion and exclusion criteria and outcome measures have been published earlier.[14] In short, patients were categorized as high or low risk of developing CTEPH based on the CTEPH prediction score. During the 3-6 month follow-up, patients at high risk of CTEPH or with persistent symptoms were subjected to the

CTEPH rule-out criteria. If a patient had a normal NTproBNP and no ECG signs of right ventricle pressure overload, CTEPH was considered ruled out i.e. echocardiogram deemed unnecessary. If a patient had an abnormal NTproBNP or ECG signs of right ventricle pressure overload, an echocardiogram was performed according to the 2015 ESC/ERS guidelines on PH.[26] If the echocardiogram showed low probability of PH, CTEPH was considered to be ruled out. Patients with an intermediate or high probability of pulmonary hypertension on echocardiogram were referred to a CTEPH expertise center for a diagnostic workup of suspected CTEPH. All study patients received an echocardiogram at 2 years of follow-up. The primary outcome of the InShape II study was to determine the failure rate of the screening algorithm, which was defined as the 2-year incidence of confirmed CTEPH in patients with PE in whom echocardiogram was deemed unnecessary by the algorithm.

The current study included all patients from the InShape II study with an indication for applying the rule-out criteria according to the algorithm, in whom a baseline ECG at the moment of the acute PE diagnosis could also be retrieved. Patients were excluded from the current analysis if (1) the baseline ECG and the acute PE event were > 14 days apart, (2) the follow-up ECG and the follow-up moment at the outpatient clinic (3-6 months after the acute PE event) were > 3 months apart, or (3) the original digital recording of the ECG was not stored. We did not include patients in whom CTEPH was considered ruled out based on a low prediction score and no CTEPH specific symptoms (i.e. patients without an indication for application of the rule-out criteria), since replacement of manual ECG reading with the VG-RVPO would not have resulted in a different outcome in these patients.

Study objectives

The main aim of this study was to investigate the diagnostic accuracy of the VG-RVPO for the detection of CTEPH in a population of PE patients with a high a-priori probability of CTEPH. Other objectives were to assess the optimal cut-off value of VG-RVPO for detecting CTEPH and to determine the additional diagnostic value of the VG-RVPO to the InShape II algorithm i.e. whether changing the rule-out criteria (manual ECG reading plus NT-proBNP measurement) to rule out criteria based on the VG-RVPO (±NT-proBNP measurement) would allow for more efficient selection of patients in whom CTEPH can be ruled out without the need for echocardiography.

ECG measurements

ECGs were standard 10-s 12recorded in (25 mm/s). To determine the ECG variables, the dedicated Leiden ECG analysis and decomposition software program (LEADS) was used.[27] An independent investigator performed all LEADS analyses, blinded to the patients' characteristics and outcome. The LEADS software computed multiple vector-cardiogram (VCG) values of which the ventricular gradient (VG) is most important for this study. The VG is defined as the 3D integral of the heart vector over the QT interval. Therefore, the VG is an indicator for how the action potential morphology is distributed over the heart.[28] For detection of right ventricular pressure overload previous research has shown that the projection in the 155° azimuth and 27° elevation direction is the most optimal, since this projection is directed over the right ventricle.[19, 20, 22-24] This projection is called the VG-RVPO (ventricular gradient – optimized for right ventricular pressure overload). Since in a normal heart the VG points in a left direction, a normal VG-RVPO is negative and with increase of right ventricular pressure the VG-RVPO becomes more positive.

Study definitions

CTEPH was diagnosed if the following diagnostic criteria were met after ≥3 months of adequate therapeutic anticoagulation according to the relevant guidelines at the moment of the study initiation: (1) ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning; (2) mean pulmonary artery pressure ≥25 mmHg at rest measured by invasive right heart catheterization; (3) pulmonary artery wedge pressure ≤15 mmHg.[26]All diagnoses of CTEPH were assessed in a recognized CTEPH expertise center.

The baseline VG-RVPO was derived from the ECG made at time of acute PE diagnosis (±14 days; [mV · ms]). The follow-up VG-RVPO was derived from the ECG that was made at the follow-up moment 3-6 months after the acute PE diagnosis, at which the CTEPH rule-out criteria were applied (±91 days; [mV · ms]). Δ VG-RVPO was defined as the difference between follow-up VG-RVPO and baseline VG-RVPO (mV · ms).

The (baseline or follow-up) VG-RVPO cut-off point for the detection of pulmonary hypertension derived from previous studies is <-13 mV · ms.[22-25] This means a VG-RVPO <-13 mV · ms was considered normal (pulmonary hypertension ruled out) and a VG-RVPO of ≥ -13 mV · ms was considered abnormal (possible

pulmonary hypertension) although different cut-off points have been evaluated in this study.

Statistical analysis

Normally distributed continuous data were described as a mean (±standard deviation [SD]) and compared using an independent *t*-test. Abnormally distributed continuous data were described as a median (interquartile range [IQR]). Categorical variables were described as numbers (percentage).

For the analysis of diagnostic accuracy of the VG-RVPO for the detection of CTEPH, sensitivity and specificity of the VG-RVPO with confidence interval (95%CI) were calculated. Moreover, ROC curves were plotted, the area under the curve (AUC) with 95%CI was assessed and odds ratios (ORs) were calculated and depicted with a 95%CI.

For the selection of optimal cut-off points for baseline, follow-up and Δ VG-RVPO, cut-off points with the highest Youden-index have been evaluated.[29]

Finally, hypothetical scenarios of application of the InShape II algorithm with new rule-out criteria based on the VG-RVPO have been evaluated. These scenarios are combinations of the previously described cut-off values with a NTproBNP measurement. Moreover, based on the VG-RVPO values of the CTEPH cases, a scenario with other cut-off values has also been selected to diagnose all CTEPH cases and avoid most echocardiograms. Statistical analysis was performed using SPSS version 25.0 (IBM, Chicago, Illinois).

RESULTS

Study population

Out of the 424 patients included in the InShape II study, 222 had an indication for application of the rule-out criteria according to the InShape II algorithm of which a total of 60 patients were included in this study after applying in- and exclusion criteria (supplementary data **figure S1**). The baseline characteristics of the study patients are described in **table 1**; 50.0% was male, the mean age was 60 (SD 15) years. The median time between the PE event and the follow-up date was four months (IQR 3-6) and five patients (8.3%) were diagnosed with CTEPH.

Table 1: baseline characteristics of the included patients.

Characteristics	n=60
Age (years, mean ±SD)	60 (15)
Male gender (n, %)	30 (50.0)
BMI (kg/m^2, median, IQR)	27.8 (24.5-30.3)
Unprovoked PE (n, %)	44 (73.3)
Previous VTE (n, %)	12 (20.0)
Right ventricle/left ventricle ratio >1 on CT (n, %)	26 (43.3)
Comorbidities (n, %)	
Anaemia	5 (8.3)
COPD/asthma	5 (8.3)
Active malignancy	5 (8.3)
Diabetes mellitus	0 (0)
Coronary artery disease	3 (5.0)
Rheumatic disease	5 (8.3)
Hypothyroidism	4 (6.7)
Interstitial lung disease	0 (0)
Inflammatory bowel disease	2 (3.3)
Known antiphospholipid antibodies	1 (1.7)
Major vasculitis syndromes	0 (0)
Prior infected pacemaker leads	0 (0)
Splenectomy	0 (0)
Anticoagulant treatment at 3 month follow-up visit (n, %)	
DOAC	35 (58.3)
VKA	22 (36.7)
LMWH	4 (6.7)
Time between PE primary event and follow-up date (months, median, IQR)	4 (3-6)
Mean time between baseline ECG and follow-up ECG (months, median, IQR)	4 (2-6)

Active malignancy was defined as diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months or recurrent metastatic cancer. Rheumatic disease was defined as known rheumatic arthritis, osteoarthritis, connective tissue disease, systemic lupus erythematosus, ankylosing spondylitis or Sjögren syndrome. Anaemia was defined as: males <8.5 mmol/L or <13.5 g/Dl; females <7.5 mmol/L or <12.0 g/dL. BMI, body mass index; DOAC direct oral anticoagulant; LMWH, low-molecular weight heparin; PE pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

VG-RVPO results

Table 2 presents the VG-RVPO measurements in the study patients. For patients with CTEPH the mean baseline VG-RVPO was -18.12 mV · ms and for patients without CTEPH this was -21.58 mV · ms (mean difference 3.46 mV · ms [95%CI -29.03 to 35.94]). For patients with CTEPH the mean follow-up VG-RVPO was -26.80 mV · ms and for patients without CTEPH this was -30.00 mV · ms (mean difference 3.20 mV · ms [95%CI -13.05 to 19.46]). The mean Δ VG-RVPO therefore was -8.68

mV · ms for CTEPH patients and -8.42 mV · ms for patients without CTEPH (mean difference -0.25 mV · ms [95%CI -12.94 to 12.44]).

Baseline VG-RVPO with a cut-off point of <-13 mV · ms had a sensitivity of 40% (95%CI 5.3-85) and a specificity of 73% (95%CI 59-84). Follow-up VG-RVPO with a cut-off point of <-13 mV · ms had a sensitivity of 20% (95%CI 0.51-72) and a specificity of 80% (95%CI 67-90). Most patients (39/60; 65%) had a normal VG-RVPO of <-13 mV · ms at baseline which remained normal during follow up. There was no association between CTEPH and an abnormal baseline VG-RVPO (OR 1.8 [95%CI 0.27-12] cut-off point of <-13 mV · ms) or abnormal follow-up VG-RVPO (OR 1.0 [95%CI 0.10-9.9] cut-off point of <-13 mV · ms).

The overall predictive accuracy of baseline VG-RVPO, follow-up RVPO and Δ VG-RVPO for detection of CTEPH was moderate to poor, with an AUC of the ROC of 0.615 (95%CI 0.286-0.943), 0.520 (95%CI 0.252-0.788) and 0.538 (95%CI 0.207-0.869), respectively.

Table 2: VG-RVPO measurements in the study patients.

ECG parameters	All patients (n = 60)	No CTEPH (n = 55)	CTEPH (n = 5)	Mean difference (95%CI)
VG-RVPO at baseline (mV . ms), mean ± SD	−21.28 ± 14.70	−21.58 ± 13.56	−18.12 ± 26.33	3.46 (−29.03 to 35.94)
VG-RVPO during follow-up (mV . ms), mean ± SD	−29.73 ± 17.26	−30.00 ± 17.41	−26.80 ± 17.00	3.20 (−13.05 to 19.46)
Δ VG-RVPO (mV . ms), mean ± SD	−8.45 ± 13.46	−8.42 ± 12.76	−8.68 ± 21.70	−0.25 (−12.94 to 12.44)
Change in VG-RVPO, n (%)a				
Normal-normal	39 (65.0)	36 (65.5)	3 (60.0)	
Abnormal-abnormal	8 (13.3)	7 (12.7)	1 (20.0)	
Abnormal-normal	9 (15.0)	8 (14.5)	1 (20.0)	
Normal-abnormal	4 (6.7)	4 (7.3)	0 (0.0)	

[a] [baseline VG-RVPO]-[follow-up VG-RVPO]. The cut-off value for a normal value of the VG-RVPO set at − 13 mV ms, with < −13 mV ms being considered normal and ≥ −13 mV ms as abnormal. CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; VG-RVPO ventricular gradient optimized for right ventricular pressure overload.

Evaluating different VG-RVPO cut-off values

Based on the highest Youden-Index the best cut-off value for baseline VG-RVPO is <2 mV · ms (sensitivity 40% [95%CI 5.3-85]; specificity 96% [95%CI 87-100]), <-3 mV · ms for follow-up VG-RVPO (sensitivity 20% [95%CI 0.51-72]; specificity 95% [95%CI 85-99]) and <5 mV · ms for ΔVG-RVPO (sensitivity 40% [95%CI 5.3-85]; specificity

87% [76-95]). (Supplementary data **table S2** and **table S3**). There was an association between CTEPH and a baseline VG-RVPO with a cut-off value of <2 mV · ms (OR 17.7 [95%CI 1.8-173). There was no association between CTEPH and an abnormal follow-up VG-RVPO with a cut-off value of <-3 mV · ms (OR 4.3 [95%CI 0.36-52]) or abnormal ΔVG-RVPO with a cut-off point of <5 mV · ms (OR 4.6 [95%CI 0.65-32]). We were unable to identify thresholds with a relevant higher sensitivity and specificity ratio.

Changing rule-out criteria based on VG-RVPO

Application of the InShape II rule-out criteria (normal NTproBNP and no ECG signs of RV overload) in our study population would have resulted in diagnosis of all CTEPH cases (n=5) and need for 21 echocardiograms. For different VG-RVPO rule-out criteria with different cut-off values, the hypothetical number of echocardiograms prevented compared to application of the rule-out criteria of the original InShape II algorithm and the proportion of missed CTEPH diagnoses were evaluated (**Table 3**).

Three of the strategies with rule-out criteria based on the previously described cut-off values failed to decrease the number of echocardiograms needed and missed 20-40% of the CTEPH diagnoses (**Table 3**; scenario B, C, and G). In three strategies the number of echocardiograms needed would be reduced with 29-76% at the cost of 20-80% missed CTEPH diagnoses (**Table 3**; strategy D, E and F). A scenario in which CTEPH would be considered ruled-out based on a combination of normal baseline VG-RVPO of <2 mV · ms, follow-up VG-RVPO <-3 mV · ms and Δ VG-RVPO of <5 mV · ms in combination with normal NTproBNP measurement would have resulted in diagnosis of all CTEPH cases, but would have increased the need for echocardiography with 9.5% (**Table 3**; option H).

To select a scenario in which most echocardiograms were avoided without missing CTEPH diagnosis, cut-off values were selected based on the VG-RVPO values of CTEPH cases with a normal NTproBNP during follow-up (supplementary data **table S1**). In this scenario CTEPH was considered ruled out based on a baseline VG-RVPO <5 mV · ms, follow-up VG-RVPO of <0 mV · ms , ΔVG-RVPO of <13 mV · ms and normal NTproBNP. All CTEPH patients would have been detected and a limited number of 2 echocardiograms would have been prevented (-9.5% of all echocardiograms) (**Table 3**; strategy I).

Table 3: results of change in rule-out criteria

Rule out criteria (cut-off value^)	Patients with an echocardiography indication because rule-out criteria are not met			Patients where CTEPH is considered ruled out without the need for echocardiography because rule-out criteria are met		
	CTEPH n (% of all CTEPH diagnosis)	No CTEPH, n	Total, n (% difference with InShape II[α])	CTEPH, n (% of all CTEPH diagnosis)[β]	No CTEPH, n	Total, n
A: No ECG abnormalities plus normal NTproBNP (InShape II)	5 (100.0)	16	21 (n.a.)	0 (0.0)	39	39
B: normal baseline VG-RVPO (<-13) plus normal NTproBNP	4 (80.0)	20	24 (+14.3)	1 (20.0)	35	36
C: normal follow-up VG-RVPO (<-13) plus normal NTproBNP	3 (60.0)	18	21 (±0.0)	2 (40.0)	37	39
D: No ECG abnormalities plus normal NTproBNP and normal follow up VG-RVPO (<-13)[*]	1 (20.0)	4	5 (-76.2)	4 (80.0)	51	55
E: normal baseline VG-RVPO (<2) plus normal NTproBNP	4 (80.0)	11	15 (-28.6)	1 (20.0)	44	45
F: normal follow-up VG-RVPO (<-3) plus normal NTproBNP	3 (60.0)	12	15 (-28.6)	2 (40.0)	43	45
G: Δ VG-RVPO (<5) plus normal NTproBNP	4 (80.0)	17	21 (0.0)	1 (20.0)	38	39
H: normal baseline VG-RVPO (<2), follow-up VG-RVPO (<-3) and Δ VG-RVPO (<5) plus normal NTproBNP	5 (100)	18	23 (+9.5%)	0 (0.0)	37	37
I: normal baseline VG-RVPO (<5), follow-up VG-RVPO (<0) and Δ VG-RVPO (<13) plus normal NTproBNP	5 (100.0)	14	19 (-9.5%)	0 (0.0)	41	41

This table presents multiple hypothetical strategies in which the original rule-out criteria of the InShape II study have been changed into new criteria. If the rule-out criteria are met CTEPH is considered ruled out and no further diagnostics should be needed. If the rule-out criteria are not met there is an echocardiography indication for further evaluation of CTEPH according to the InShape II algorithm. Online appendix A provides flow-charts of the suggested algorithms. All NTproBNP measurement have been performed during the 3-6 month follow-up moment [α] depicts number of echocardiograms avoided per changed algorithm compared to application of the InShape II algorithm. [β] depicts the number of false negatives per algorithm. [^]The cut-off value for a specific VG-RVPO measurement is depicted between the brackets in mV · ms. A value < this number is being considered normal and ≥ this value as abnormal. [*]Adding an abnormal follow-up VG-RVPO of ≥-13 mV · ms as a criterium for the echocardiogram on top of the rule-out criteria of InShape II. CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; VG-RVPO ventricular gradient optimized for right ventricular pressure overload.

DISCUSSION

This predefined analysis of the InShape II study showed limited additional value of VG-RVPO as standalone test for the detection of CTEPH after acute PE and as a component within the InShape II algorithm. We observed the expected VG-RVPO improvement over time after acute PE, but the extent of improvement did not differentiate CTEPH from non-CTEPH patients.

We had anticipated a better diagnostic value of VG-RVPO for the detection of CTEPH than observed based on previous literature. The VG is a vectorial measurement over the QRS complex and T-wave. Chronic increased right ventricle pressure load will lead to changed action potential duration resulting in a VG change.[21] Therefore, a change in magnitude and/or orientation of the VG represents a change in right ventricle pressure load.[21, 28] Previous research confirmed the diagnostic value of the VG. The VG magnitude projected over the x-axis (VG-X) has shown an improved diagnostic accuracy of chronic right ventricle pressure overload for the detection of pulmonary arterial hypertension patients compared to conventional ECG parameters (rSR' or rSr' in V1, R:S > 1 with R > 0.5 mV in V1, and QRS axis > 90°).[21] Also, the VG-RVPO significantly correlates with mean pulmonary artery pressure in patients with suspected PH.[19] Furthermore, VG-RVPO has been shown to be a sensitive measurement for early detection of pulmonary hypertension in systemic sclerosis patients.[20, 24]

We have three main explanations for our findings. First, the InShape II algorithm had a sensitivity of 100% for CTEPH in the study population, and a specificity of 71%. Therefore, by definition, the sensitivity could not be improved by any test. Of note, this very high sensitivity and moderately high specificity may have been overestimated in the small patient cohort available for analysis.

Second, in contrast to pulmonary arterial hypertension and pulmonary hypertension associated with systemic sclerosis, where the course of disease shows gradual increase of pulmonary artery pressure and change of the vector, the majority of patients with acute PE have acute right ventricle dysfunction, which will show improvement in the course of time.[30-33] Even though most CTEPH patients likely already have CTEPH at the time of the index PE event, a temporary improvement of right ventricle function and pulmonary artery pressure can be expected after initiation of anticoagulant therapy as most patients have acute on chronic PE at presentation.[3, 7, 34-37] Due to the occurrence of right ventricle dysfunction and recovery in both CTEPH and non-CTEPH post-acute PE patients,

the diagnostic value, and in specific the specificity, may have been diluted. Moreover, in acute PE artery obstruction with neurogenic reflexes and myocardial ischemia may result in ECG changes. [22, 38] In CTEPH the right ventricular response to chronic increased pulmonary artery pressure first leads to hypertrophy, but when the ventricle is not able to sustain the long-term pressure, the right ventricle starts to dilate with ultimately right ventricle failure as a result.[39] The VG-RVPO detects right ventricle pressure overload due to right ventricle hypertrophy resulting in changes in the action potential duration heterogeneity.[21] Fibrosis, changes in ventricular function and the extend of dilatation also influence the VG-RVPO. The speed and extend of adaptation of the right ventricle as a response to increased pulmonary artery pressure differs among CTEPH patients. Measuring the VG-RVPO 3-6 months after the acute PE event therefore might have resulted in missing elevated pulmonary artery pressure since right ventricular adaptation and remodeling might still be ongoing in some CTEPH patients. Therefore, the additional value of the VG-RVPO for the detection of CTEPH in PE patients may only become apparent after a longer duration of follow-up than available for the study patients.Third and importantly, our study population may have been too small to identify relevant differences. Our study did nonetheless show a numerical higher mean baseline and follow-up VG-RVPO in CTEPH patients compared to non-CTEPH patients, a difference that may become significant when studied in a larger study population.

Strong points of this study are the prospective design of the InShape II study and the novelty of the approach. Some limitations should be taken into account, mainly the small sample size and low number of CTEPH cases leading to reduced statistical power for the performed analysis. Second, over half of the patients included in the InShape II study had to be excluded due to the unavailability of two ECGs since a baseline ECG was not a requisite for InShape II study participation. However, presence of a baseline ECG has not influenced follow-up management or increased the risk of an abnormal VG-RVPO or eventual CTEPH diagnosis. Therefore, no systematic selection bias has been introduced. Moreover, we studied selected patients with a higher likelihood of CTEPH. Consequently, our findings are not generalizable to all PE survivors. Overall, and because of these limitations, our findings should be regarded as hypothesis generating.

Early detection of CTEPH remains crucial for improving outcomes of CTEPH patients.[1-3, 5-7] While a larger study with longer follow-up may show a potential role for VG-RVPO, alternative strategies may also be relevant. Mainly, more focus on

computed tomography pulmonary angiogram (CTPA) images at baseline may also help identifying patients with CTEPH early in the course of time. We and others showed that signs of chronicity, e.g. the presence of webs/bands, bronchial artery dilatation and right ventricle hypertrophy identified on CTPA images is a strong predictor of a future CTEPH diagnosis.[34, 35, 37] Indeed, these radiological signs are not effected by anticoagulation therapy and can be evaluated by CTEPH experts as well as by non-specifically trained board-certified radiologists.[40-42]

In conclusion, in this predefined analysis of the InShape II study we could not demonstrate additional diagnostic value of VG-RVPO as standalone test or as integrated part of the InShape II algorithm for CTEPH. Future studies with longer follow-up and a larger sample size are needed to ultimately determine the role of VG-RVPO as diagnostic test for CTEPH in PE survivors.

REFERENCES

1. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
2. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
3. Lang IMandMadani M. Update on chronic thromboembolic pulmonary hypertension. Circulation 2014: 130(6): 508-518.
4. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. The European respiratory journal 2017: 49(2).
5. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation 2016: 133(9): 859-871.
6. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. Eur Respir J 2018: 52(6).
7. Klok FA, Couturaud F, Delcroix M, et al. Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. The European respiratory journal 2020: 55(6).
8. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011: 124(18): 1973-1981.
9. Ende-Verhaar YM, van den Hout WB, Bogaard HJ, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2018: 16(11): 2168-2174.
10. Boon G, Bogaard HJandKlok FA. Essential aspects of the follow-up after acute pulmonary embolism: An illustrated review. Research and practice in thrombosis and haemostasis 2020: 4(6): 958-968.
11. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014: 28(6): 221-226.
12. Guth S, D'Armini AM, Delcroix M, et al. Current strategies for managing chronic thromboembolic pulmonary hypertension: results of the worldwide prospective CTEPH Registry. ERJ Open Research 2021: 7(3): 00850-02020.
13. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019: 54(3).
14. Boon G, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021: 76(10): 1002-1009.
15. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016: 14(1): 121-128.
16. Klok FA, Surie S, Kempf T, 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): 21-26.

17. Klok FA, Tesche C, Rappold L, 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.
18. Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a Simple Noninvasive Screening Algorithm for Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism. TH Open 2018: 2(1): e89-e95.
19. Kamphuis VP, Haeck MLA, Wagner GS, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. Journal of Electrocardiology 2014: 47(2): 175-182.
20. Meijer FMM, Kies P, Jongbloed MRM, et al. ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients. Int J Cardiol 2018: 273: 203-206.
21. Henkens IR, Mouchaers KTB, Vonk-Noordegraaf A, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. Am J Physiol Heart Circ Physiol 2008: 294(5): H2150-H2157.
22. Meijer FMM, Hendriks SV, Huisman MV, et al. The prognostic value of ECG-derived ventricular gradient in early adverse events in acute pulmonary embolism patients. Thrombosis Update 2021: 2: 100033.
23. Meijer FMM, Hendriks SV, Huisman MV, et al. Lack of diagnostic utility of the ECG-derived ventricular gradient in patients with suspected acute pulmonary embolism. J Electrocardiol 2020: 61: 141-146.
24. Couperus LE, Vliegen HW, Henkens IR, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. J Electrocardiol 2016: 49(1): 60-68.
25. Scherptong RWC, Henkens IR, Man SC, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol 2008: 41(6): 648-655.
26. Galie N, Humbert M, Vachiery JL, 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.
27. Draisma HHM, Swenne CA, van de Vooren H, et al. LEADS An interactive research oriented ECG/VCG analysis system. Computers in cardiology 2005: 515–518.
28. Draisma HHM, Schalij MJ, van der Wall EE, et al. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm 2006: 3(9): 1092-1099.
29. Youden WJ. Index for rating diagnostic tests. Cancer 1950: 3(1): 32-35.
30. Ribeiro A, Lindmarker P, Johnsson H, et al. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. Circulation 1999: 99(10): 1325-1330.
31. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007: 28(20): 2517-2524.
32. Kline JA, Steuerwald MT, Marchick MR, et al. 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): 1202-1210.
33. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following

pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
34. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
35. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014: 112(3): 598-605.
36. Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017: 26(143): 160112.
37. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. AJR Am J Roentgenol 2020: 215(4): 800-806.
38. Alpert JS, Godtfredsen J, Ockene IS, et al. Pulmonary hypertension secondary to minor pulmonary embolism. Chest 1978: 73(6): 795-797.
39. Delcroix M, Vonk Noordegraaf A, Fadel E, et al. Vascular and right ventricular remodelling in chronic thromboembolic pulmonary hypertension. European Respiratory Journal 2013: 41(1): 224-232.
40. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2021.
41. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021: 93: 64-70.
42. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. Eur Respir J 2021.

Supplementary file

9

Optimisation of detecting chronic thromboembolic pulmonary hypertension in acute pulmonary embolism survivors: the InShape IV study

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Eur Respir J. Oct 2024, 64 (4) 2400544

ABSTRACT

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is often diagnosed late in acute pulmonary embolism (PE) survivors: more efficient testing to expedite diagnosis may considerably improve patient outcomes. The InShape II algorithm safely rules out CTEPH (failure rate 0.29%) while requiring echocardiography in only 19% of patients but may be improved by adding detailed reading of the computed tomography pulmonary angiography (CTPA) diagnosing the index PE.

Methods: We evaluated 12 new algorithms, incorporating the CTEPH prediction score, ECG reading, N-terminal pro-brain natriuretic peptide levels and dedicated CTPA reading were evaluated in the international InShape II cohort (n=341) and part of the German FOCUS cohort (n=171). Evaluation criteria included failure rate, defined as the incidence of confirmed CTEPH in PE patients in whom echocardiography was deemed unnecessary by the algorithm, and the overall net reclassification index (NRI) compared to the InShape II algorithm.

Results: The algorithm starting with CTPA reading of the index PE for six signs of CTEPH, followed by the ECG/NT-proBNP assessment and echocardiography resulted in the most beneficial change compared to InShape II with a need for echocardiography in 20% (+5%), a failure rate of 0%, and an NRI of +3.5%, reflecting improved performance over the InShape II algorithm. In the FOCUS cohort, this approach lowered echocardiography need to 24% (-6%) and missed no CTEPH cases, with an NRI of +6.0%.

Conclusion: Dedicated CTPA reading of the index PE improved the performance of the InShape II algorithm and may improve the selection of PE survivors who require echocardiography to rule out CTEPH.

GRAPHICAL ABSTRACT

Introduction

InShape II algorithm	Safely rules out CTEPH in acute PE survivors
Detailed CTPA reading of index PE	Signs on CTPA are highly specific for future CTEPH diagnosis

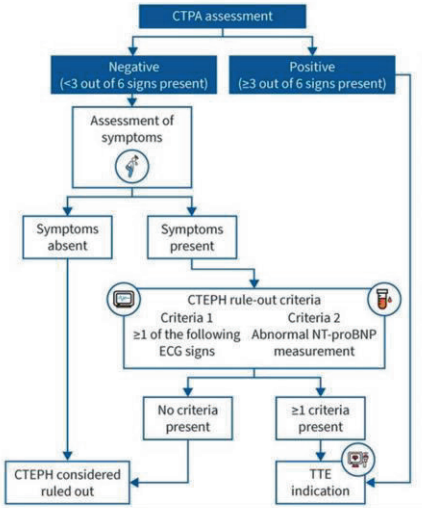
Can the InShape II algorithm be improved by adding detailed reading of the CTPA diagnosing the index PE?

Methods

Design	12 new algorithms incorporating the CTEPH prediction score, ECG reading, NT-proBNP levels and dedicated CTPA
	Evaluated in two prospective cohorts: • InShape II cohort (n=341) • FOCUS cohort (n=171)
Evaluation of	Failure rate (%): Incidence of confirmed CTEPH in PE patients in whom echocardiography was deemed unnecessary by the algorithm
	Net reclassification index (NRI): Evaluates shifts in risk categories for both CTEPH and non-CTEPH patients compared to the InShape II algorithm

Results

InShape IV resulted in the most beneficial change compared to InShape II



InShape II cohort

- Failure rate of 0%
- Need for echocardiography in 20%
- NRI of +3.5%

FOCUS cohort

- Failure rate of 0%
- Need for echocardiography in 24%
- NRI of +6.0%

Conclusion

Dedicated CTPA reading of the index PE incorporated in the new InShape IV algorithm improved the performance of the InShape II algorithm and may improve the selection of PE survivors who require echocardiography to rule out CTEPH

INTRODUCTION

In chronic thromboembolic pulmonary hypertension (CTEPH), a feared but rare complication of acute pulmonary embolism (PE), thrombotic and fibrotic occlusions of pulmonary arteries lead to increased pulmonary artery pressure and ultimately right heart failure.[1-3] Treatment should be initiated without delay to prevent loss of quality-adjusted life years and mortality; diagnosing CTEPH as early as possible therefore remains one of the priorities of PE aftercare.[2-7]

To achieve an early CTEPH diagnosis, several follow-up algorithms for PE survivors have been developed and evaluated. The current European Society of Cardiology (ESC) guidelines recommend echocardiography in all patients with symptoms of CTEPH and/or predisposing factors to CTEPH.[8] The InShape II algorithm is an alternative algorithm that has been prospectively validated in a management study.[9, 10] Patients with either a high-pretest probability of CTEPH or suggestive symptoms were subjected to the "CTEPH rule-out criteria", consisting of electrocardiogram (ECG) reading for the presence of right ventricular (RV) strain and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement.[10-12] CTEPH is ruled out if both are normal, otherwise echocardiography is necessary (**Figure 1**). This algorithm has been proven safe and efficient with an indication for echocardiography in only 19% of patients and a diagnostic failure rate of 0.29%, and may prove particularly useful for settings where (high-quality) echocardiography is not readily available.[10] Recent studies support the potential relevance of dedicated evaluation of the computed tomography pulmonary angiogram (CTPA), used to diagnose the index PE, for signs of CTEPH (**Appendix A**).[13-16] These signs are detectable by CTEPH experts and non-specifically trained board-certified radiologists, and they are highly specific for a future diagnosis of CTEPH (reported specificity 90-94%, sensitivity 44-89%).[13, 17-19] Based on its strong predictive performance, we hypothesised that incorporating advanced CTPA reading into the InShape II algorithm, either as an additional test or to replace of an existing component, may further improve the yield and efficiency of the algorithm. This hypothesis was tested and evaluated in the current study.

METHODS

Study objectives

The objectives of this study were to investigate whether the InShape II algorithm can be improved by incorporating detailed CTPA assessment of signs of chronic

thrombi and pulmonary hypertension, and to externally evaluate the improved algorithms.

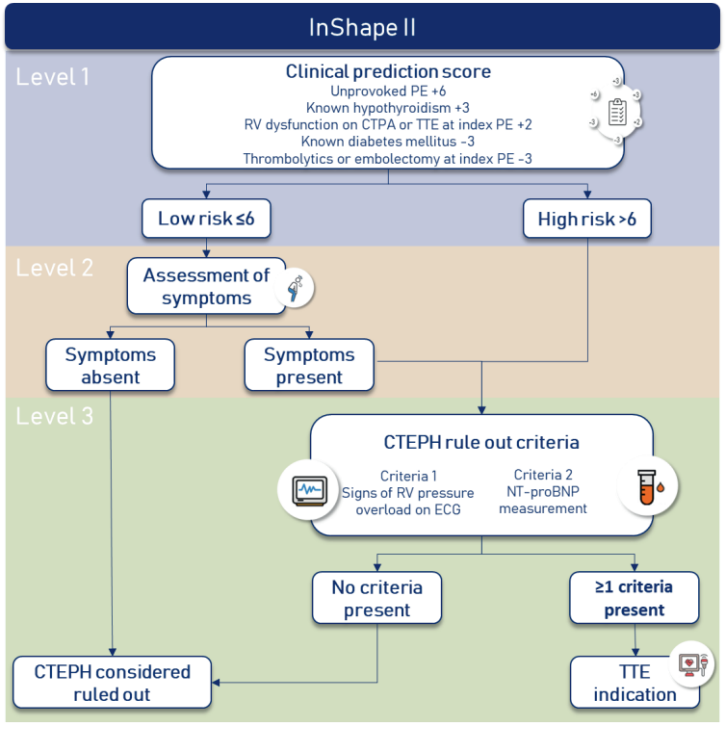
Part 1: improving the InShape II algorithm

Patients and study design

This study is a post-hoc analysis of the prospective, multicentre InShape II study, which investigated the safety and effectiveness of a noninvasive follow-up algorithm for the early detection of CTEPH in acute PE patients between February 2016 and October 2017. The study design, selection criteria and outcome measures have been published previously.[10] All patients were managed according to the previously described InShape II algorithm (**Figure 1**). After 2 years, all patients received an echocardiogram. Patients with intermediate or high echocardiographic probability of pulmonary hypertension were referred for further diagnostic work-up of CTEPH following standard of care, e.g. consisting of a ventilation/perfusion (V/Q) scintigraphy and right heart catheterisation (RHC).[8] CTEPH was defined as (1) ≥1 mismatched segmental perfusion defect demonstrated by V/Q scanning; (2) mean pulmonary artery pressure ≥25 mmHg at rest; and (3) pulmonary artery wedge pressure ≤15 mmHg (4) after ≥3 months of adequate anticoagulant treatment.[3, 8] An independent interdisciplinary working group of pulmonary hypertension specialists adjudicated all results and CTEPH diagnoses. CTEPH diagnosis was assigned by an independent expert panel to three patients in whom RHC was not performed due to clinical circumstances; these were included to make sure our definition of the primary outcome was as sensitive as possible.[10]

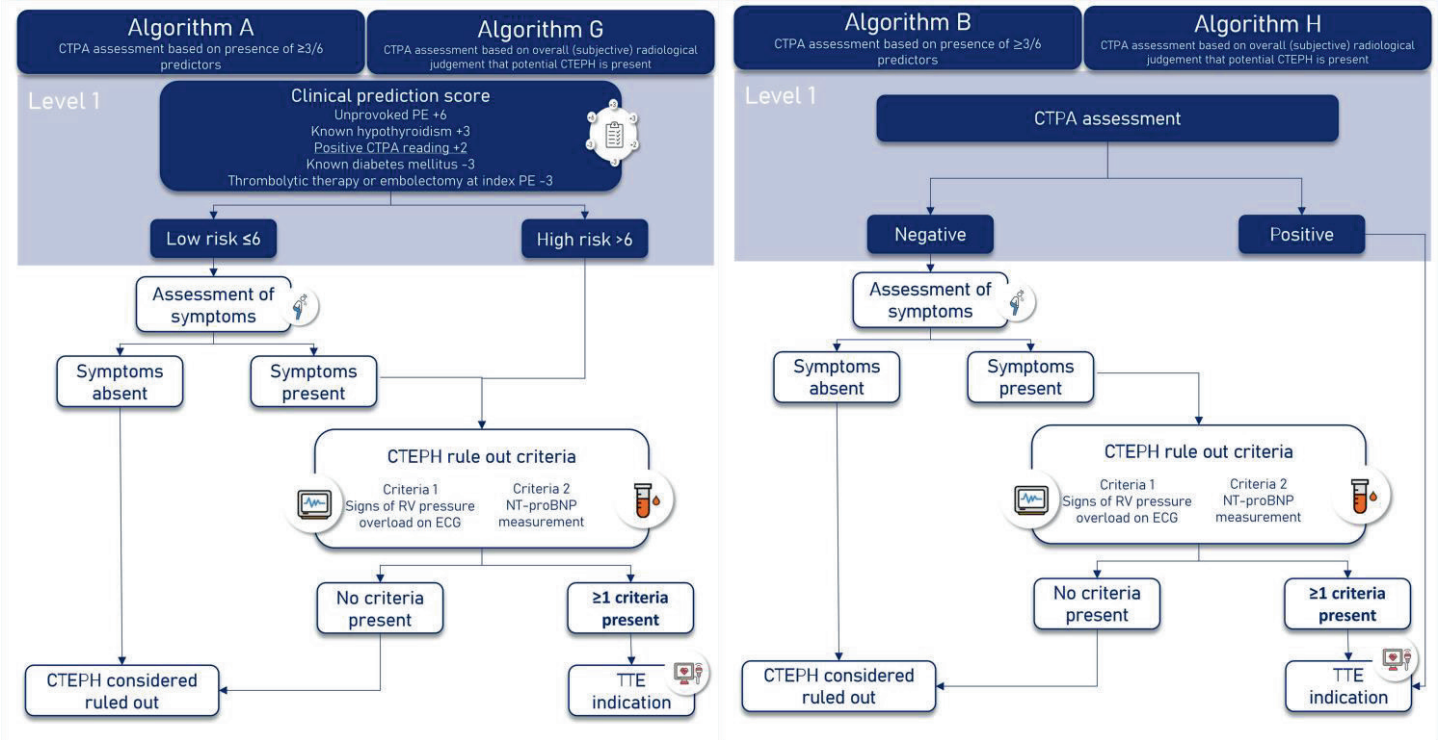
In a subsequent pre-planned analysis of the InShape II study, CTPA scans of the index PE event were evaluated by an independent radiologist blinded for the ultimate presence of CTEPH.[14 17] Two approaches were used: (1) the radiologist made an overall judgment on the potential presence of CTEPH based on their subjective assessment of signs of CTEPH on index CTPA, and (2) the radiologist separately assessed the following six individual signs: dilated pulmonary trunk (diameter >30 mm or larger than aortic diameter), arterial retraction, intravascular web, dilated bronchial arteries, RV wall hypertrophy (>4 mm) and flattening of the interventricular septum (**Appendix A)**. If ≥3 out of 6 signs were present, the patient was considered to have signs of CTEPH.

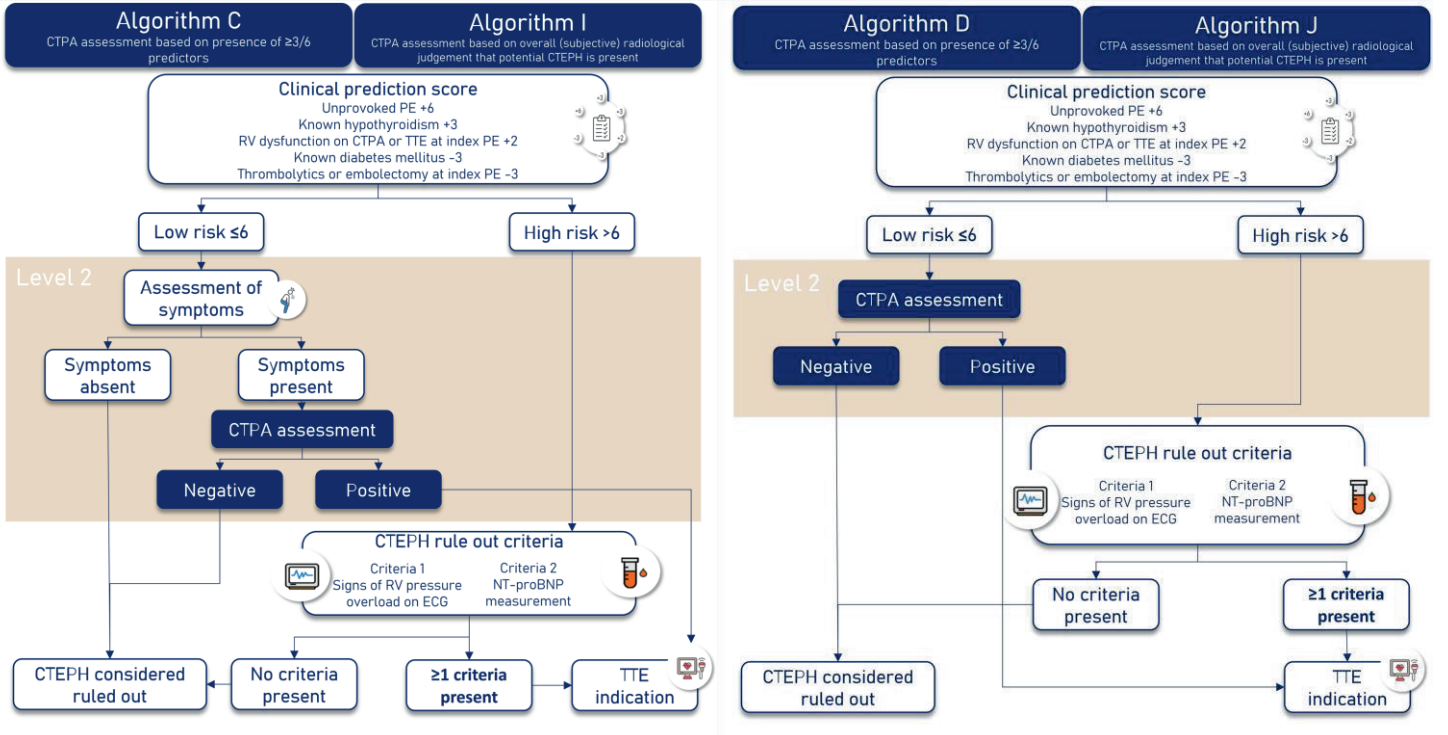
Figure 1a: The InShape II algorithm



This figure depicts the InShape II algorithm and the twelve hypothetical algorithms to improve the InShape II algorithm using CTPA assessment that were considered. Differences between these new hypothetical algoritms and the InShape II algorithm are depicted in the blue boxes. The CTPA assessment can be incorporated in the InShape II algorithm at 3 different levels: 1) integration in the CTEPH prediction score (Algorithm A or G: by replacing the item "RV dysfunction on CTPA or TTE at index PE" with the CTPA assessment) or replacement of the score (Algorithm B or H), 2) added as an extra step in symptomatic patients with a low CTEPH risk according to the prediction score (Algorithm C or I) or replacement of this assessment (Algorithm D or J), 3) combined with the CTEPH rule-out criteria (Algorithm E or K) or replacement of these criteria (Algorithm F). For all algorithms were the CTPA reading was an independent test rather than part of the prediction score, a positive CTPA assessment would have directly resulted in a referral for echocardiographic evaluation. Two methods of discriminating positive and negative CTPA assessments have been used, i.e. the presence of ≥3 out of 6 signs of CTEPH or overall judgement of radiologist regarding the presence of CTEPH. With this in mind, algorithm A-F applied the assessment of 6 independent CTPA signs of CTEPH, while algorithm G-L were the same as A-F except for the fact that the overall radiological assessment was used. The algorithms should be initiated approximately 3 months after the index PE. Specific symptoms are symptoms suggestive for CTEPH i.e. dyspnoea on exertion, oedema, newly developed palpitations, syncope or chest pain at 3 month follow-up. Signs of RV pressure overload on ECG were defined as ≥1 of the following: 1) rSR' or rSr' pattern in lead V1; 2) R:S >1 in lead V1 with R >0.5 mV; 3) QRS axis >90°. For algorithm A-F: 6 independent CTPA signs of CTEPH: dilated pulmonary trunk (diameter >30 mm or larger than aortic diameter), arterial retraction, intravascular web, dilated bronchial arteries, RV wall hypertrophy (>4 mm) and flattening of the interventricular septum. Abbreviations: Chronic thromboembolic pulmonary hypertension, CTEPH; Electrocardiogram, ECG; Transthoracic echocardiogram, TTE; N-terminal-prohormone of brain natriuretic peptide, NT-proBNP . Right ventricle, RV

Figure 1b: The new hypothetical algorithms




Algorithm C
CTPA assessment based on presence of ≥3/6 predictors
Algorithm I
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Clinical prediction score
Unprovoked PE +6
Known hypothyroidism +3
RV dysfunction on CTPA or TTE at index PE +2
Known diabetes mellitus -3
Thrombolytics or embolectomy at index PE -3
Low risk ≤6
High risk >6
Level 2
Assessment of symptoms
Symptoms absent
Symptoms present
CTPA assessment
Negative
Positive
CTEPH rule out criteria
Criteria 1
Signs of RV pressure overload on ECG
Criteria 2
NT-proBNP measurement
CTEPH considered ruled out
No criteria present
≥1 criteria present
TTE indication
Algorithm D
CTPA assessment based on presence of ≥3/6 predictors
Algorithm J
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Clinical prediction score
Unprovoked PE +6
Known hypothyroidism +3
RV dysfunction on CTPA or TTE at index PE +2
Known diabetes mellitus -3
Thrombolytics or embolectomy at index PE -3
Low risk ≤6
High risk >6
Level 2
CTPA assessment
Negative
Positive
CTEPH rule out criteria
Criteria 1
Signs of RV pressure overload on ECG
Criteria 2
NT-proBNP measurement
No criteria present
≥1 criteria present
CTEPH considered ruled out
TTE indication

Algorithm F
CTPA assessment based on presence of ≥3/6 predictors
Clinical prediction score
Unprovoked PE +6
Known hypothyroidism +3
RV dysfunction on CTPA or TTE at index PE +2
Known diabetes mellitus -3
Thrombolytics or embolectomy at index PE -3
Low risk ≤6
High risk >6
Assessment of symptoms
Symptoms absent
Symptoms present
CTEPH considered ruled out
CTPA assessment
Negative
Positive
TTE indication
Level 3
Algorithm L
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Algorithm E
CTPA assessment based on presence of ≥3/6 predictors
Algorithm K
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
CTEPH rule out criteria
Criteria 1 Signs of RV pressure overload on ECG
Criteria 2 NT-proBNP measurement
Criteria 3 Positive CTPA assessment
No criteria present
≥1 criteria present

Approach to improving the InShape II algorithm

We considered 12 hypothetical algorithms to improve the InShape II algorithm and evaluated these in the InShape II cohort (**Figure 1 and Appendix B**). The CTPA assessment was incorporated into the InShape II algorithm at 3 different levels: 1) integration in the CTEPH prediction score (Algorithm A or G) or replacement of the score (algorithm B or H), 2) added as an extra step in symptomatic patients with a low CTEPH risk according to the prediction score (algorithm C or I) or replacement of this assessment (algorithm D or J), or 3) combined with the CTEPH rule-out criteria (algorithm E or K) or replacement of these criteria (algorithm F or L). For all algorithms in which the CTPA reading was an independent test rather than part of the prediction score, a positive CTPA assessment would have directly resulted in a referral for echocardiographic evaluation.

Moreover, two methods of discriminating positive and negative CTPA assessments were used, i.e. the presence of ≥3 out of 6 signs of CTEPH or overall judgement of the radiologist regarding the presence of CTEPH.[14, 18] With this in mind, algorithms A-F applied the assessment of 6 independent CTPA signs of CTEPH, while algorithms G-L were the same as A-F except for the fact that the overall radiological assessment was used.

All screening algorithms were initiated during a patient's routine visits to the outpatient clinic 3 months after their diagnosis of acute PE (i.e. index PE event). However, the prediction score and CTPA assessment, which use data from the index PE event, could be prepared before this follow-up visit, expediting detection and management.

It is essential to recognise that while CTPA assessment of the index PE offers valuable insights, it is not diagnostic for CTEPH but rather serves as an indicator of potential CTEPH, facilitating the targeted selection of acute PE patients for further evaluation via echocardiography. Subsequently, individuals identified as having an intermediate to high risk of pulmonary hypertension on echocardiography in combination with chronic clots on V/Q-scan should be promptly referred to pulmonary hypertension expert centres. Here, the gold standard diagnostic methods for CTEPH, including V/Q-scan and RHC, should be employed to confirm diagnosis, ensuring accurate assessment and appropriate management.

Part 2: Evaluation in the FOCUS cohort

Patients and study design

All algorithms where both methods of discriminating positive and negative CTPA resulted in a positive change compared to InShape II (defined as a net reclassification index [NRI] >0%) were subsequently evaluated in the prospective multicentre observational FOCUS cohort. The study design, selection criteria and outcome measures have been published previously.[20, 21] In the FOCUS study, patients with a confirmed diagnosis of acute symptomatic PE and without a documented history of confirmed CTEPH were followed over a 2-year period after the index PE episode with a standardised assessment plan at 5 pre-specified visits (at enrolment, at hospital discharge, and during follow-up at 3, 12 and 24 months). During follow-up, patients received (among other tests) a 12-lead ECG, NT-proBNP blood test and echocardiography.[21] The FOCUS study was an observational study. Consequently the study protocol mandated neither diagnostic nor therapeutic decisions: patients were treated according to local protocols in adherence with European and national guidelines. All CTEPH diagnoses were adjudicated by an independent Clinical Events Committee.

Because the CTPA assessment in both the FOCUS and InShape II cohorts had been conducted prior to the commencement of our study, index PE CTPA scans of the FOCUS cohort were separately assessed for the presence of signs of CTEPH by three board-certified radiologists blinded to each other's assessment and to the eventual CTEPH diagnosis.[19] The same two approaches to discriminate negative from positive CTPAs were used as in the InShape II cohort: 1) overall radiologist's judgment and 2) presence of ≥3 out of 6 signs. Details on the assessment process are further described in **appendix A.** The ECG assessment was independently performed for the current analysis by two researchers (FAK and SB), who were unaware of the CTEPH outcomes. Discrepancies were resolved by discussion.

Statistical analysis

Baseline characteristics were described as mean (±SD) or median (interquartile range [IQR]). For each algorithm the efficiency and safety of the detection of CTEPH was calculated. All guidelines recommend performing echocardiography before confirming CTEPH with V/Q scan and RHC. Our new algorithms therefore aim to optimize the selection of patients with acute PE with a need for echocardiography,

and the failure rate was defined as the 2-year incidence of confirmed CTEPH in patients with PE in whom echocardiography was deemed unnecessary by the algorithm at baseline. To evaluate efficiency, the number of performed ECGs, NT-proBNP measurements and echocardiograms per algorithm were calculated. The overall NRI was calculated for each algorithm compared to the InShape II algorithm, which computes the proportions moving up or down in risk strata in cases and non-cases separately. The overall NRI was calculated as: event NRI + non-event NRI. The event NRI was calculated for each algorithm: (number of CTEPH patients classified up – number of CTEPH patients classified down)/number of CTEPH patients. The non-event NRI was calculated as following (number of non-CTEPH patients classified down – number of non-CTEPH patients classified up)/number of non-CTEPH patients.[22] Moreover, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was assessed.

In the FOCUS cohort, we addressed missingness by performing a complete case analysis as the main analysis. This means that patients in whom not all algorithms could be performed (e.g. because of missing ECG evaluation) were excluded from the main analysis. However, some of these patients were eligible for evaluation of some (but not all) of the algorithms. We performed a sensitivity analysis in which we selected complete cases based on the algorithm under evaluation, resulting in a different number of patients included in each analysis (Appendix C, figure S1). We also conducted a sensitivity analysis to explore the potential impact of including patients who were initially excluded from the main analysis due to missing data. In this analysis, we considered all missing test results for non-CTEPH patients as abnormal and all missing test results for CTEPH patients as normal, investigating the potentially most extreme outcome.

Definitions that were used are described in Appendix D. All analyses were performed using R, version 4.3.1 (www.R-project.org).

RESULTS

Part 1: improving the InShape II algorithm

Study population

Of the 424 PE patients included in the InShape II study, CTPA scans of the acute PE event were available in 341 patients. Mean age was 56 years, 49% were men (**Table 1**). Most patients received a direct oral anti-coagulant as treatment for the index PE (68%). At index PE, radiological signs of CTEPH were present in 12% when

assessing presence of CTEPH with ≥3/6 signs and 7.9% when using the overall radiologist's judgement. During follow-up 31% of the patients had symptoms suggestive for CTEPH. After 2-years of follow-up, a total of 12 patients were adjudicated as having CTEPH (3.6%; **Appendix C, Table S1**).

Table 1: baseline characteristics of the included patients.

	InShape II cohort (n=341)	**FOCUS cohort (n=171)**
Age (years, mean ±SD)	56 (16)	60.7 (15.7)
Male gender (n, %)	167 (49)	101 (59.1)
BMI (kg/m^2, mean ±S)	28 (5.9)	29.0 (5.4)
Unprovoked PE (n, %)	187 (55)	67 (39.2)
Right ventricular dysfunction at index PE (n, %)	96 (28)	119 (78.3)
Comorbidities (n, %)		
Active malignancy	31 (9.1)	16 (9.4)
Anemia	71 (21)	*
COPD/asthma	38 (11)	24 (14.0)
Coronary artery disease	22 (6.5)	23 (13.5)
Diabetes mellitus	24 (7.0)	23 (13.5)
Hypothyroidism	14 (4.1)	34 (19.9)
Inflammatory bowel	4 (1.2)	2 (1.2)
Interstitial lung disease	4 (1.2)	*
Known antiphospholipid antibodies	5 (1.5)	1 (0.6)
Major vasculitis syndromes	2 (0.6)	0 (0.0)
Rheumatic disease	15 (4.4)	5 (2.9)
Previous VTE	71 (21)	53 (31.0)
Prior infected pacemaker leads	1 (0.3)	4 (2.3)
Splenectomy	1 (0.3)	2 (1.2)
Anticoagulant treatment at 3-month follow-up (n, %)		
DOAC	233 (68)	135 (80.8)
VKA	87 (26)	8 (4.8)
LMWH	29 (8.5)	24 (14.4)
Symptoms suggestive for CTEPH at the 3 month follow up (n, %)	107 (31)	45 (26.3)
Pre-defined radiological signs of CTEPH		
Arterial retraction	41 (12)	10 (6.1)
Dilated bronchial arteries	24 (7.0)	12 (8.2)
Dilatation of the pulmonary trunk	119 (35)	74 (48.1)
Flattening of the interventricular septum	84 (25)	58 (39.5)
Intravascular webs	41 (12)	9 (5.7)
RV hypertrophy	19 (5.6)	3 (2.1)
≥3/6 signs of CTEPH present	40 (12)	14 (8.2)
Overall judgement CTEPH present	27 (7.9)	27 (15.8)

* unknown. Symptoms suggestive for CTEPH are i.e. dyspnoea on exertion, oedema, newly developed palpitations, syncope or chest pain. Abbreviations: PE, pulmonary embolism; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; LMWH, low-molecular weight heparin; VKA, vitamin K antagonist; DOAC, direct oral anti-coagulant

Table 2: overview of the performance of the hypothetical algorithms

	Failure rate in %* (95%CI)	Number of patients with an indication to perform ECG and NT-proBNP testing [n (%)]	Number of patients with an indication to perform TTE [n (%)]	AUC of ROC (95%CI)	Non-event NRI [%]	Event NRI [%]	Overall NRI [%]
InShape II cohort (n=341)							
InShape II	0.34 (0.06-1.9)	157 (46)	51 (15)	0.90 (0.81-0.90)	n.a.	n.a.	n.a.
CTPA criteria: ≥3/6 signs of CTEPH present							
Algorithm A^	0.35 (0 - 1.0)	147 (43)	53 (16)	0.89 (0.81-0.98)	-0.6	0	-0.6
Algorithm B	0 (0 - 0)	94 (28)	68 (20)	0.91 (0.89-0.94)	-4.9	8.3	3.5
Algorithm C	0.66 (0 - 1.6)	96 (28)	38 (11)	0.87 (0.76-0.99)	3.6	-8.3	-4.7
Algorithm D	0.69 (0 - 1.6)	96 (28)	51 (15)	0.85 (0.74-0.97)	-0.3	-8.3	-8.6
Algorithm E	0 (0 - 0)	157 (46)	62 (18)	0.92 (0.90-0.94)	-3	8.3	5.3
Algorithm F	1.27 (0.03 - 2.5)	0 (0)	27 (8)	0.80 (0.66-0.94)	6.4	-25	-18
CTPA criteria: CTEPH present according to overall judgement of radiologist							
Algorithm G^	0.34 (0 - 1.02)	144 (42)	50 (15)	0.90 (0.82-0.98)	0.3	0	0.3
Algorithm H	0 (0 - 0)	96 (28)	55 (16)	0.93 (0.92-0.95)	-0.9	8.3	7.4
Algorithm I	0.65 (0 - 1.6)	96 (28)	35 (10)	0.88 (0.77-0.99)	4.6	-8.3	-3.8
Algorithm J	0.67 (0 - 1.6)	96 (28)	42 (12)	0.87 (0.76-0.98)	2.4	-8.3	-5.9
Algorithm K	0 (0 - 0)	157 (46)	56 (16)	0.93 (0.91-0.95)	-1.2	8.3	7.1
Algorithm L	0.62 (0 - 1.5)	0 (0)	20 (6)	0.90 (0.79-1.0)	9.1	-8.3	0.8
FOCUS cohort (n=171)							
InShape II	0 (0 - 0)	74 (43)	51 (30)	0.86 (0.83-0.89)	n.a.	n.a.	n.a.
CTPA criteria: ≥3/6 signs of CTEPH present							
Algorithm B	0 (0 - 0)	39 (23)	41 (24)	0.89 (0.86-0.92)	6.0	0	6.0
Algorithm E	0 (0 - 0)	74 (43)	51 (30)	0.86 (0.83-0.89)	0	0	0
CTPA criteria: CTEPH present according to overall judgement of radiologist							
Algorithm H	0 (0 - 0)	33 (19)	51 (30)	0.86 (0.83-0.89)	0	0	0
Algorithm K	0 (0 - 0)	74 (43)	56 (33)	0.84 (0.81-0.88)	-3.0	0	-3.0

* Failure rate defined as the 2-year incidence of confirmed CTEPH in patients with PE in whom echocardiography was deemed unnecessary by the algorithm at baseline ^ missing NT-proBNP and ECG results in 2-5 non-CTEPH patients have been interpreted as not being able to rule-out CTEPH and therefore indication to TTE. Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; ECG, electrocardiogram; NRI netto, reclassification index; NT-proBNP, N-terminal-prohormone of brain natriuretic peptide TTE, transthoracic echocardiogram

Performance of newly designed algorithms

Table 2 provides an overview of the performance of the potentially new algorithms to rule out CTEPH. Application of the InShape II algorithm resulted in a failure rate of 0.34% (95% 0.0-1.0) with a need for echocardiographic evaluation in 51 patients (15%), and an AUC of 0.90.

Algorithms C, D and F and corresponding algorithms I, J and L resulted in a higher failure rate compared to InShape II (range 0.62-1.3%) with a minimal reduction in the need for echocardiographic evaluation (range 6-15%) and similar AUC (range 0.80-0.90). Algorithm A and corresponding algorithm G resulted in a similar safety (failure rate of 0.34% [95%CI 0.0-1.0]), efficiency (need for echocardiogram 15-16%) and AUC (0.90) to InShape II. Algorithms B and H, in which CTPA signs suggestive for CTEPH replaced the CTEPH prediction score, and algorithms E and K, in which CTPA signs suggestive for CTEPH were combined with the CTEPH rule-out criteria, showed the lowest failure rate of 0.0% (95%CI 0.0-0.0) with a small increase in the need for echocardiography (range 15-18%) and improved AUC (0.92-0.94).

Algorithms G and L had a positive overall NRI (0.3% and 0.8% respectively) showing minimal superiority over InShape II. Algorithm B with corresponding algorithm H and algorithm E with corresponding algorithm K performed the best in terms of overall NRI (3.5%, 7.4%, 5.3% and 7.1% respectively). All other algorithms had a negative overall NRI, indicating a worse performance than InShape II.

If all patients with an echocardiography indication had undergone echocardiography and those with an intermediate-high probability of pulmonary hypertension would have been subjected to CTEPH diagnostic work-up including V/Q-scan and RHC, 11 out of 12 CTEPH cases would have been identified by InShape II, algorithms A, B, E, G, H and K. For the other algorithms ≥3 CTEPH cases would have been missed (CTEPH detection rate of 58-75%; **appendix C, Table S2**).

Part 2: Evaluation in the FOCUS cohort

Study population

A total of 171 acute PE patients of the FOCUS cohort in whom the new algorithms could be evaluated were included. Mean age was 61 years and 59% were men (**Table 1**). Most patients received a direct oral anticoagulant as anticoagulant treatment for the acute PE (81%). At index PE, radiological signs of CTEPH were

present in 8.2% when assessing the presence of CTEPH with ≥3/6 signs and 16% when using the overall judgement of the expert radiologist. During follow-up 26.3% of the patients had symptoms suggestive for CTEPH. After follow-up, a total of four patients (2.3%) were adjudicated as having CTEPH. There was no clear difference in baseline characteristics between patients included in our study and all patients in the cohort (**Appendix C, Table S3 and S4**).

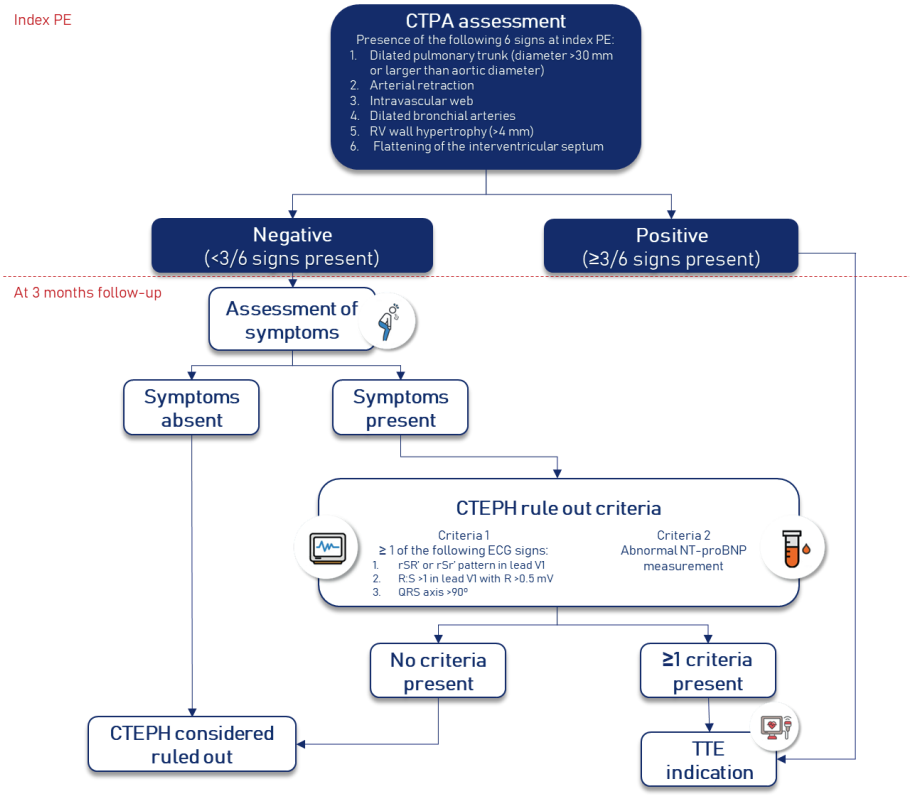
Performance of algorithms within the FOCUS cohort

Algorithm B with corresponding algorithm H and algorithm E with corresponding algorithm K had a positive NRI within the InShape II cohort and were thus evaluated within the FOCUS cohort. In the FOCUS cohort, the InShape II algorithm resulted in a failure rate of 0% (95%CI 0.0-0.0) with need for echocardiographic evaluation in 51 patients (30%) and an AUC of 0.86. All new algorithms resulted in a failure rate of 0% because no CTEPH patients were missed. In terms of efficiency, algorithm B was the most efficient with a need for echocardiography in only 24% of the patients and an AUC of 0.89. Algorithms E and H resulted in similar efficiency compared to InShape II (30%) and algorithm K resulted in a small increase in the need for echocardiography (33%) (AUC of 0.86, 0.86 and 0.84 respectively). When looking at NRI, algorithm B resulted in the highest change of 6.0%, reflecting better efficiency and similar safety compared to InShape II.

If all patients with an echocardiography indication had undergone to echocardiography and those with an intermediate-high probability of pulmonary hypertension would have been subjected to CTEPH diagnostic work-up including V/Q-scan and RHC, all CTEPH cases would have been detected by InShape II, algorithms B and H and algorithm E and K **(Appendix C, Table S2**).

Sensitivity analyses where we included patients based on complete cases within each algorithm showed similar results (**Appendix C, Table S5**). We also conducted a sensitivity analysis to explore the most extreme hypothetical scenario of including all 108 patients initially excluded from the main analysis due to missing data (**Appendix C, Table S6**). Assuming missing tests were abnormal for non-CTEPH patients and normal for CTEPH patients, CTEPH would have been missed in one patient by all algorithms, and 42-54% of the patients would have needed echocardiography. Similar to the main analysis, algorithm B resulted in the highest NRI of 11%. However, algorithm B also had a lower failure rate compared to InShape II of 0.62% (95% CI 0-1.8) versus 0.75% (95% CI 0-2.2).

Figure 2: The InShape IV algorithm



This figure depicts the InShape IV algorithm (algorithm B). Above the dashed red line in the CTPA reading of the CTPA reading of the index PE. While this CTPA reading utilized the CTPA performed to diagnose the acute PE, the detailed reading for signs of CTEPH can be conducted at any point between the index PE and the scheduled outpatient visit. Below the dashed red line are the screening items performed during acute PE follow-up approximately 3 months after acute PE diagnosis. 6 independent CTPA signs of CTEPH were evaluated: dilated pulmonary trunk (diameter >30 mm or larger than aortic diameter), arterial retraction, intravascular web, dilated bronchial arteries, RV wall hypertrophy (>4 mm) and flattening of the interventricular septum. Specific symptoms are symptoms suggestive for CTEPH i.e. dyspnoea on exertion, oedema, newly developed palpitations, syncope or chest pain at 3 month follow-up. Abnormal NT-proBNP measurement was defined as the NT-proBNP or BNP above center-, sex-, age-specific cut-off as defined by the assay's manufacturer; Abbreviations: Chronic thromboembolic pulmonary hypertension, CTEPH; Electrocardiogram, ECG; Transthoracic echocardiogram, TTE; N-terminal-prohormone of brain natriuretic peptide, NT-proBNP . Right ventricle, RV.

DISCUSSION

In this study, we aimed to improve the InShape II algorithm by incorporating advanced reading of the CTPA performed for the index PE, either as additional test or by replacing one of its components. We evaluated 12 new algorithms with two

different ways to discriminate positive from negative CTPA. Algorithm B (**Figure 2**), which we will refer to as the InShape IV algorithm, starting with reading the CTPA for 6 signs of CTEPH, followed by symptom evaluation, ECG/NT-proBNP assessment and echocardiography, was the best performing algorithm because it resulted in a positive NRI in both cohorts.

Around 2.7% of all acute PE patients are eventually diagnosed with CTEPH.[23] Minimising the diagnostic delay of CTEPH improves quality of life and life expectancy.[7] While dedicated acute PE follow-up algorithms exist, the average time to diagnosis in European CTEPH cohorts remains 15 months.[6, 24, 25] This situation underscores the need for more efficient, user-friendly acute PE follow-up algorithms, potentially leading to a wider adoption. Two extremes for the development of CTEPH are hypothesised: 1) 'incident' CTEPH, where incomplete acute PE thrombus resolution causes fibrotic obstruction and increased pulmonary artery pressure, and 2) 'prevalent' CTEPH, where an initially undiagnosed CTEPH patient experiences an acute-on-chronic event 'misdiagnosed' as acute PE, only to be diagnosed with CTEPH after a minimum of 3 months of anticoagulation. This hypothesis is supported by the predictive value of careful CTPA readings of index PE diagnosis focusing on signs of pre-existing CTEPH for the future CTEPH diagnosis.[14-18, 26] Use of these signs might help to identify patients with potential prevalent CTEPH, thereby prompting further evaluation.

In InShape IV, patients with 1) a positive index PE CTPA reading or 2) symptoms with either signs of RV pressure strain on ECG or abnormal NT-proBNP levels are referred to echocardiography; in all other patients, CTEPH is ruled out. InShape IV used the ≥3/6 signs of CTEPH to discriminate positive from negative CTPA. Compared to the radiologist's overall subjective evaluation of potential CTEPH, the use of ≥3/6 signs reduces subjectivity and enhances applicability in various clinical settings, including those with less experienced radiologists.[18] Another advantage is that the CTPA reading of the index PE can be conducted at any point between the index PE and the scheduled outpatient visit. This deferral from the acute setting of PE diagnosis aids logistics and avoids increasing workload for radiologists in settings where time constraints are prevalent and allows reading to be performed by a dedicated thoracic radiologist. The CTPA reading in InShape IV replaced the CTEPH prediction score in InShape II, which was designed to predict rather than demonstrate causality, leading to the inclusion of factors without an obvious pathophysiological link to CTEPH (e.g. diabetes). Thus, InShape IV not only

improves the performance of InShape II, but is also more consistent with the potential pathophysiology of acute-on-chronic CTEPH. InShape IV resembles the acute PE follow-up algorithm of the ESC guidelines.[8] However, notable distinctions exist. While the ESC guideline recommends screening for CTEPH only in patients with persistent symptoms or functional limitations, InShape IV uses CTPA analysis in all acute PE patients. Nevertheless, in both algorithms, CTEPH is ruled out in patients without symptoms or limitations and lacking suggestive CTEPH indicators on CTPA. Another difference lies in the consideration of risk factors for CTEPH. The ESC guideline suggests performing echocardiography in asymptomatic patients with significant risk factors, while risk factors are not explicitly outlined in the InShape IV algorithm. However, some are indirectly included, such as CTPA findings suggestive of preexisting chronic thromboembolic disease, other (often very rare) risk factors such as splenectomy or infected pacemaker leads are not considered. Of note, it is likely that the prognostic value of the CTPA reading actually supersedes that of the individual clinical risk factors. Also, InShape IV incorporates ECG reading and NT-proBNP assessment, minimizing the need for echocardiography, which is relevant in settings where high-quality echocardiography is not routinely available.[8] As described above, InShape IV has clearly defined criteria and aligns closely to the pathophysiology of potential acute-on-chronic CTEPH. This aspect makes it particularly useful for non-CTEPH expert physicians, potentially enhancing its applicability in various clinical settings. The choice which of algorithm to adopt in daily practice should be tailored to the resources of local healthcare systems, considering factors such as the qualifications of the physicians conducting the PE follow-up and the availability of tests.

Compared to InShape II, InShape IV resulted in an improved failure rate: one CTEPH patient in whom CTEPH was ruled out by InShape II based on negative rule-our criteria, had an echocardiography indication in InShape IV due to a positive CTPA reading. However, this improved failure rate did not result in an overall improved CTEPH detection rate because echocardiography was negative 6 months after the acute PE diagnosis in this patient, suggesting incident CTEPH that would have been missed by all algorithms including the current ESC guideline (**Appendix C, nr 12 in Table S1**, described in Boon et al.[10]). Notably, the InShape IV algorithm has important potential improvements over InShape II due to its clear initiation point and streamlined evaluation process. Under this algorithm, CTEPH patients promptly undergo to echocardiography without the prerequisite of first

performing ECG or NT-proBNP testing along with reducing the overall necessity for such tests (23% for InShape IV compared to 43% for InShape II), potentially resulting in a more cost-effective approach. Moreover, by efficiently selecting patients with an echocardiography indication, we anticipate expedited referrals to expert pulmonary hypertension centres of those with abnormal echocardiography and V/Q-scans and minimised diagnostic delays in CTEPH resulting in improve outcomes.[7] Widespread adoption of the InShape IV algorithm could thus potentially improve outcomes for CTEPH patients.

Our study has strengths and limitations. A strength is the evaluation of multiple algorithms and their subsequent assessment in different cohorts for which the data were prospectively collected. Examination of the performance in a non-derivation cohort enhances the robustness of our findings. A limitation is the post-hoc design of this study, because of which not all tests were performed in all patients, possibly leading to selection bias because patients with missing data within the FOCUS study were excluded from our analyses. We mitigated this concern by performing sensitivity analyses and by comparing the characteristics of included and excluded patients, and observed no clear differences (Appendix C, Table S3). Second, the InShape II study and FOCUS study were performed before the 2022 ESC pulmonary hypertension guidelines recommended to adjusting the definition of pre-capillary pulmonary hypertension to a pulmonary artery pressure of >20 mmHg in combination with a pulmonary artery wedge pressure ≤15 mmHg and a pulmonary vascular resistance of >2 Wood units.[27] With the new guidelines, a difference in classification as currently performed in daily practice might alter the performance of the algorithms, but this remains to be investigated. Last, the algorithms are specifically designed to detect CTEPH as early and efficiently as possible. Consequently, they do not help identify other potential causes of persistent dyspnea in PE survivors, such as chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension. Finding an explanation for the patient's symptoms using, for example, cardiopulmonary exercise testing, is as important as early CTEPH detection, although alternative diagnoses including CTEPD without pulmonary hypertension have not been shown to be associated with higher mortality and longer diagnostic delay may be acceptable.

In conclusion, dedicated CTPA reading of the index PE improved the performance of the InShape II algorithm. The newly derived InShape IV algorithm, in which the clinical CTEPH prediction score is replaced by detailed CTPA readings

of index PE, appears to be the best algorithm because it resulted in the highest classification improvement compared to InShape II. Detailed CTPA reading as part of a dedicated follow-up algorithm or as a single test may indeed be valuable to select PE survivors with a higher prevalence of CTEPH.

REFERENCES

1. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *European Respiratory Journal* 2019: 53(1): 1801915.
2. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. *Nature reviews Disease primers* 2018: 4: 18028.
3. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *The European respiratory journal* 2021: 57(6).
4. Lang IMandMadani M. Update on chronic thromboembolic pulmonary hypertension. *Circulation* 2014: 130(6): 508-518.
5. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. *Circulation* 2016: 133(9): 859-871.
6. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. *Eur Respir J* 2018: 52(6).
7. Boon G, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. *ERJ open research* 2021: 7(3).
8. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2019: 54(3).
9. Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a Simple Noninvasive Screening Algorithm for Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism. *TH Open* 2018: 2(1): e89-e95.
10. Boon G, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. *Thorax* 2021: 76(10): 1002-1009.
11. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost* 2016: 14(1): 121-128.
12. Klok FA, Surie S, Kempf T, 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): 21-26.
13. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. *Thromb Haemost* 2014: 112(3): 598-605.
14. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
15. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. *AJR Am J Roentgenol* 2020: 215(4): 800-806.
16. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. *Eur Respir J* 2021.
17. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography

pulmonary angiography performed for suspected acute pulmonary embolism. *Eur Radiol* 2021.
18. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. *Eur J Intern Med* 2021: 93: 64-70.
19. Barco S, Mavromanoli AC, Kreitner KF, et al. Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism. *Chest* 2023: 163(4): 923-932.
20. Valerio L, Mavromanoli AC, Barco S, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. *Eur Heart J* 2022.
21. Konstantinides SV, Barco S, Rosenkranz S, et al. Late outcomes after acute pulmonary embolism: rationale and design of FOCUS, a prospective observational multicenter cohort study. *J Thromb Thrombolysis* 2016: 42(4): 600-609.
22. Leening MJ, Vedder MM, Witteman JC, et al. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Ann Intern Med* 2014: 160(2): 122-131.
23. Luijten D, Talerico R, Barco S, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. *Eur Respir J* 2023: 62(1).
24. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011: 124(18): 1973-1981.
25. Guth S, D'Armini AM, Delcroix M, et al. Current strategies for managing chronic thromboembolic pulmonary hypertension: results of the worldwide prospective CTEPH Registry. *ERJ Open Research* 2021: 7(3): 00850-02020.
26. Barco S, Mavromanoli AC, Kreitner K-F, et al. Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism. *CHEST*.
27. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European heart journal* 2022: 43(38): 3618-3731.

Supplementary file

10

Cost-effectiveness of follow-up algorithms for chronic thromboembolic pulmonary hypertension in pulmonary embolism survivors

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ERJ Open Res. 2025 Jan 13;11(1):00575-2024

ABSTRACT

Introduction: Achieving an early diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) in pulmonary embolism (PE) survivors results in better quality of life and survival. Importantly, dedicated follow-up strategies to achieve an earlier CTEPH diagnosis involve costs that were not explicitly incorporated in the models assessing their cost-effectiveness. We performed an economic evaluation of 11 distinct PE follow-up algorithms to determine which should be preferred.

Materials and methods: 11 different PE follow-up algorithms and one hypothetical scenario without a dedicated CTEPH follow-up algorithm were included in a Markov model. Diagnostic accuracy of consecutive tests was estimated from patient-level data of the InShape II study (n=424). The lifelong costs per CTEPH patient were compared and related to Quality-Adjusted Life-Years (QALYs) for each scenario.

Results: Compared to not performing dedicated follow-up, the integrated follow-up algorithms are associated with an estimated increase of 0.89-1.2 QALYs against an incremental cost-effectiveness ratio (ICER) of 25,700-46,300 € per QALY per CTEPH patient. When comparing different algorithms with each other, the maximum differences were 0.27 QALYs and €27,600. The most cost-effective algorithm was the InShape IV algorithm, with an ICER of €26,700 per QALY compared to the next best algorithm.

Conclusion: Subjecting all PE survivors to any of the currently established dedicated follow-up algorithms to detect CTEPH is cost-effective and preferred above not performing a dedicated follow-up, evaluated against the Dutch acceptability threshold of €50,000 per QALY. The model can be used to identify the locally preferred algorithm from an economical point-of-view within local logistical possibilities.

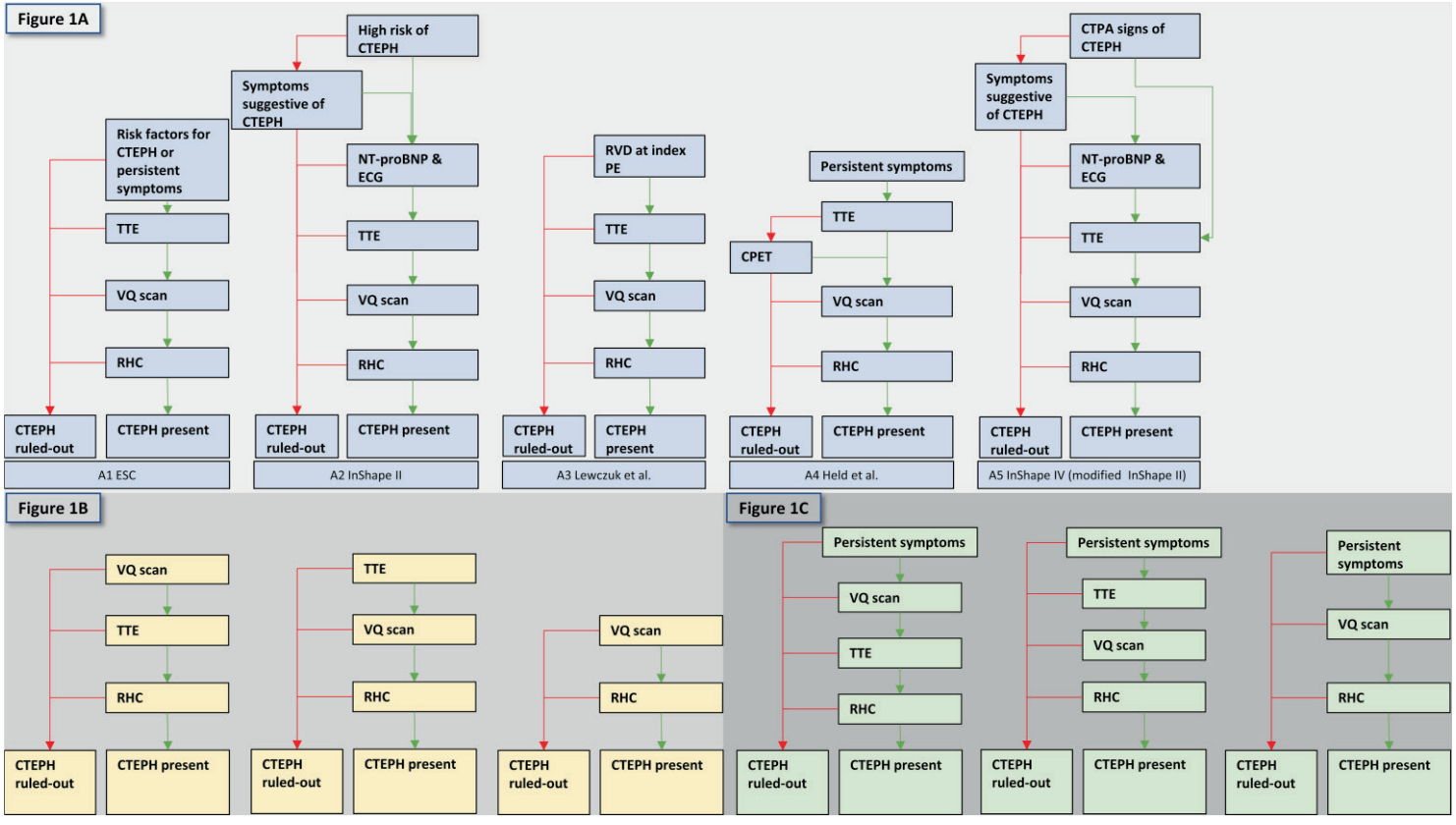
INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potential rare complication of acute pulmonary embolism (PE), and is fatal unless it is diagnosed in time and treated adequately.[1-4] Notably, the international prospective CTEPH registry reported a median diagnostic delay of 14.1 months in 2007-2009, which remained 15 months in a second registry covering 2015-2018, highlighting that implementation of strategies for early CTEPH detection is an unmet clinical need.[5,6]

Approximately 2.7% of all acute PE survivors are eventually diagnosed with CTEPH. Focused attention on CTEPH in acute PE survivors has been proven to reduce the diagnostic delay, which is associated with better quality of life and survival.[7, 8] There are several strategies to establish earlier diagnosis of CTEPH in acute PE survivors. The European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline on acute PE suggests performing an echocardiogram in PE survivors with persistent dyspnea, functional limitations or risk factors for CTEPH.[9] Alternative approaches include follow-up algorithms consisting of long-term telephonic follow-up of PE survivors, a clinical decision rule for estimating the CTEPH pre-test probability, application of an N-terminal pro brain natriuretic peptide (NT-proBNP) blood test combined with an electrocardiogram (ECG), dedicated review of index computed tomography pulmonary angiogram (CTPA) images and/or routine follow-up ventilation/perfusion scans (VQ-scan).[4, 10-13]

A previously developed economic model showed that earlier CTEPH diagnosis results in better survival at costs remaining below the limit of €50,000 per quality adjusted life year (QALY), which is deemed acceptable in the Netherlands.[14] However, the model used a non-specified hypothetical algorithm and did not compare the different algorithms actually available. In the current study we extend the model by including costs and outcomes of distinct available PE follow-up algorithms. We set out to assess the cost-effectiveness of these algorithms to determine which algorithm should be preferred from a healthcare economics point of view.

Figure 1: the 11 scenarios evaluating different follow-up algorithms to detect CTEPH in acute PE patients



Note for figure 1: Category A represents algorithms identifying using a literature search, category B represents hypothetical algorithms where diagnostic tests are performed in all acute-PE patients, and category C represents hypothetical algorithms where diagnostic tests are only performed in patients that remain symptomatic during follow-up. A green line presents a "positive result" and a red line presents a "negative result" of the diagnostic test. All algorithms start approximately 3 months after an index PE diagnosis. Assumptions made in the evaluation of the algorithms: If available, we used the echocardiogram performed as a part of the InShape II algorithm we used the 2-year follow-up echocardiogram as a surrogate outcome. The algorithms by Lewczuk et al. (A3) used repeating measurement of diagnostic tests at different time-points in case of a negative test result in the preceding test. The InShape II study did not perform all diagnostic tests in all patients at different time-points. We therefore modified the algorithm of Lewczuk et al. to fit a one time-point approach which could be evaluated using the InShape II cohort. We had no data on the sensitivity and specificity of VQ-scans or on echocardiography in patients with a positive VQ scan in the InShape II study. Taking CTEPH incidence after acute PE[8] and the rate of positive scans after acute PE into account (Cimini et al.[15]), we made the assumption that the false-positive rate for VQ scan performed approximately 3 months after acute PE diagnosed would be 36%, meaning that 36% of the non-CTEPH patients were assumed to have persistent perfusion defects on VQ-scan after 3 months.[16, 17] We had no data on the false-positive rate for echocardiography in patients with persistent perfusion defects on VQ scan. Prevalence of an estimated pulmonary artery pressure of >30 mmHg is estimated to be 25-48%.[18] Therefore, we assumed that 37.5% of the non-CTEPH patients with an abnormal VQ-scan would have an intermediate-high risk of pulmonary hypertension on echocardiography. Abbreviations: CPET cardiopulmonary exercise test; CTEPH chronic thromboembolic pulmonary hypertension; CTPA computed tomography pulmonary angiogram; ECG electrocardiogram; NT-proBNP N-terminal pro b-type natriuretic peptide; PE pulmonary embolism; RHC right heart catheterization; RVD right ventricular dysfunction; TTE trans-thoracic echocardiogram; VQ scan ventilation/perfusion scan.

METHODS

Objective

The aim of this study was to evaluate QALYs and healthcare costs for different PE follow-up algorithms. For this purpose, all algorithms that have been proposed, evaluated or described in studies, reviews or guidelines were identified by an extensive literature search (search last updated in October 2023; **Appendix A**). We evaluated 329 publications and detected 5 relevant follow-up algorithms (**Appendix B, Figure S1** flow chart of literature search; **Figure 1A**): the (simplified) ESC algorithm (A1)[9], the InShape II algorithm (A2)[4], an algorithm published by Lewczuk et al. (A3)[19], an algorithm published by Held et al. (A4)[20], and the InShape IV algorithm, a modified version of the InShape II algorithm where the CTEPH prediction score is replaced by the presence of signs of CTEPH on the index computed tomography pulmonary angiogram (CTPA) (A5)[21]. In addition, we studied hypothetical algorithms where echocardiogram, VQ scan or right heart catheterisation (RHC) are routinely performed in all patients (scenario B1-B3; **Figure 1B**), or in all symptomatic patients (scenario C1-C3; **Figure 1C**), and lastly, a scenario without dedicated follow-up (scenario 0).

Estimation of accuracy of different scenarios

We used patient-level data of the InShape II study to calculate the diagnostic accuracy of each test, conditional on the outcome of the preceding test. The

InShape II study was a prospective international multicenter management study performed in 2016-2017 where 424 consecutive patients were managed according to a dedicated algorithm to determine whether echocardiographic evaluation of CTEPH was indicated. All patients in whom CTEPH was considered to be absent were subjected to follow-up echocardiography 2 years later. The InShape II cohort was performed before the 2022 ESC pulmonary hypertension guideline recommended to adjust the definition of pre-capillary pulmonary hypertension to a pulmonary artery pressure of >20 mmHg in combination with a pulmonary vascular resistance of >2 woods units. Therefore CTEPH was diagnosed according to the 2015 ESC/ERS guideline with a mean pulmonary artery pressure of ≥25 mmHg in combination with a pulmonary arterial wedge pressure of ≤15 mmHg.[9, 22] In a subsequent preplanned analysis, CTPA scans of the acute PE event were evaluated for signs of chronicity by an independent radiologist blinded for the ultimate presence of CTEPH.[23, 24]

To assess their diagnostic accuracy, the overall number of true-positives, true-negatives and false-negatives were calculated for each scenario. The final step of each follow-up algorithm was application of RHC (Figure 1). As the InShape II study did not include cardio pulmonary exercise test, we used data from the Held et al. paper to evaluate diagnostic accuracy of scenario A4.[20] Definitions used for the dedicated follow-up algorithms are described in **Appendix C**.

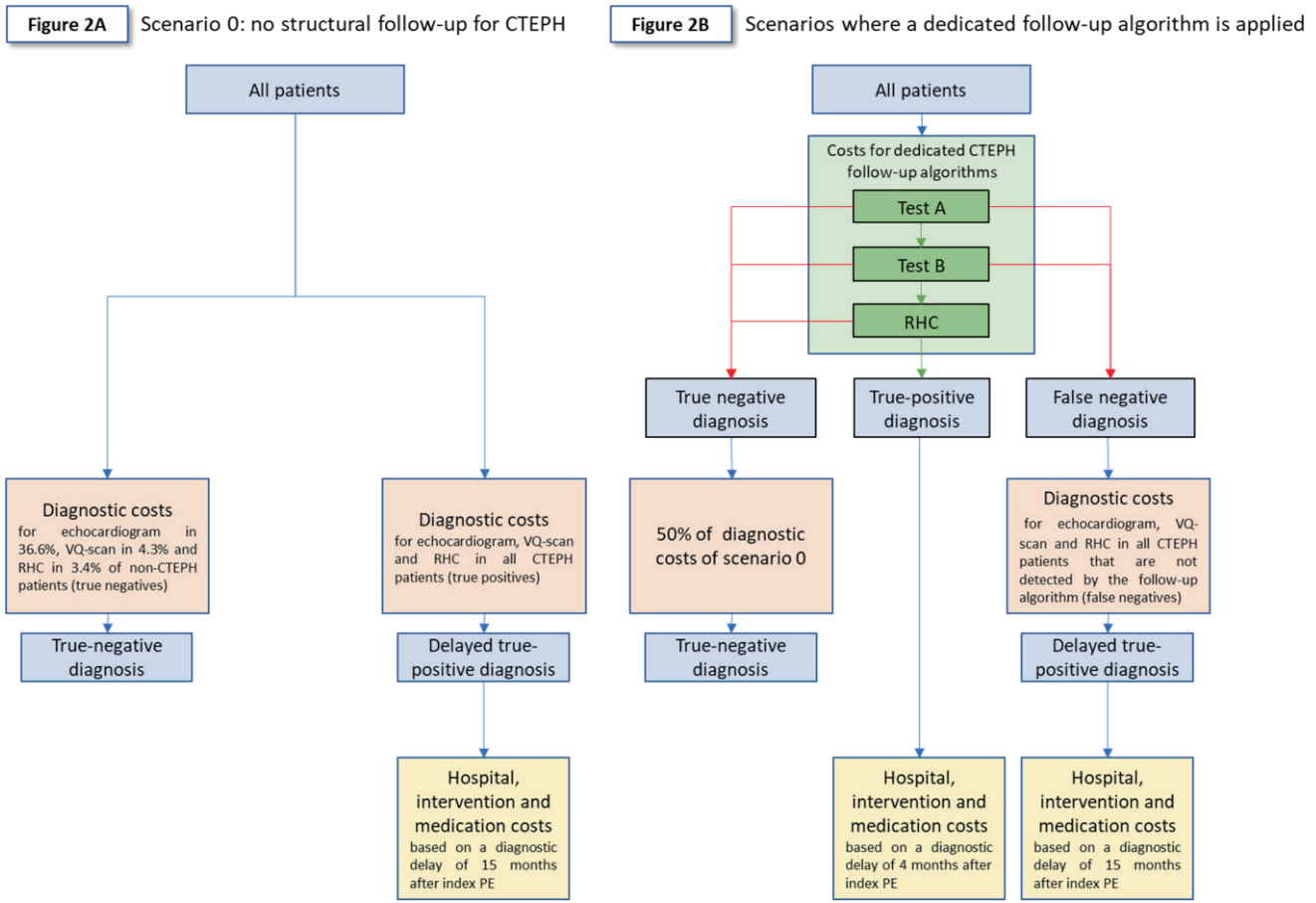
Costs

Lifelong healthcare costs were estimated in euros at price level 2022. For each scenario we calculated the (1) costs for all diagnostic tests performed in the follow-up algorithm, (2) (additional) diagnostic costs later on and (3) hospital, intervention and medication costs (**Figure 2**).

Costs for all diagnostic tests performed in the follow-up algorithms

Costs per diagnostic test are depicted in **table 1**, including costs for associated consultations and travel costs for the patients.[25] Costs of follow-up tests were counted for the number of patients undergoing the tests. For scenario 0 there are by definition no costs for tests performed within the algorithm.

Figure 2: Flowchart of dedicated follow-up, (additional) diagnostic and treatment costs of each scenario



As RHC is the golden standard for CTEPH diagnosis, there were considered to be no false-positive CTEPH diagnoses. However, a false-negative result from a diagnostic test prior to RHC is possible, therefore a temporarily false-negative CTEPH diagnosis is included in our model (Figure 2B).

(Additional) diagnostic costs

(Additional) diagnostic costs are costs for test performed for the detection of CTEPH outside the dedicated follow-up algorithm. For each CTEPH patient that is not detected by the dedicated follow-up algorithm (true-positives in scenario 0 and false-negatives in scenario A1-C3; **figure 2**), (additional) diagnostic costs consist of an echocardiogram, VQ-scan and RHC. Non-CTEPH patients (true-negatives) might also have persistent post-PE symptoms resembling CTEPH; it is therefore to be expected that (additional) diagnostic tests are also performed in this patient category. In scenario 0, we assumed the number of diagnostic tests performed for each true-negative patient based on the frequency of test performed in a retrospective study (**Figure 2a**).[28] For the other scenarios, we expect that initially performing a follow-up algorithm would reduce the subsequent number of diagnostic tests. Therefore we assumed the additional diagnostic costs in true-negative patients at 50% of the diagnostic costs for true-negative patients in scenario 0 (**Figure 2b**), and performed a sensitivity analysis with 0-100% of the costs.

Hospital, intervention and medication costs

For each true-positive patient, additional hospital, medication and intervention costs were counted, dependent on the duration of the delay. These costs were derived from the Markov model that was developed to predict average lifelong outcomes of CTEPH patients depending on the degree of diagnostic delay for a CTEPH diagnosis.[14] For true-positive patients, we assumed that CTEPH is diagnosed within 4 months after index PE, as CTEPH follow-up is initiated 3 months after acute PE and application of the follow-up algorithms would take approximately 1 month. For true-positives in scenario 0 and false-negatives in A1-C3, we assumed that CTEPH is diagnosed 15 months after diagnosis as this is the currently described diagnostic delay in CTEPH patients, leading to a delayed true-positive diagnosis.[5, 6] Long-term outcomes were given less weight by discounting costs at 4% according to Dutch guidelines for economical evaluation of healthcare.[29]

Table 1: Costs of diagnostic tests

	Costs per test, €
CTPA reading of index PEα	0
Assessment of symptoms	0
Assessment of risk factors for CTEPH	0
Application of CTEPH prediction score	0
ECG & NT-proBNP*	193
TTE*	269
CPET*	348
VQ scan*	494
RHC*β	609

Costs per test are derived from the costs per performed tests derived from the passerby list of the Leiden University Medical Center published in 2022[25] *We assumed that each acute PE patient would have a consultation at the outpatient clinic as part of follow-up. For each diagnostic test performed we decided if outcomes of these tests would require an extra consultation. Costs of an extra consultation and travel costs are therefore incorporated in the costs per diagnostic test marked with an asterisk, according to the Dutch cost manual.[26] α in sensitivity analysis 6 these costs ranged from €45-€153. β Including potential costs for hospitalization after RHC complication with an incidence of 0.003%[25, 27] Abbreviations: CPET cardiopulmonary exercise test; CTEPH chronic thromboembolic pulmonary hypertension; CTPA computed tomography pulmonary angiogram; ECG electrocardiogram; NT-proBNP N-terminal pro b-type natriuretic peptide; PE pulmonary embolism; RHC right heart catheterization; TTE trans-thoracic echocardiogram; VQ scan ventilation/perfusion scan.

Cost-effectiveness model

The reported CTEPH incidence of 2.7% within acute PE survivors was used to calculate overall costs per CTEPH patient.[8] We reported outcomes per CTEPH patient because the share of CTEPH patients is fixed and with this approach the differences between algorithms are not diluted by the small percentage CTEPH patients. We used the previously built Markov model to estimate life-expectancy and health related quality of life, which were combined to calculate lifelong QALYs depending on the diagnostic delay for each algorithm.[14] This model included excess CTEPH mortality and health-related quality of life. Excess CTEPH mortality was modelled by subtracting standard Dutch mortality from the mortality reported in CTEPH patients then fitting a two-group mixed-exponential model and extrapolating that model for 10 years.

We subsequently plotted the lifelong costs against the QALYs for each scenario. The scenarios that are not (weakly) dominated by others are potentially cost-effective and together form the efficient frontier.[30, 31] Among pairs of scenario α and β along the efficient frontier, we calculated the incremental cost-effectiveness ratios (ICERs):

$$\text{ICER} = \frac{\text{Costs}^{\text{scenario } \alpha} - \text{Costs}^{\text{scenario } \beta}}{\text{QALY}^{\text{scenario } \alpha} - \text{QALY}^{\text{scenario } \beta}}$$

The economically preferred algorithm is the scenario with the best QALYs at an acceptable ICER. According to Dutch health-economic standards an ICER of €50,000 per QALY is acceptable in this patient population.[29]

Sensitivity analysis

We performed six sensitivity analyses. First, as the reported rate of positive VQ-scans after acute PE ranges in the literature, we performed a sensitivity analysis with a false-positive VQ-scan rate ranging from 23 to 78%.[15] Second, as the reported diagnostic delay of CTEPH may differ by region, we performed the analysis with delay ranging from 12.0 (Japan) to 23.5 months (America and others).[6] Third, because the false-positive rate of echocardiography in patients with a positive VQ scan was assumed rather than estimated, we performed a sensitivity analysis with a false-positive rate ranging from 25-48%.[18] Fourth, as the incidence of CTEPH after acute PE may differ per region, we performed a sensitivity analysis with CTEPH incidence ranging from 2.3% (Europe) to 6.1% (Middle-East).[8] Also, as described above, we performed a sensitivity analysis where we assumed the additional diagnostic costs in true-negative patients in scenario A1-C3 at 0-100% of the diagnostic costs for true-negative patients in scenario 0. Finally, in the base case model, we assumed that the CTPA conducted at the time of the index PE event could be evaluated at the same center without additional costs for detailed reading, as it's typically available for each acute PE patient and can be interpreted by both expert and non-expert radiologists.[23] However, we acknowledge the possibility of reassessment in a non-acute setting by an expert radiologist or even transferring CTPA imaging to another center for reevaluation due to potential expertise limitations. To address this, we conducted a sixth sensitivity analysis considering varying costs for CTPA reading, ranging from €45 to €153.

RESULTS

Study patients

A total of 424 patients were included in the InShape II study. Baseline characteristics are described in the previously published study and in **appendix B, table S1**.[4]

Diagnostic accuracy

The diagnostic accuracy of each test within each scenario is summarized in **Appendix B, Table S2**. Sensitivity and specificity for a certain test could differ between scenarios depending on the preceding test results. In short, sensitivity for CTPA reading was 67%, 85% for presence of right ventricular dysfunction at index PE, 92-100% for positive symptoms or risk factors for CTEPH, 92-100% for ECG and NT-proBNP testing, and 83-92% for echocardiography. Specificity was 90% for CTPA reading, 70% for presence of right ventricular dysfunction at index PE, 20-70% for positive symptoms or risk factor for CTEPH, 66-73% for ECG and NT-proBNP testing and 63-92% for echocardiography. The overall sensitivity of performing a dedicated follow-up algorithm for detecting CTEPH ranged from 77-100%.

Costs

The estimated lifelong healthcare costs per CTEPH patient for each scenario are depicted in **Figure 3** and **Table S2**. Lifelong healthcare costs mainly consisted of hospital, intervention and medication costs and ranged from €129,300 to €157,000. Costs for the dedicated follow-up were highest for scenarios where all patients received diagnostic tests (scenario B1-B3; range €12,800-€26,400) and lowest if patients were not subjected to a dedicated follow-up algorithm (scenario 0; €0). Additional diagnostic costs were highest if patients were not subjected to a dedicated follow-up algorithm (scenario 0; €6,100), while for the other scenarios additional diagnostic costs were similar and low (range €2,500 to €2,700).

Based on our model, when comparing total lifelong healthcare costs per CTEPH patient between scenarios, performing VQ-scan and if abnormal RHC in all acute PE patients (scenario B3) was the most expensive scenario with lifelong healthcare costs of €185,900 per CTEPH patient. The least expensive scenario was scenario 0 (no dedicated follow-up for CTEPH) with lifelong healthcare costs of €135,500 per CTEPH patient.

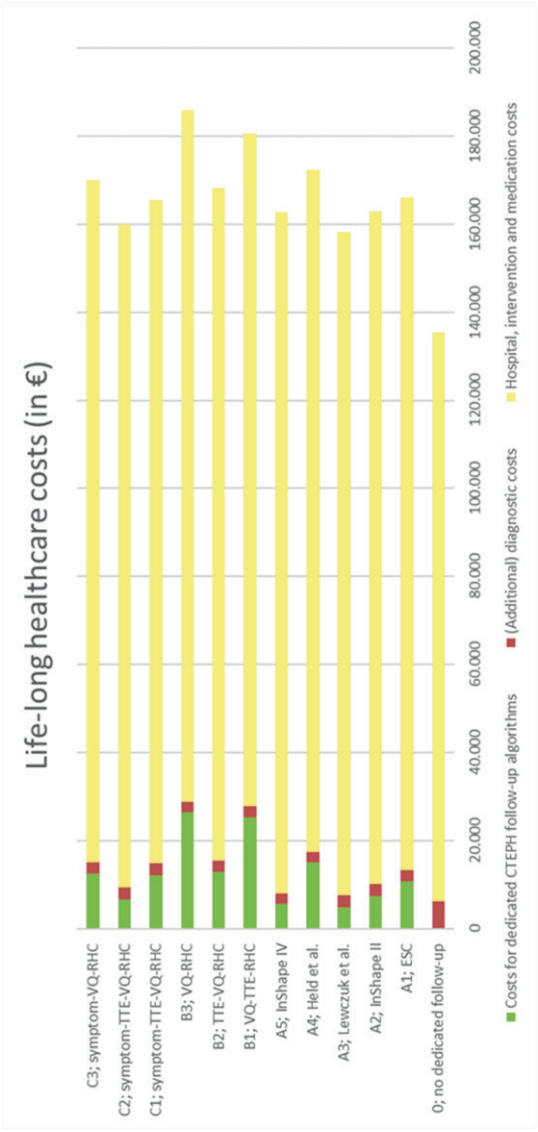
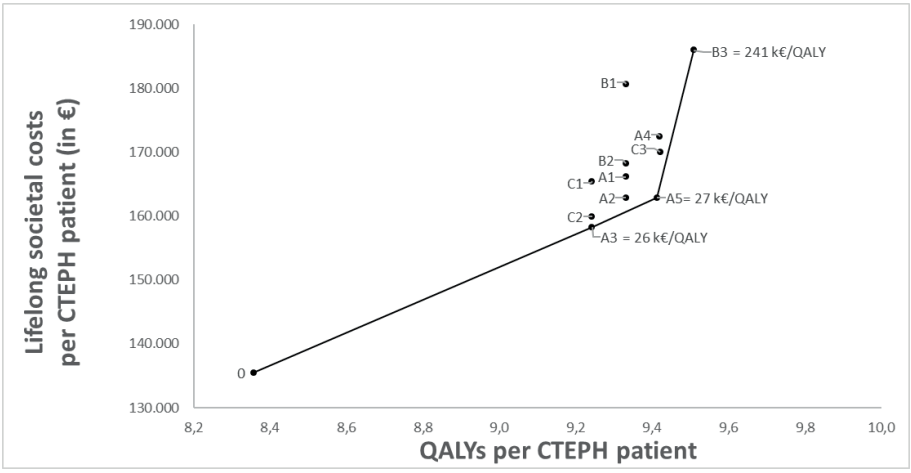


Figure 3: lifelong healthcare costs per CTEPH patients for the 12 scenarios

Cost-effectiveness

Estimated lifelong healthcare costs per CTEPH patient were plotted against the predicted QALYs for each scenario (**Figure 4**). The more cost-effective strategies are located in the right-lower corner of the graph, reflecting higher QALYs and lower lifelong healthcare costs.

Figure 4: Total lifelong healthcare costs and QALYs per CTEPH patient



A scenario is dominated if there is another algorithm that is at least as good on both costs and QALYs, and strictly better on at least one of costs and QALYs. A scenario is weakly dominated if it is dominated by a mixture of two other algorithms. The scenarios that are not (weakly) dominated by others are potentially cost-effective and together form the efficient frontier (black line).
0 no dedicated CTEPH follow-up; A1 ESC; A2 InShape II; A3 Lewczuk et al.; A4 Held et al.; A5 InShape IV; B1 TTE-VQ-RHC; B2 VQ-TTE-RHC; B3 VQ-RHC; C1 symptom-TTE-VQ-RHC; C2 symptom-VQ-TTE-RHC; C3 symptom-VQ-RHC

Four scenarios are on the efficient frontier, indicating the potentially most cost-effective scenarios: the least expensive and least effective scenario 0: no follow-up for CTEPH; scenario A3: the algorithm by Lewczuk et al.[19]; scenario A5: the InShape IV algorithm; and the most expensive and most effective scenario B3: performing VQ-scan and subsequent RHC if abnormal in all acute PE survivors.

Compared to scenario 0, the next best scenario A3 on the efficient frontier provides a gain of 0.89 QALYs at €22,800 additional costs, with an ICER of €25,700 per QALY. Compared to scenario A3, the next best scenario A5 provides a gain of 0.17 QALYs at €4,500 additional costs, with an ICER of €26,700 per QALY. Finally, compared to scenario A5, the next best scenario B3 provides a gain of 0.10 QALYs at €23,000 additional costs, with an ICER of €240,700 per QALY. The latter is too expensive, compared to the Dutch acceptability threshold of €50,000 per QALY. Therefore, the economically preferred scenario is A5; the InShape IV algorithm.

Depending on the availability of different tests, algorithms outside the efficient frontier could also be relevant. When comparing all scenarios to not performing a dedicated follow-up algorithm (scenario 0), all algorithms have acceptable cost-effectiveness with ICERS ranging from €27,600 (scenario C3) to €46,300 per QALY

(scenario B1; **Appendix B, Table S2**). However, when available, scenarios A3 and A5 on the efficient frontier already obtain most of the QALY gain, at lower costs.

Table S3 in **appendix B** illustrates outcomes of the sensitivity analyses. For almost all sensitivity analyses, scenarios 0, A3, A5 and B3 remained on the efficient frontier and the economically preferred scenario remained A5. Only in the sensitivity analysis where we assumed costs for detailed CTPA reading consisted of €152, scenario 0, A3, A2, A5, C3 and B3 where on the efficient frontier. The most cost-effective algorithm in this sensitivity analysis was algorithm A3 with an ICER of €25,700 per QALY. When comparing each scenario to not performing a dedicated follow-up algorithm (scenario 0) in different sensitivity analyses, almost all scenarios have acceptable cost-effectiveness below Dutch acceptability threshold of €50,000 per QALY (except for B3 in sensitivity analysis 1 and 4, and B1 in sensitivity analysis 2; **appendix B, table S3**).

DISCUSSION

Our study presents a unique Markov model for quantifying the impact of reducing the diagnostic delay of CTEPH on lifelong costs and QALYs which explicitly modelled different follow-up strategies aimed at earlier CTEPH diagnosis. 2.7% of all acute PE survivors are eventually diagnosed with CTEPH while up to 50% of acute PE patients remain symptomatic.[8, 32-36] Without a systematic approach, it remains difficult to identify in which of these symptomatic patients CTEPH is the underlying cause.[37] Integrating any of the algorithms to detect CTEPH at an early stage in daily clinic is preferred above not performing a dedicated follow-up, as it will result in an increase of 0.89-1.2 QALYs against an ICER of €25,700-€46,300 per QALY, remaining below the Dutch acceptability threshold of €50,000 per QALY providing a cost-effective approach. This result underlines the relevance of implementing a dedicated PE follow-up pathway. When comparing different algorithms with each other, algorithm B3 resulted in the highest QALYs, but also had the highest lifelong costs (9.51 QALYs, €185,900 per CTEPH patient) and algorithm A3 resulted in the lowest QALYs, but at the lowest costs (9.24 QALYs, €158,300 per CTEPH patient). Algorithm A5, the InShape IV algorithm, had the best QALYs relative to an acceptable ICER (9.41 QALYs, €162,800 per CTEPH patient, with an ICER of €26,700 per QALY compared to the next best algorithm).

It has been shown that that in the majority of PE survivors eventually diagnosed with CTEPH, radiological signs of CTEPH were retrospectively observed at the index

diagnosis. This is highlighted by multiple studies that have shown that certain radiological signs of chronicity present at the moment of an acute PE diagnosis are highly predictive for a future CTEPH diagnosis.[23, 24, 38-40] The InShape IV algorithm (algorithm A5) resembles the ESC follow-up algorithm, with 'risk factors for CTEPH' captured by the presence of these signs of chronicity on the index CTPA[21]. Furthermore, compared to the ESC follow-up algorithm, the InShape IV algorithm is enriched with ECG and NT-proBNP measurement to detect signs of right ventricular overload before performing echocardiography. Only if either of these show signs of right ventricular overload echocardiography is indicated, minimizing the need to perform echocardiography.[10-12] The latter is especially relevant for healthcare settings where access to echocardiography is challenging, for example when cardiologists are not the primary caretakers of acute PE, or in community care.

When choosing which algorithm to implement into daily practice, the InShape IV algorithm is preferred from an economical perspective as it resulted in the best QALYs relative to an acceptable ICER. However, local circumstances also need to be taken into account. If acute PE follow-up is performed by a cardiologist, performing an echocardiography might be easier than performing detailed CTPA review of the acute PE as a first step in acute PE follow-up. Therefore, other algorithms beside the InShape IV algorithm might be preferred based on local healthcare organization. All follow-up algorithms resulted in more favourable costs and outcomes compared to not performing a dedicated follow-up algorithm. Therefore, implementation of any (other) algorithm based on the possibilities within local healthcare organization is a valid and cost-effective improvement over not performing dedicated follow-up. As the ICER balances gain in QALYs against additional costs to evaluate cost-effectiveness, it is relevant to look at absolute differences between algorithms when choosing which algorithm to implement in daily practice. Between algorithms there was a maximum difference of 0.27 QALYs at the increased lifelong costs of €27,600 per CTEPH patient. Notably, these costs are reported per CTEPH patient. When calculating costs in the total population of PE survivors, the difference is much smaller, as a cost increase of €27,600 per CTEPH patient equals an increase of only €745 per PE survivor.

Our model has limitations. First, because we extended the previously build Markov model by including overall costs and outcomes of available distinct PE follow-up algorithms, limitations previously described are also applicable to the current analysis. Modelling assumptions were made based on available literature

to estimate quality of life and mortality outcomes in CTEPH patients. Moreover, we had to make further assumptions regarding; 1) the false-positive rate of VQ scans, 2) the false-positive rate of echocardiography in patients with persistent perfusion defects on VQ-scans, 3) the diagnostic delay in false-negative patients and 4) the amount of diagnostic test performed outside the follow-up algorithms per scenario. For each of these assumptions we performed a sensitivity analysis which supported the results of our main analysis. Second, our model is based on individual patient data of the InShape II cohort which was performed in 2016-2017 before the 2022 ESC pulmonary hyperntesion guideline recommended to adjust the definition of pre-capillary pulmonary hypertension to a pulmonary artery pressure of >20 mmHg in combination with a pulmonary vascular resistance of >2 woods units.[3] With this change, patients classified as non-CTEPH might currently be classified as CTEPH patients or vice versa, resulting in a different incidence of CTEPH. With increased CTEPH incidence, the treatment, medical and hospital costs per CTEPH patient will remain equal. For diagnostic costs, it will result in an increase of performed tests, but the costs of these tests will be divided over an increased proportion of CTEPH patients, resulting in decreased diagnosed costs per CTEPH patient (see sensitivity analysis 4). Therefore, if the change in classification would only result in an increased CTEPH incidence, but the diagnostic accuracy and impact of the treatment would remain similar to our current CTEPH population, application of the new pulmonary hypertension guidelines will only result in an even better cost-effectiveness. Even so, the performance of our model in the practice based setting using the novel pulmonary hypertension definition may be different than shown in this study.. A third limitation is that chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension was not included in our model. The definition of CTEPD as well as the benefit of early diagnosis in this patient category is currently debated. Finally, our model is developed for the Dutch healthcare setting, which may not be representative for other settings. Costs are derived from the passerby list of the Leiden University Medical Center published in 2022.[25] Uninsured patients or those with insurance from companies lacking contracted pricing agreements are charged according to this list. However, it's important to note that insured care costs, not covered by this model, typically run 10-15% lower than passerby list prices. This distinction highlights a potential limitation in the model's representation of total costs. Nonetheless, as the model is available in the supplement, it can be adjusted to fit other regions or healthcare settings to evaluate cost-effectiveness.

Our study demonstrates that subjecting all PE survivors to any of the currently established dedicated follow-up algorithms for early CTEPH detection is cost-effective, underscoring the importance of such dedicated PE follow-up pathways in clinical practice. Our model evaluated multiple algorithms, all of which are preferable to not performing a dedicated follow-up.

The model can be used to identify preferred algorithms from an economical point-of-view within local logistical possibilities. The choice of algorithm should be based on local logistical considerations, such as test availability. If there is no clear preference based on these factors, the InShape IV algorithm is recommended for its superior cost-effectiveness.

REFERENCES

1. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
2. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature reviews Disease primers 2018: 4: 18028.
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European heart journal 2022: 43(38): 3618-3731.
4. Boon GJAM, Ende-Verhaar YM, Bavalia R, et al. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021: 76(10): 1002-1009.
5. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011: 124(18): 1973-1981.
6. Guth S, D'Armini AM, Delcroix M, et al. Current strategies for managing chronic thromboembolic pulmonary hypertension: results of the worldwide prospective CTEPH Registry. ERJ Open Research 2021: 7(3): 00850-02020.
7. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. Eur Respir J 2018: 52(6).
8. Luijten D, Talerico R, Barco S, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. The European respiratory journal 2023: 62(1).
9. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). The European respiratory journal 2019: 54(3): 1901647.
10. Klok FA, Tesche C, Rappold L, 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.
11. Klok FA, Surie S, Kempf T, 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): 21-26.
12. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016: 14(1): 121-128.
13. Barco S, Mavromanoli AC, Kreitner KF, et al. Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism. Chest 2023.
14. Boon G, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Res 2021: 7(3).
15. Cimini LA, Luijten D, Barco S, et al. Pulmonary perfusion defects or residual vascular obstruction and persistent symptoms after pulmonary embolism: a systematic review and meta-analysis. ERJ Open Research 2024: 01010-02023.
16. Nijkeuter M, Hovens MM, Davidson BL, et al. Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. Chest 2006: 129(1): 192-197.
17. Robin P, Le Pennec R, Eddy M, et al. Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism: a systematic review and meta-analysis of individual participant data. J Thromb Haemost 2023.

18. Jankowich M, Maron BAandChoudhary G. Mildly elevated pulmonary artery systolic pressure on echocardiography: bridging the gap in current guidelines. Lancet Respir Med 2021: 9(10): 1185-1191.
19. Lewczuk J, Romaszkiewicz R, Lenartowska L, et al. The natural history of thromboembolic pulmonary hypertension. since when is it chronic? A proposal of an algorithm for the diagnosis and treatment. Kardiologia Polska 2013: 71(5): 522-526.
20. Held M, Hesse A, Gött F, et al. A symptom-related monitoring program following pulmonary embolism for the early detection of CTEPH: a prospective observational registry study. BMC Pulm Med 2014: 14: 141.
21. Luijten D, Valerio L, Boon GJAM, et al. Optimisation of detecting chronic thromboembolic pulmonary hypertension in acute pulmonary embolism survivors: the InShape IV study. European Respiratory Journal 2024: 2400544.
22. Galiè N, Humbert M, Vachiery JL, 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.
23. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021: 93: 64-70.
24. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
25. Leids Universitair Medisch Centrum. Passanten prijslijst DBC-zorgproducten en overige zorgproducten jaar 2022. 2022 [cited; Available from: https://www.lumc.nl/siteassets/patientenzorg/patientenzorg-algemeen/uw-bezoek-aan-het-lumc/uw-ervaring-rechten-en-zorgkosten/zorgkosten/vergoedingen-en-facturen/passantenprijslijst-dbc-en-overig-vanaf-1-januari-2022.pdf
26. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, et al. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. In opdracht van Zorginstituut Nederland. 2015. [cited; Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn%2Bvoor%2Bhet%2Buitvoeren%2Bvan%2Beconomische%2Bevaluaties%2Bin%2Bde%2Bgezondheidszorg%2B%2528verdiepingsmodules%2529.pdf
27. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006: 48(12): 2546-2552.
28. Cirulis MM, Knox DB, Stoddard GJ, et al. The CTEPH Trajectories Study: Assessment of Follow-Up after Acute Pulmonary Embolism to Identify Missed Opportunities for Chronic Thromboembolic Pulmonary Hypertension Diagnosis. Ann Am Thorac Soc 2022: 19(8): 1428-1432.
29. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. 2016 [cited; Available from:
30. Mühlbacher ACandSadler A. The Probabilistic Efficiency Frontier: A Framework for Cost-Effectiveness Analysis in Germany Put into Practice for Hepatitis C Treatment Options. Value Health 2017: 20(2): 266-272.
31. Caro JJ, Nord E, Siebert U, et al. The efficiency frontier approach to economic evaluation of health-care interventions. Health Econ 2010: 19(10): 1117-1127.

32. Kahn SR, Akaberi A, Granton JT, 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 e999-990 e921.
33. Sista AKandKlok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. Thromb Res 2018: 164: 157-162.
34. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
35. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010: 104(11): 1744-1749.
36. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007: 28(20): 2517-2524.
37. Ende-Verhaar YM, van den Hout WB, Bogaard HJ, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Journal of thrombosis and haemostasis : JTH 2018: 16(11): 2168-2174.
38. Boon GJAM, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2021.
39. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. AJR Am J Roentgenol 2020: 215(4): 800-806.
40. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. The European respiratory journal 2021: 58(6): 2100699.

Supplementary file

11

Pulmonary perfusion defects or residual vascular obstruction and persistent symptoms after pulmonary embolism: a systematic review and meta-analysis

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ERJ Open Res. 2024 Jul 29;10(4):01010-2023

ABSTRACT

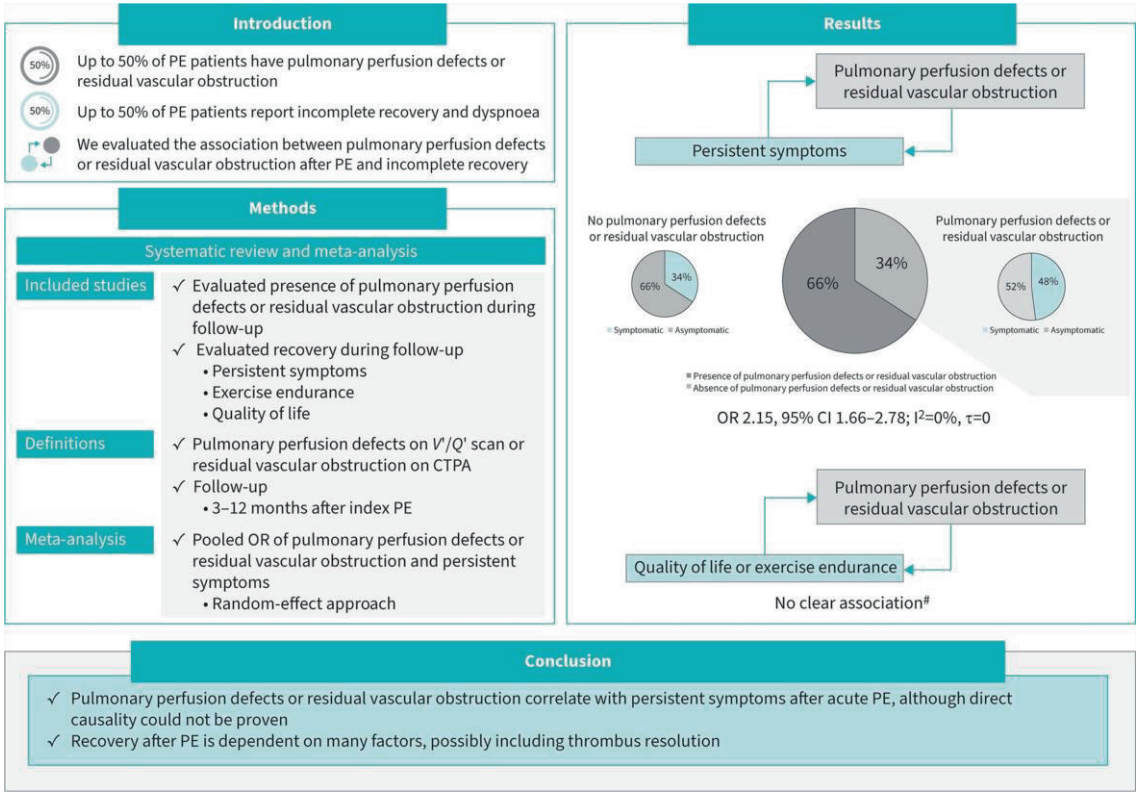
Introduction: Up to 50% of pulmonary embolism (PE) patients have perfusion defects or residual vascular obstruction during follow-up despite adequate anticoagulant treatment and a similar percentage experience chronic functional limitations and/or dyspnoea post-PE. We aimed to evaluate the association between pulmonary perfusion defects or residual vascular obstruction and functional recovery after PE.

Methods: We performed a systematic review and meta-analysis including studies assessing both the presence of perfusion defects or residual vascular obstruction and functional recovery (i.e. persistent symptoms, quality of life, exercise endurance). An odds-ratio (OR) was pooled for perfusion defects or residual vascular obstruction and persistent symptoms using a random-effect model.

Results: 12 studies were included totaling 1,888 PE patients; at a median of 6 months after PE (range 2-72 months), 34% had perfusion defects or residual vascular obstruction and 37% reported persistent symptoms. Among patients with perfusion defects or residual vascular obstruction, 48% (95%CI 37-60, I^2=82%) remained symptomatic during follow-up, compared to 34% (95%CI 20-51, I^2=96%) of patients without such defects. Presence of perfusion defects or residual vascular obstruction was associated with persistent symptoms (OR 2.15, 95%CI 1.66-2.78; I^2=0%, τ=*0*). Notably, there was no association between these defects and quality of life or cardiopulmonary exercise test parameters.

Conclusion: While the odds of having persistent symptoms was higher in patients with perfusion defects or residual vascular obstruction after acute PE, a significant proportion of these patients reported no limitations. A possible causality between perfusion defects or residual vascular obstruction and residual functional limitation therefore remains to be proven.

GRAPHICAL ABSTRACT



 # no meta-analysis performed due to heterogeneity

INTRODUCTION

Up to 50% of the acute pulmonary embolism (PE) survivors have persistent symptoms or alterations of cardiocirculatory function, as well as a reduction in the quality of life (QoL).[1-4] Patients who remain symptomatic despite receiving a minimum of 3 months of adequate anticoagulant treatment are considered to have the post-PE syndrome (PPES).[5] PPES consists of various aetiologies explaining a lack of recovery from acute PE: chronic thromboembolic pulmonary hypertension (CTEPH) (i.e. patients with 1) mismatched perfusion defects on ventilation/perfusion (V'/Q') and specific diagnostic signs for CTEPH on computed tomography pulmonary angiography [CTPA] in combination with 2) mean pulmonary artery pressure at rest >20 mmHg, pulmonary artery wedge pressure of ≤15 mmHg and a pulmonary vascular resistance of > 2 woods units[6]), chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension (PH) (i.e. patients present mismatched perfusion defects on ventilation/perfusion [V'/Q'] scan and specific signs of organised fibrotic clots on CTPA, magnetic resonance imaging (MRI) or conventional pulmonary cineangiography, without increased pulmonary artery pressure at rest[7, 8]), post-PE cardiac dysfunction (characterised by persistent right ventricle [RV] impairment after PE), post-PE functional impairment (possibly related to deconditioning) or other cardiopulmonary comorbidities.[6, 8-10] PPES is a large burden for patients and society, as these patients have decreased QoL[1], healthcare utilisation searching for an explanation for incomplete recovery is associated with high costs [11] and work-related productivity loss due to PPES is the main driver for the economic burden of acute PE.[12]

CTEPD is the overarching term for CTEPH and CTEPD without PH, and is characterised by persistent thrombi. CTEPH is the most serious presentation of PPES and has clear diagnostic criteria; however, only 2.7% of acute PE survivors are diagnosed with CTEPH during follow-up.[10] CTEPD without PH is characterised by persistent thrombi and normal pulmonary artery pressure in rest. However, the current definition does not distinguish between patients who show exercise-induced haemodynamic limitations and those who don't, despite having persistent thrombi. This lack of specific diagnostic criteria during exercise leads to a homogeneous classification of these potentially diverse patient groups under CTEPD without PH. Some therefore suggest that CTEPD without PH should only be

classified in patents with limited exercise tolerance which is attributed to an increased slope of pulmonary artery pressure-flow relationship during exercise of dead space ventilation.[8] It remains unknown what proportion of acute PE survivors suffer from incomplete recovery due to CTEPD without PH, and whether CTEPD without PH is an early presentation of CTEPH or an 'end-stage disease'. Interestingly, recent studies have suggested that incidence of CTEPD without PH is comparable to that of CTEPH and disease progression is hardly observed.[13, 14] The clinical relevance of incomplete thrombus resolution as assessed by pulmonary perfusion defects or residual vascular obstruction in acute PE patients who do not have CTEPH, as well as its association with recovery after acute PE is debated and remains unknown.

In this systematic review and meta-analysis, we aimed to evaluate the association between pulmonary perfusion defects or residual vascular obstruction and recovery (i.e., symptom burden, exercise endurance, QoL).

METHODS

Study selection, data extraction and quality assessment

PubMed, Web of Science, Cochrane Library, Emcare and Embase were searched from inception to February 2023 (complete search string available in **appendix 1**) focusing on cohort studies that evaluated presence of pulmonary perfusion defects or residual vascular obstruction and recovery during acute PE follow-up. Two authors (L.A. Cimini and D. Luijten) independently reviewed the search list by title and abstract and determined study eligibility. Full text candidate records were subsequently reviewed and selected for data retrieval. Disagreements were resolved through discussion or by consulting a third author (F.A. Klok).

Inclusion criteria were as follows i) Prospective or retrospective cohort studies, ii) with at least 50 patients included, iii) that systematically assessed presence of pulmonary perfusion defects by routine repeat V'/Q' scan, perfusion (Q') scan or residual vascular obstruction on CTPA after at least 3 months of adequate anticoagulation therapy, iv) and performed a systematic assessment of symptom burden, QoL and/or functional outcomes (i.e. cardiopulmonary exercise test [CPET], 6-min walk test [6MWT], and/or incremental shuttle walk test [ISWT]) at the time of imaging assessment. Only articles in English language were considered. If more than one study reported on the same cohort, the most appropriate one for our study question was included.

Two authors (L.A. Cimini and D. Luijten) independently performed quality assessment and data extraction for each included study using standardised extraction forms. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies. Individual study quality was assessed according to the following domains: cohort study selection, comparability, outcome assessment, and overall study quality (range, 1-9 [1-3 indicates low quality, 4-6 indicates moderate quality, and 7-9 indicates high quality]).[15] Disagreements were resolved through discussion or by consulting a third author (F.A. Klok). Extracted data included information on study design, patient characteristics, timing of the follow up, type of imaging assessing pulmonary perfusion defects or residual vascular obstruction, clinical outcome assessment and results of functional tests. Study authors were contacted whenever data for meta-analysis could not be extrapolated from the text. The study was registered at www.crd.york.ac.uk/prospero/ (identifier CRD42023397676)

Study outcome and measurements

The primary outcome was the association between presence of pulmonary perfusion defects or residual vascular obstruction and symptoms in acute PE patients during follow-up. Secondary outcomes were the associations between presence of pulmonary perfusion defects or residual vascular obstruction and other functional outcomes, i.e. 6MWT, CPET (e.g. oxygen consumption [V'O2], V'E/V'CO2 slope), ISWT, and/or QoL data. Pulmonary perfusion defects or residual vascular obstruction during follow-up could be evaluated by CTPA, V'/Q' or Q' scan independent of size of perfusion defect or vascular obstruction at index PE (Table 1). Patients without pulmonary perfusion defects or residual vascular obstruction were considered to have a normal V'/Q'-scan or CTPA during follow-up.

Statistical analysis

To evaluate the association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms we performed a meta-analysis where we calculated the pooled prevalence of persistent symptoms in patients with and without pulmonary perfusion defects or residual vascular obstruction using a generalised linear mixed-effect model, as well as the pooled odds-ratio (OR) with 95% confidence intervals (95%CI) using a random effect model (according to Mantel–Haenszel method with Restricted Maximum

Likelihood). The following subgroups were subsequently evaluated: according to i) type of imaging technique (V'/Q' scan, Q' scan or CTPA)), ii) timing of imaging during follow-up (3, 6 or 12 months, and iii) study design (retrospective or prospective).

To evaluate the association between presence of pulmonary perfusion defects or residual vascular obstruction and the 6MWT, we calculated the mean distance (m) achieved for patients with and without pulmonary perfusion defects or residual vascular obstruction within each study and calculated the standardised mean difference. The standardised mean difference was subsequently pooled across studies using a random-effect model. For all other outcomes we reported the incidence or median values in patients with and without pulmonary perfusion defects or residual vascular obstruction per individual study.

The appropriateness of pooling data across studies was assessed using the I^2 test for heterogeneity.[16] Heterogeneity was defined as low in when I^2< 25%, moderate when I^2= 25–75%, and high when I^2> 75%. The presence of publication bias was evaluated by visually inspecting funnel plots. The statistical analyses, forest plots, and publication bias analyses were performed using R version 4.2.1. (metabin, metacont, metaprop).

RESULTS

Figure 1: PRISMA flow diagram of the study

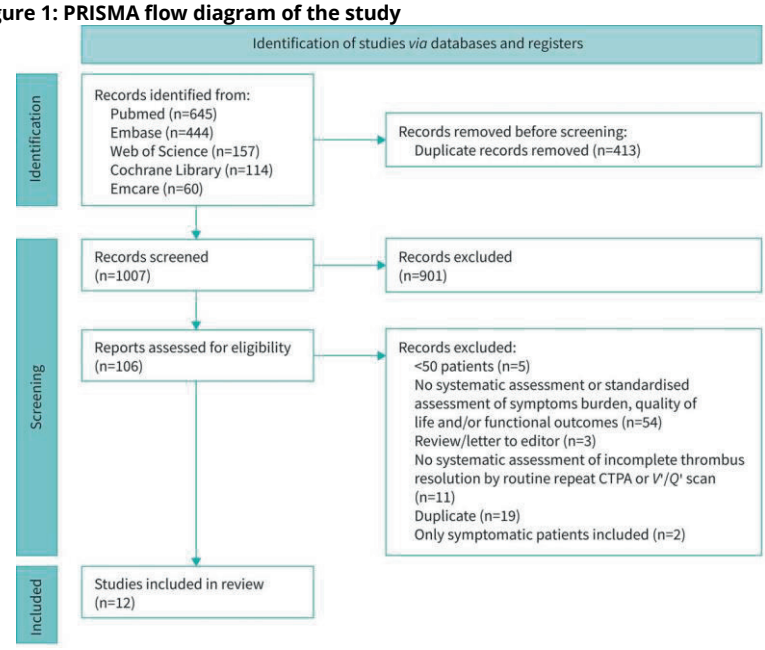


Table 1: characteristics of the included studies

	pro- or retro-spective	Single/ multi-centre	Study design	Included patients	age in years	Prior VTE	Malign ancy	Cardio-pulmonary disease	Centrally located PE	Reperfus ion therapy	RVD at TTE or CTPA at index PE
				n	median/ mean [SD/ IQR]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alblas et al. [17]	R$^{\Omega}$	S	OB	179	56 [18-88]	29 (16)	13 (7)	18 (10)	75 (42)	28 (16)	
Amato et al.[#18]	P	S	OB	166							
Aranda et al.[20]	R	S	OB	150	61 [±18]		13 (9)		52 (34)†		35 (24)$^{\alpha}$
Aranda et al.[19]	R	S	OB	241	64[48-80]		45 (19)		59 (25)$^{\pm}$		42 (18)$^{\alpha}$
Chopard et al.[21]	P	M	OB	241	65 [±16]		20 (8)	0			160 (66)$^{\beta}$
George at al.[#22]	P	S	OB	67							
Golpe et al.[23]	P	S	OB	91							
Jervan et al.[#24]	P		RCT	274							
Lachant at al.[25]	R$^{\Omega}$	S	OB	104	60[47-72]	23 (22)	7 (7)		31 (31)	14 (13)	64, (63)$^{\omega}$
Ma/Kahn et al.[26,27]	P	M	OB	100	50 [±15]		1 (1)	13 (13)		2 (2)	32 (32)$^{\alpha}$
Nakano et al.[28]	P	M	OB	43†	59[±16]	8 (19)	4 (9)			2 (5)	7 (17)$^{\flat}$
Sanchez et al.[29]	P	S	OB	254	61[18]	58 (23)	32 (15)	37 (15)		14 (6)	36 (14)§

[#] abstract only; [†] 52 patients were enrolled in this study. However, seven patients were unable to visit our outpatient clinic at the 1-year point and two died. Therefore a total of 43 patients were included in this meta-analysis. Since originally 52 were included we concluded the exclusion criterium of < 50 patients included was not met and we included this study in our systematic review and meta-analysis. ; [Ω] initially retrospective and subsequently prospective; S single center; M multicenter; OB observational; RCT randomised controlled trial; [†] massive/submassive PE; [±] massive PE; [α] RV/LV>1; [β] RV/LV >1, sPAP >30 mmHg or paradoxical septal motion; [φ] troponin rise or echo RV strain (not further classified); [ω] moderate to severe RV dysfunction (not further classified); [♭] TRPG>60 mmHg; [§] Signs of RV failure(not further classified); Abbreviations: CTPA computed tomography pulmonary angiogram; OB observational; P prospective; PE pulmonary embolism; Q perfusion-scan; R retrospective; RCT randomised controlled trial; RVD right ventricular dysfunction; RVPO Residual Pulmonary Vascular Obstruction; SD standard deviation; TTE trans-thoracic echocardiogram; V'/Q' ventilation-perfusion scan; VTE venous thromboembolism;

Table 1 continued

	Timing of follow-up after acute PE	Imaging during follow-up	Definition of	Definition of
	months		Presence of pulmonary perfusion defects or residual vascular obstruction	Persistent symptoms
Alblas et al. [17]	6	Q	Residual abnormalities according to the revised PISAPED criteria; coded as the following: complete reperfusion and incomplete or absent reperfusion	A
Amato et al.[# 18]	6	V'/Q'	Persistent perfusion defects	
Aranda et al.[20]	12	CTPA	Presence of filling defects (occlusive or partial) were defined as visualization of thrombus on follow-up CTPA	B
Aranda et al.[19]	6-12[π]	CTPA	Visualization of thrombus on follow-up CTPA	C
Chopard et al.[21]	3	V'/Q'[×]	RVPO of > 15%	D
George at al.[# 22]	3	V'/Q'	Persistent perfusion defects	
Golpe et al.[23]	6	CTPA	Residual intraluminal filling defects	A
Jervan et al.[# 24]	6-72	V'/Q'	Residual perfusion defect According to the European Association of Nuclear Medicine criteria	E
Lachant at al.[25]	2-4	V'/Q'	Mismatched or partly mismatched segmental V/Q defects	F
Ma/Kahn et al.[26,27]	12	Q /CTPA	Q: Persistent perfusion defects defined as persistent vascular obstruction score >0% CTPA: CT obstruction score of >0% (Qanaldi score)	G
Nakano et al.[28]	12	CTPA	CT obstruction score >0% (Qanaldi score)	H
Sanchez et al.[29]	12	V'/Q'	Perfusion defects defined as residual pulmonary vascular obstruction ≥10% (modified Qanaldi score)	J

[π] CTPA at 6-months, assessment of symptoms at 12 months; × Residual vascular obstruction > 15% ; A Patients reported dyspnoea/shortness of breath; B symptoms suggestive of CTEPH; C clinical resolution; D heart failure of worsening dyspnoea; E modified Medical Research Council Score ≥1; F Reported self-limited activities; G University of California at San Diego Shortness of Breath Questionnaire > 5 points; H NYHA class ≥2; J NYHA class ≥ 1. Abbreviations: CTPA computed tomography pulmonary angiogram; OB observational; P prospective; PE pulmonary embolism; Q perfusion-scan; R retrospective; RCT randomised controlled trial; RVD right ventricular dysfunction; RVPO Residual Pulmonary Vascular Obstruction; SD standard deviation; TTE trans-thoracic echocardiogram; V'/Q' ventilation-perfusion scan; VTE venous thromboembolism;

Study selection

The primary search identified 1420 records; 413 duplicate records were removed and another 901 were excluded after screening title and abstract (**Figure 1**). An additional 94 papers were excluded after full text examination, mainly for the lack of (systematic and standardised) assessment of persistent symptoms or functional outcomes (n=54). Overall, 12 studies provided data on presence of pulmonary perfusion defects or residual vascular obstruction during acute PE follow-up as well as functional outcomes and were included in this systematic review.[17-29]

Quality assessment and risk of bias

Results of the NOS scale assessments are reported in **Table S1**. Only one study was judged as high quality.[21] The other studies were judged as moderate quality. The main reasons for moderate quality of studies were (1) potential bias in selection (e.g. retrospective design), (2) potential bias in outcome (e.g. unclear if follow-up procedures were systematically performed according to a pre-defined standardised protocol), and (3) lack of adjustment for potential confounders.

Included studies

The main characteristics of the included studies are reported in the **Table 1**. Eight studies were prospective. Four studies provided the localisation of emboli (central/peripheral) at the baseline PE imaging test.[17, 19, 20, 25] Five studies reported on the number of patients who underwent reperfusion treatment (range 2-16%).[17, 25-29] Seven studies reported the number of patients with right ventricular dysfunction at index PE; the proportion ranged from 17 to 66%.[19-21, 25-29] The timing of the follow-up procedures ranged from 2 months after the index PE episode up to 72 months, but were mostly within 3-12 months (11 out of 12 studies). Presence of pulmonary perfusion defects or residual vascular obstruction during follow-up was assessed in four studies by CTPA to evaluate residual vascular obstruction, six studies used V/Q scan to evaluate perfusion defects and one study used a Q' scan only. The presence of pulmonary perfusion defects or residual vascular obstruction was mostly defined as no residual thrombi/ vascular obstruction on CTPA and/or no persistent perfusion defects on (V'/)Q' scan (supplementary material: **table S3**). Only one study used a threshold for residual vascular obstruction of >15%.[21] In the Evaluation of Long-term Outcomes after PE (ELOPE)

cohort study, the presence of pulmonary perfusion defects or residual vascular obstruction was assessed by both CTPA and Q' scan .[26, 27] The most common assessment of persistent symptoms was patient reported dyspnoea, used in two studies.[17, 23]

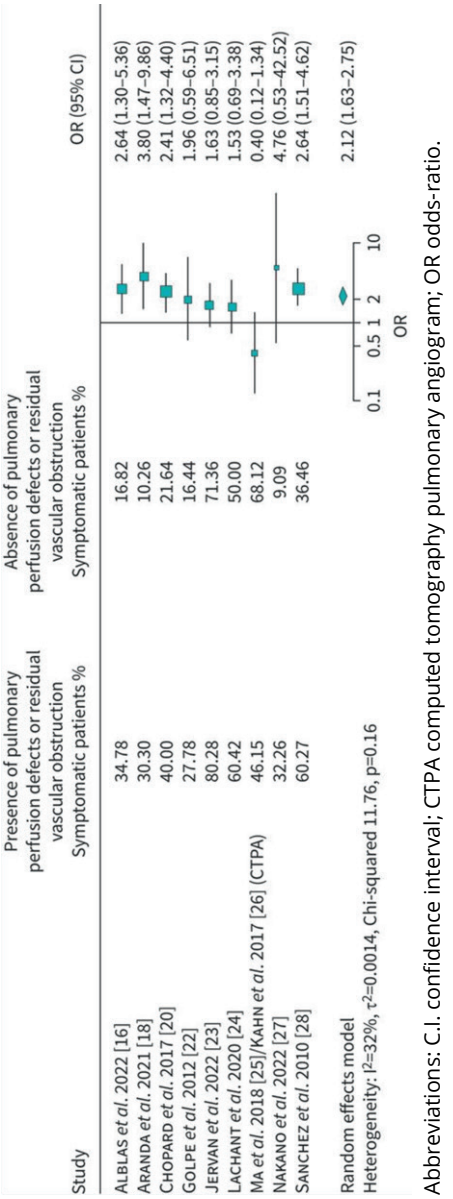
Association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms

12 studies reported on the number of patients with pulmonary perfusion defects or residual vascular obstruction during follow-up: the pooled proportion was 34% (95%CI 24-46%; I^2=91%; **Figure S1**). When using (V)Q' scan 38% of the patients had persistent perfusion defects during follow-up; this was only 29% when using CTPA to evaluate residual vascular obstruction (**Figure S1**). Nine studies reported on the number of patients with persistent symptoms during follow-up: the pooled proportion was 37% (95%CI 24-53%; I^2=97%; **Figure S2**). Nine studies reported on the number of symptomatic/asymptomatic patients with pulmonary perfusion defects or residual vascular obstruction and the number of symptomatic/asymptomatic patients with a normal V'/Q'-scan/CTPA during follow-up: among patients with pulmonary perfusion defects or residual vascular obstruction, the pooled proportion of persistent symptomatic patients was 48% (95%CI 37-60; I^2=82%), compared to 34% (95%CI 20-51; I^2=96%) of patients with a normal V'/Q'-scan/CTPA. The ELOPE cohort study reported the frequency of pulmonary perfusion defects or residual vascular obstruction assessed by both CTPA and Q' scan.[26, 27] In pooled analyses, patients with pulmonary perfusion defects or residual vascular obstruction had an increased odds of having persistent symptoms during follow-up (when including the CTPA data of the ELOPE cohort: OR 2.12 [95%CI 1.63-2.75; I^2=32%; **Figure 2**]; when including the Q' scan data of the ELOPE cohort: OR 2.15 [95%CI 1.66-2.78; I^2=0%, τ=0;**Figure S3**]).

A subgroup analysis based on the modality of imaging used, showed comparable odds ratios, although for CTPA the 95%CI included 1.0 (V'/Q'/Q' scan: 2.03 [95%CI 1.54-2.68; I^2=9%]; CTPA 1.80 [95%CI 0.59-5.49; I^2=67%]; **Figure S5**). When performing a subgroup analysis based on the timing of imaging after acute PE, pulmonary perfusion defects or residual vascular obstruction were associated with persistent symptoms at 3-months (OR 2.04; 95%CI 1.25-3.30; I^2=0%, τ=0), 6-months (OR 2.44; 95%CI 1.33-4.50; I^2=0%, τ=0) and 12-months (OR 2.00; 95%CI 0.69-5.77; I^2=70%; **Figure S6**).

When pooling data separately for prospective versus retrospective studies, we found comparable results (**Figure S7**). Funnel plot analysis illustrated asymmetry, which was most likely due to between-study heterogeneity, but without a clear indication of publication bias (**Figure S4**)

Figure 2: presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms during follow-up



Abbreviations: C.I. confidence interval; CTPA computed tomography pulmonary angiogram; OR odds-ratio.

Table 2: quality of life and functional test in patients with/without pulmonary perfusion defects or residual vascular obstruction

Study	Quality of life assessment	Patients with pulmonary perfusion defects or residual vascular obstruction, median (IQR)	Patients without pulmonary perfusion defects or residual vascular obstruction, median (IQR)	p-values
Alblas et al.[17]	PEmb-QoL[α] [%]	16 (7.4-38)	13 (4.5-32)	0.424
Jervan et al.[24]	EQ-5D visual analogue scale [0-100%]	65 (50-80)	71 (60-80)	0.02
	EQ-5D-index value	0.94 (0.80-1.0)	0.92 (0.81-1.0)	0.86
Nakano et al.[28]	HRQoL(SF-36)			NA
	PCS	47.4 (38.0-53.7)	42.5 (29.4-48.0)	
	MCS	59.8 (50.7-65.6)	53.8 (45.9-55.4)	
	RCS	54.3 (45.6-57.0)	57.9 (53.6-64.3)	
	Functional tests	Patients with pulmonary perfusion defects or residual vascular obstruction, mean (±SD)	Patients without pulmonary perfusion defects or residual vascular obstruction, mean (±SD)	
Amato et al.[18]	6MWT [meters]	504 (99)	486 (142)	NA
George at al.[22]	Peak V'O2 [% of predicted]	80.26 (3.36)	99.93 (8.77)	<0.05
	V'E/V'CO2 [ratio]	31.34 (1.07)	27.19 (0.74)	<0.005
Jervan et al.[# 24]	ISWT [meters]	660	805	0.01
Ma/Kahn et al.[26,27] (CTPA)	Peak V'O2 [% of predicted]	95.7	81.8	0.098
Nakano et al.	6MWT [meters]	454 (112)	480 (145)	NA
Sanchez et al.[29]	6MWT [meters]	374 (122)	427 (99)	0.004

[α] at 5 years; a higher number presents lower quality of life. NA not applicable/not reported. Abbreviations: 6MWT 6-minute walk test; CTPA computed tomography pulmonary angiogram; EQ5D EuroQol-5 Dimension; HrQoL Health-related quality of life; IQR inter quartile range; ISWT incremental shuttle walk test; MCS: Mental component summary; PCS: Physical component summary; PEmb-QoL Pulmonary Embolism Quality of Life questionnaire; RCS: Role/Social component summary; SD standard deviation

Quality of life and functional tests

Three studies reported QoL, but using three different tools: the Pulmonary Embolism Quality of Life questionnaire, EuroQol FiveD-imension questionnaire and 36-item Short-Form Health Survey (**Table 2**).[17, 24, 28] The heterogeneity between assessment of QoL was too large to pool data across studies. However, when looking at the QoL outcomes per individual study, we observed no clear

difference between QoL in patients with pulmonary perfusion defects or residual vascular obstruction versus in patients with a normal V'/Q'-scan/CTPA.

Three types of functional tests were reported: CPET in two studies [22, 26, 27], ISWT in one study[24], and 6MWT reported in three studies.[18, 28, 29] For CPET outcomes, the percentage of predicted oxygen consumption at maximal exercise ($V'O_2$-peak) reported was higher in patients with pulmonary perfusion defects or residual vascular obstruction in one study, but the difference was not significant, while another study reported significantly lower $V'O_2$-peak (**Table 2**).[22, 26, 27] Patients with pulmonary perfusion defects or residual vascular obstruction had a higher $V'E/V'CO_2$ ratio compared to patients with a normal V'/Q'-scan/CTPA, reflecting decreased ventilatory efficiency due to increased dead space ventilation (**Table 2**).[22] Patients with pulmonary perfusion defects or residual vascular obstruction had a lower ISWT compared to patients with a normal V'/Q'-scan/CTPA(**Table 2**).[24] We observed no difference in the outcome of 6MWT between patients with pulmonary perfusion defects or residual vascular obstruction and patients with a normal V'/Q'-scan/CTPA (pooled standardised mean difference -0.20; 95%CI -1.05-0.65; I^2=74%; **Supplementary material Figure S8**).

DISCUSSION

In the studies included in this meta-analysis, 34% of acute PE patients had pulmonary perfusion defects or residual vascular obstruction during follow-up. Among patients with pulmonary perfusion defects or residual vascular obstruction, 48% reported persistent symptoms during follow-up, indicating incomplete recovery, compared to 34% of patients with a normal V'/Q'-scan/CTPA. Our data showed a moderate association between presence of pulmonary perfusion defects or residual vascular obstruction and incomplete recovery: patients with pulmonary perfusion defects or residual vascular obstruction had a two-fold increased odds for persistent symptoms, which was irrespective of timing of imaging during follow-up or imaging modality.

Our findings do not clearly support a causal relation between persistent clots visualised by pulmonary perfusion defects on V'/Q'-scan or residual vascular obstruction on CTPA (in patients without CTEPH) and incomplete recovery for several reasons. First, half of the patients with pulmonary perfusion defects or residual vascular obstruction had completely recovered (i.e. were asymptomatic). Second, most of the included studies did not subject the study patients to

systematic screening for CTEPH. In CTEPH, patients with persistent clots have increased pulmonary artery pressure due to an increase in pulmonary vascular resistance caused in part by intravascular fibrotic obstruction and in part by arteriopathy.[6,7] In CTEPH a causal relationship between persistent clots and symptoms has been demonstrated, as treatment focusing on the removal of clots results in an improvement in pulmonary artery pressure resulting in an improvement of symptoms.[30] For daily practice it is important to understand the association between persistent clots, visualised by presence of pulmonary perfusion defects or residual vascular obstruction, and incomplete recovery in patients who do not have CTEPH as the causality between and the clinical implication of having persistent clots in patients without CTEPH remains unknown. The possible involvement of CTEPH patients in the pooled OR may have led to an overestimation of the OR. Third, it could be argue that the expected relationship between pulmonary perfusion defects or residual vascular obstruction and altered haemodynamic (as measured by CPET) would be stronger than the relationship between pulmonary perfusion defects or residual vascular obstruction and persistent symptoms. After all, the causal mechanism would be that pulmonary perfusion defects or residual vascular obstruction as a surrogate marker for residual thrombi lead to altered haemodynamics, causing persistent symptoms. Of note, patients with chronic thrombi might less frequently report the presence of persistent symptoms, as they may have become 'used' to these symptoms. However, haemodynamic changes are however not affected by the patient's perspective. Importantly, the studies included in this systematic review did not find a clear and consistent association between presence of pulmonary perfusion defects or residual vascular obstruction and quality of life or exercise capacity. Specifically, the ELOPE cohort study showed no differences in functional limitation in patients with pulmonary perfusion defects or residual vascular obstruction and patients with a normal Q' scan /CTPA at 1 year follow up. In this prospective follow-up study, having pulmonary perfusion defects or residual vascular obstruction was not associated with a decreased $V'O_2$-peak measured using CPET.[26] Finally, if a causal relationship would be present, it is to be expected that patients receiving reperfusion therapy may show better recovery than those who received anticoagulation alone. The randomised Pulmonary Embolism Thrombolysis trial showed that primary reperfusion by full dose systemic thrombolysis did not improve long-term outcomes: among 709 patients who had long-term follow-up, there was no difference in the proportion of patients with persistent symptoms,

the degree of functional limitations or echocardiographic measures between patients who received Tenecteplase versus placebo.[31]

What are the clinical implications of our findings? Current guidelines suggest to first perform echocardiography in PE survivors with persistent symptoms to rule-out CTEPH, as minimising the diagnostic delay of CTEPH results in improved outcomes.[6, 7, 32] In patients without CTEPH, CPET can be considered to evaluate potential causes of persistent symptoms. CTEPH or CTEPD without PH can be expected if there is an increase dead space volume/tidal volume ratio or insufficient increase in O2 pulse during exercise (reflecting poor stroke volume augmentation) on CPET.[33] Only in case of suspected CTEPH or CTEPD without PH (based on clinical presentation as well as the results of echocardiography and/or CPET), imaging tests to qualify and quantify persistent vascular obstruction and perfusion defects should be performed, to avoid finding nonrelevant residual thrombi and thus 'false positive' results for which there is no treatment option, and to avoid unnecessary costs and exposure to radiation and contrast media. Our findings do not give any evidence to deviate from these recommendations and therefore do not suggest to routinely repeating imaging tests in (symptomatic) PE survivors, as causality and clinical implication of presence of pulmonary perfusion defects or residual vascular obstruction in acute PE patients without CTEPH or CTEPD without PH remains unclear. Additionally, in recent years, there is an increasing focus on advanced reperfusion techniques to improve the short-term outcomes of PE care, both in high and intermediate-risk PE patients. However, improved short-term outcomes of catheter directed treatment in these patients as well as benefits for long-term prognosis remain to be proven. Future randomised studies on advanced reperfusion treatment of acute PE should incorporate dedicated long-term follow-up, to inform decision making in the acute setting.[34, 35]

The strengths of this study are the large cohort of patients studied, as well as the inclusion of unpublished data from the selected studies. Moreover, we found a consistent association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms with low to moderate heterogeneity in most analyses. This study has some limitations: first, there is heterogeneity in the definition of presence of persistent symptoms across the included studies as almost all studies used a different definition. In addition, there is heterogeneity in the definition of pulmonary perfusion defects or residual vascular obstruction. Three types of imaging techniques have been used: CTPA,

V'/Q' scan and Q scan. Studies using (V)Q' scans evaluated persistent perfusion defects and studies using CTPA evaluated residual vascular obstruction. It should be noted that persistent perfusion defects might also occur in absence of a thrombus. When comparing CTPA to V'/Q' scan: persistent perfusion defects are more frequently identified by V'/Q' scan than residual vascular obstruction by CTPA.[36] This is also confirmed in our study: (V)Q' scan identified 38% of the patients as having persistent perfusion defects during follow-up, while this was only 29% when using CTPA to identify residual vascular obstruction. Furthermore, the residual vascular obstruction assessed by CTPA was mostly defined as persistent thrombi. Other signs of chronic thrombi such as arterial retraction or intravascular webs might not have been included.[37, 38] Even so, we observed no clear difference in the association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms when comparing CTPA to V(Q) scan. Besides, different imaging techniques, different proportions of vascular obstruction were used, but mostly presence of one (small) perfusion defect or vascular obstruction was sufficient to classify as presence of pulmonary perfusion defects or residual vascular obstruction. We had no data on the severity of pulmonary perfusion defects or residual vascular obstruction; smaller defects leading to no symptoms could have diluted the association. Due to the lack of data we could not investigate a "dose-response" association to support a causal association between pulmonary perfusion defects or residual vascular obstruction and recovery. Also, as we did not have patient-level imaging data available, we could not further investigate thrombus morphology or thrombus resolution relative to thrombotic burden at index PE in relation to recovery. Second, patients with CTEPH were not systematically excluded, resulting in possible overestimating of the association between pulmonary perfusion defects or residual vascular obstruction and symptoms in patients without CTEPH. Third, despite our efforts, it was not possible to correct for potential confounders such as index PE severity, since data were lacking. Finally, studies included in our meta-analysis were of moderate quality as only one study included in our meta-analysis had a low risk of bias.

In conclusion, we found an increased odds for persistent symptoms in patients with pulmonary perfusion defects or residual vascular obstruction after acute PE, compared to those with a normal V'/Q'-scan/CTPA. However, our meta-analysis of observational studies cannot support any causal relationship. The fact that presence of pulmonary perfusion defects or residual vascular obstruction displayed varying degrees of association with quality of life and functional tests indicates that the clinical and functional recovery after PE is dependent on many factors, which may possibly include thrombus resolution.

REFERENCES

1. Kahn SR, Akaberi A, Granton JT, 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 e999-990 e921.
2. Sista AK, Miller LE, Kahn SR, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. Vasc Med 2017: 22(1): 37-43.
3. Klok FA, van Kralingen KW, van Dijk AP, et al. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010: 104(11): 1744-1749.
4. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007: 28(20): 2517-2524.
5. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014: 28(6): 221-226.
6. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022: 43(38): 3618-3731.
7. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. The European respiratory journal 2021: 57(6).
8. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2022: 43(3): 183-189.
9. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research:Official Communication from the SSC of the ISTH. J Thromb Haemost 2021: 19: 297–303.
10. Luijten D, Talerico R, Barco S, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. Eur Respir J 2023: 62(1).
11. Ende-Verhaar YM, van den Hout WB, Bogaard HJ, et al. Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2018: 16(11): 2168-2174.
12. Farmakis IT, Barco S, Mavromanoli AC, et al. Cost-of-Illness Analysis of Long-Term Health Care Resource Use and Disease Burden in Patients With Pulmonary Embolism: Insights From the PREFER in VTE Registry. Journal of the American Heart Association 2022: 11(20): e027514.
13. Held M, Pfeuffer-Jovic E, Wilkens H, et al. Frequency and characterization of CTEPH and CTEPD according to the mPAP threshold > 20 mm Hg: Retrospective analysis from data of a prospective PE aftercare program. Respir Med 2023: 210: 107177.
14. Reddy SA, Swietlik EM, Robertson L, et al. Natural history of chronic thromboembolic pulmonary disease with no or mild pulmonary hypertension. J Heart Lung Transplant 2023: 42(9): 1275-1285.
15. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford. asp
16. Higgins JPandThompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002: 21(11): 1539-1558.
17. Alblas H, van Kan C, van het Westeinde SC, et al. Persistent dyspnea after acute pulmonary embolism is related to perfusion defects and lower long-term quality of life. Thrombosis Research 2022: 219: 89-94.

18. Amato RDandRamírez Martín MP. Prevalence and clinical predictors of persistent perfusion defects after acute pulmonary embolism [abstract]. European Respiratory Journal 2017: 50(suppl 61): PA566.
19. Aranda C, Gonzalez P, Gagliardi L, et al. Prognostic factors of clot resolution on follow-up computed tomography angiography and recurrence after a first acute pulmonary embolism. Clin Respir J 2021: 15(9): 949-955.
20. Aranda C, Peralta L, Gagliardi L, et al. A significant decrease in D-dimer concentration within one month of anticoagulation therapy as a predictor of both complete recanalization and risk of recurrence after initial pulmonary embolism. Thromb Res 2021: 202: 31-35.
21. Chopard R, Genet B, Ecarnot F, et al. Detection of Residual Pulmonary Vascular Obstruction by Ventilation-Perfusion Lung Scan Late After a First Pulmonary Embolism. Am J Cardiol 2017: 119(11): 1883-1889.
22. George PM, Fagerbrink S, Meehan S, et al. Effects of Pulmonary Embolism on Medium Term Cardiopulmonary Physiology: A Prospective Cohort Study [abstract]. American Thoracic Society, 2015; pp. A4861-A4861.
23. Golpe R, de Llano LA, Castro-Añón O, et al. Long-term outcome of patients with persistent vascular obstruction on computed tomography pulmonary angiography 6 months after acute pulmonary embolism. Acta Radiol 2012: 53(7): 728-731.
24. Jervan Ø PS, Gleditsch J, Rashid D, Ghanima W. Health-Related Quality of Life and physical capacity in patients with residual perfusion defects after pulmonary embolism [abstract]. 2022.
25. Lachant D, Bach C, Wilson B, et al. Clinical and imaging outcomes after intermediate- or high-risk pulmonary embolus. Pulm Circ 2020: 10(3): 2045894020952019.
26. Kahn SR, Hirsch AM, Akaberi A, et al. Functional and Exercise Limitations After a First Episode of Pulmonary Embolism: Results of the ELOPE Prospective Cohort Study. Chest 2017: 151(5): 1058-1068.
27. Ma KA, Kahn SR, Akaberi A, et al. Serial imaging after pulmonary embolism and correlation with functional limitation at 12 months: Results of the ELOPE Study. Res Pract Thromb Haemost 2018: 2(4): 670-677.
28. Nakano Y, Adachi S, Nishiyama I, et al. Usefulness of a refined computed tomography imaging method to assess the prevalence of residual pulmonary thrombi in patients 1 year after acute pulmonary embolism: The Nagoya PE study. J Thromb Haemost 2022: 20(4): 888-898.
29. Sanchez O, Helley D, Couchon S, et al. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemost 2010: 8(6): 1248-1255.
30. Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. European Respiratory Journal 2014: 44(6): 1635-1645.
31. Konstantinides SV, Vicaut E, Danays T, et al. Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. J Am Coll Cardiol 2017: 69(12): 1536-1544.
32. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Heart Journal 2019: 41(4): 543-603.
33. Morris TA, Fernandes TMandChannick RN. Evaluation of Dyspnea and Exercise Intolerance After Acute Pulmonary Embolism. Chest 2023: 163(4): 933-941.
34. Klok FA, Piazza G, Sharp ASP, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study. Am Heart J 2022: 251: 43-53.

35. Sanchez O, Charles-Nelson A, Ageno W, et al. Reduced-Dose Intravenous Thrombolysis for Acute Intermediate-High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. Thromb Haemost 2022: 122(5): 857-866.
36. van Es J, Douma RA, Kamphuisen PW, et al. Clot resolution after 3 weeks of anticoagulant treatment for pulmonary embolism: comparison of computed tomography and perfusion scintigraphy. J Thromb Haemost 2013: 11(4): 679-685.
37. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014: 112(3): 598-605.
38. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2022: 32(4): 2178-2187.

Supplementary file

12

The value of vector ECG in predicting residual pulmonary hypertension in CTEPH patients after pulmonary endarterectomy

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PLoS One. 2025 Feb 26;20(2):e0317826

ABSTRACT

Introduction: Right heart catheterization (RHC) is the diagnostic standard for establishing residual pulmonary hypertension (PH) after pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). A potential non-invasive alternative diagnostic test could be electrocardiography (ECG)-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO).

Methods: We studied 66 CTEPH patients who underwent PEA. A subgroup of 20 patients also had a cardiac MRI before and after PEA. The diagnostic performance of the VG-RVPO for the detection of residual PH as well as the potential to replace RHC were assessed. Different cut-off values to define a normal VG-RVPO were evaluated. Also, we evaluated the association between mean pulmonary artery pressure (mPAP) and CMR derived indexed right ventricular (RV) mass and the VG-RVPO.

Results: During follow-up, 28 patients had residual PH (42%). A decrease in VG-RVPO after PEA was associated with decrease in mPAP or indexed RV mass post PEA ($r=0.55$, $p<0.05$ and $r=0.64$, $p<0.05$, respectively). If a normal VG-RVPO would exclude residual PH, the need for RHC would be reduced with 15-48%, but up to 36% of the CTEPH patients with residual PH would have been missed as they had a normal VG-RVPO.

Conclusion: Although there was an association between the change in VG-RPVO and changes in mPAP or indexed RV mass, our study demonstrated that VG-RPVO has limited value in excluding the presence of residual PH post-PEA as up to 36% of the CTEPH patients with residual PH would have been missed if residual PH would have been excluded based on a normal VG-RVPO.

INTRODUCTION

Pulmonary endarterectomy (PEA) is the treatment of choice for patients with chronic thromboembolic pulmonary hypertension (CTEPH).[1-3] PEA leads to improved cardiopulmonary hemodynamics and exercise tolerance with low early mortality when performed in expert centres.[1, 4, 5] Nevertheless, residual pulmonary hypertension (PH) after PEA is not uncommon, and associated with worse long-term survival.[6, 7] For patients with significant residual PH after PEA, balloon pulmonary angioplasty (BPA) or pulmonary arterial hypertension (PAH)-specific medication are potential treatment options to lower symptom burden.

Right heart catheterization (RHC) is the diagnostic standard for diagnosing post-PEA residual PH. Current guidelines therefore advice to perform RHC 3-6 months after surgery. However, a non-invasive strategy to perform post-PEA follow-up might be preferred. A potential non-invasive alternative is the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO).[8-10] The VG-RVPO detects right ventricle pressure overload due to right ventricle hypertrophy and changes in action potential duration as a result from pressure variations.[10] In a normal heart the ventricular gradient points in a left direction, therefore a normal VG-RVPO is negative. With increase of right ventricle (RV) pressure, the VG-RVPO becomes more positive and can therefore detect RV pressure overload.[8]

Given that the VG-RVPO generates numerical values, it can be categorized into absence or presence of signs of right ventricle pressure overload using previous derived cut-off values.[11-14] The diagnostic value of VG-RVPO for post-PEA residual PH has not been established to date. Therefore, our aim was to evaluate the diagnostic accuracy of the ECG-derived VG-RVPO for detecting residual PH in CTEPH patients who underwent PEA. To our knowledge this is the first study to investigate the diagnostic accuracy of vector ECG in detecting residual PH in CTEPH patients who underwent PEA.

METHODS

Study design and patients

This was a post-hoc analysis of the VUmc observational CTEPH follow-up cohort (Amsterdam, the Netherlands).[15] All CTEPH patients undergoing PEA between July 2012 and September were eligible for inclusion. Patients were excluded if 1) they

had a follow-up of < 6 months after PEA; 2) they did not have an available baseline ECG (i.e. ECG within one month before CTEPH diagnosis or between CTEPH diagnosis and PEA); or 3) they did not have a follow-up ECG (i.e. ECG 6-21 months after PEA). Of the included patients deidentified data from the patient chart was saved in a database. Patients were diagnosed with CTEPH according to the at inclusion applicable guideline definition (mPAP ≥25 mmHg).[16] Per clinical protocol, ECG and cardiac MRI (CMR) was routinely performed before and 6 months after PEA. Residual PH was defined as mPAP ≥25 mmHg measured with RHC following at the inclusion applicable guideline definitions for pulmonary hypertension. The study did not fall within the scope of the Medical Research Involving Human Subjects Act, because the analysis was performed based on available clinical data obtained for clinical purposes and therefore no informed consent was obtained. This was confirmed by the Medical Ethics Review Committee of the VU University Medical Center (2017.313).

Objectives

The primary objective of this study was to investigate the diagnostic accuracy of the (Δ or follow-up) VG-RVPO to detect residual PH in CTEPH patient who underwent PEA, and its efficacy and safety for making management decisions. For efficacy we evaluated the percentage of patients in whom residual PH could not have been ruled out with the VG-RVPO, i.e. the number of patients who would have had an RHC indication. For safety we evaluated the percentage of patients in whom residual PH would have been missed if residual PH would have been ruled out based on a normal VG-RVPO.

Secondary objectives were (1) to investigate the optimal cut-off value of the (Δ or follow-up) VG-RVPO for the detection of residual PH and the subsequent diagnostic accuracy, efficacy and safety of this cut-off value, (2) to evaluate the correlation between VG-RVPO and the mean pulmonary artery pressure (mPAP) as measured by right heart catheterization (RHC), (3) to evaluate the correlation between VG-RVPO and right ventricular (RV) hypertrophy as measured by indexed RV mass on CMR and (4) to evaluate the diagnostic accuracy of the VG-RVPO in patients with normal versus abnormal indexed RV mass on CMR.

Procedures

RHC was performed as described previously.[17] ECGs were standard 10-s 12 lead ECGs recorded in supine position (25 mm/s). To determine the ECG variables, the dedicated Leiden ECG analysis and decomposition software program (LEADS) was performed by an independent investigator blinded to patient characteristics and outcomes.[18] The LEADS software computes multiple vector-cardiogram (VCG) values including the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval and is an indicator for how the action potential morphology is distributed in the heart.[19] For the detection of right ventricular pressure overload (RVPO) previous research has shown that the projection in the 155◦ azimuth and 27◦ elevation direction is the most optimal, since this projection is directed over the right ventricle.[8, 9, 11-13] This projection is called the VG-RVPO (ventricular gradient – optimized for right ventricular pressure overload). Since in a normal heart the VG points in a left direction, a normal VG-RVPO is negative and with increase of right ventricular pressure the VG-RVPO becomes more positive (**Figure 1 Chapter 8**). The VG-RVPO cut-off point for the detection of pulmonary hypertension derived from previous studies is <-13 mV · ms; meaning that a VG-RVPO <-13 mV · ms was considered normal (no residual PH) and a VG-RVPO of ≥ -13 mV · ms was considered abnormal (possible residual PH) although different cut-off points have been evaluated in this study.[11-14] Baseline VG-RVPO was derived from the last ECG performed before PEA, follow-up VG-RVPO was derived from the ECG performed approximately 6 months after PEA. Δ VG-RVPO was calculated as follows: follow-up VG-RVPO - baseline VG-RVPO.

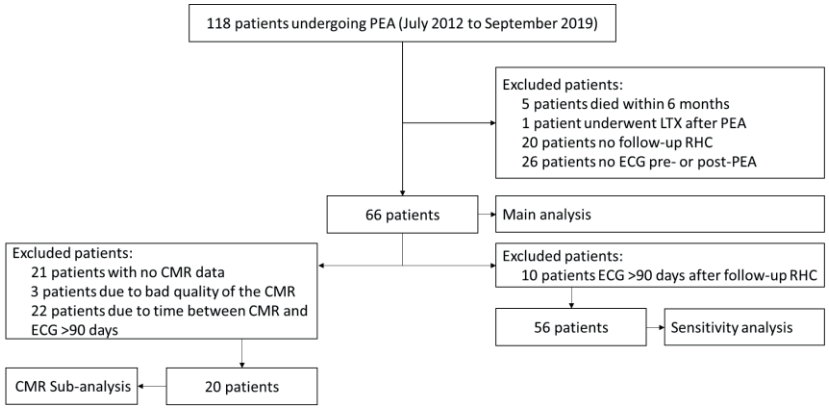
CMR were performed on a 1.5 T Sonata or 1.5 T Avanto MRI scanner (Siemens Healthcare, Erlangen, Germany). A short-axis stack was performed at breath-hold per slice, with a slice thickness and interslice gap of 5 mm. RV volume and mass were determined by manually drawing endocardial and epicardial contours at end diastole and end systole using commercially available software (QMass, Medis, Leiden, the Netherlands and Circle CVI42). RV mass was subsequently indexed to body surface area. [20] As healthy controls have an indexed RV mass of 22 ±6 g/m^2 we defined an abnormal indexed RV mass as > 33.76 g/m^2 which is the upper limit of the 95%CI in healthy controls.[20]

Statistical analysis

Normally distributed continuous data were described as a mean (±standard deviation [SD]). Abnormally distributed continuous data were described as a

median (interquartile range [IQR]) and compared using a Mann-Whitney-U test. Categorical variables were described as numbers (percentage). For the analysis of diagnostic accuracy of the VG-RVPO for post-PEA residual PH, sensitivity and specificity of the VG-RVPO (according to the predefined cut-off of ≥ -13 mV·ms) with corresponding confidence interval (95%CI) were calculated. Moreover, ROC curves were plotted, and the area under the curve (AUC) with corresponding 95%CI was determined. We subsequently calculated the optimal cut-off points for VG-RVPO after PEA and for ΔVG-RVPO by selecting cut-off values to define abnormality according to the highest negative predictive value. For these newly selected cut-off point, we also calculated the diagnostic accuracy as described above. To evaluate the correlation between the VG-RVPO and mPAP and VG-RVPO and indexed RV mass, scatter plots were drawn and a Pearson correlation coefficient was calculated to quantify the strength of the using linear regression analysis. Also we stratified all diagnostic accuracy outcomes according to normal or abnormal RV mass. Patients with bad quality CMR or those with more than 90 days between the CMR and ECG were excluded from this sub-analysis (**Figure 2**).

Figure 2: study flow chart



Abbreviations: CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; LTX, lung transplantation; PEA, pulmonary endarterectomy; RHC, right heart catheterization. * 11 patients with no CMR post PEA

We performed two sensitivity analyses: 1) residual PH defined according to the 2022 pulmonary hypertension guidelines from European Society of Cardiology (ESC); pulmonary artery pressure > 20 mmHg, pulmonary artery wedge pressure <15 mmHg and a pulmonary vascular resistance >160 dynes·s·cm^{-5}, and 2) excluding all patients where follow-up ECG was performed > 90 days after follow-

up RHC. All analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing; www.R-project.org).

RESULTS

Patients

Sixty-six CTEPH patients who underwent PEA and survived a minimum of 6 months were studied (**Figure 2**). Mean age was 57 years and 56% was male (**Table 1**); 86% had a history of acute pulmonary embolism and 35% of deep vein thrombosis. Before PEA, most patients had a New York Heart Association (NYHA) score of II and 37% used PH-specific medication. Pre-PEA RHC showed a mean mPAP of 42.5 mmHg (interquartile range [IQR]: 35-50) and a mean PVR of 600 dynes·s·cm^{-5} (IQR 376-748).

Table 1: baseline characteristics (n=66)

Age at PEA [years], mean (SD)	57.3 (14.1)
Male sex, n (%)	37 (56.1)
BMI [kg·m−2], mean (SD)	27.0 (5.9)
NYHA class, n (%)	
I	1 (1.6)
II	24 (38.1)
III	32 (50.8)
IV	6 (9.5)
Use of PH-specific medication before PEA, n (%)	24 (36.9)
Comorbidities, n (%)	
Acute PE	55 (85.9)
DVT	20 (34.5)
History of a malignancy	3 (4.6)
History of a haematological disease	2 (3.1)
Diabetes mellitus	5 (7.7)
Obstructive lung disease	8 (12.3)
Hypertension	22 (33.8)
Splenectomy	1 (1.5)
Coronary artery disease	2 (3.1)
Thyroid disease	5 (7.7)
Months between PEA to follow-up ECG/RHC, median (IQR)	6.93 (6.46-8.23)
Mean mPAP pre PEA [mmHg], mean(SD)	42.5 (10.2)*
Mean PVR pre-PEA [dynes·s·cm^{-5}], mean (SD)	600.7 (299.5)

* patients without residual PH during follow-up had a mPAP pre PEA of 41.95 mmHg (SD 10.69), which was 43.18 mmHg (9.77) for patients with residual PH during follow-up

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; ECG, electrocardiogram; IQR, interquartile range; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SD, standard deviation.

During follow-up, 28 patients were found to have residual PH (42%) with a mean mPAP of 31.0 mmHg and PVR of 303 dynes·s·cm^{-5} and 38 patients were found to have no residual PH with a mean mPAP of 19.2 mmHg and PVR of 176 dynes·s·cm^{-5}. When using the new criteria to define pulmonary hypertension based on the 2022 ESC guideline 30 patients were found to have residual PH (46%) with a mean mPAP of 28.2 mmHg and PVR of 295 dynes·s·cm^{-5} and 35 (54%) patients were found to have no residual PH with a mean mPAP of 20.9 mmHg and PVR of 136 dynes·s·cm^{-5}.

Diagnostic accuracy of VG-RVPO

If residual PH would have been considered ruled out based on a normal follow-up VG-RVPO of < -13 mV·ms, specificity and sensitivity for detecting residual PH would have been 50% and 64% respectively. RHC would have been indicated in 37 patients (56%), but residual PH would have been missed in 10 out of 28 patients (35.7%; **Table 2**), with a negative predictive value of 65.6%.

Table 2: diagnostic accuracy of specific cut-off values

		Patients without residual PH after PEA (n= 38)	Patients with residual PH after PEA (n=28)
Abnormal follow-up VG-RVPO of ≥-13 mV·ms (previously defined cut-off value)	VG-RVPO normal, n (%)	19 (50)	10 (35.7)
	VG-RVPO abnormal, n (%)	19 (50)	18 (64.3)
Abnormal follow-up VG-RVPO of ≥-14.7 mV·ms	VG-RVPO normal, n (%)	18 (47.3)	9 (32.1)
	VG-RVPO abnormal, n (%)	20 (52.6)	19 (67.9)
Abnormal Δ VG-RVPO of ≥-24.9 mV·ms	VG-RVPO normal, n (%)	8 (21.1)	2 (7.1)
	VG-RVPO abnormal, n (%)	30 (79.0)	26 (92.9)

Abbreviations: PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SD, standard deviation; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

Based on the highest negative predictive value, the best cut-off value for a normal follow-up VG-RVPO would be <-14.7 mV·ms (negative predictive value of 66.7%), and the best cut-off a normal ΔVG-RVPO would have been <-24.9 mV·ms (negative predictive value of 80%). For the newly defined cut-off for follow-up VG-RVPO, the specificity would have been 47.3% and sensitivity 67.9%. RHC would have been indicated in 39 patients (59%), but residual PH would have been missed in 9 patients (32.1%). For the newly defined cut-off for ΔVG-RVPO, the specificity

would have been 21.1% and sensitivity 92.9%. RHC would have been indicated in 56 patients (84%), but residual PH would have been missed in 2 patients (7.1%). The overall predictive accuracy of follow-up RVPO and Δ VG-RVPO for detection of CTEPH was moderate to poor, with a AUCs of the ROC ranging from 0.546 to 0.626 (**Table 3**).

Table 3: AUC ROC curve

	AUC (95%CI)
follow-up VG-RPVO	0.546 (0.396-0.697)
follow-up VG-RVPO ≥-13 mV·ms	0.571 (0.45-0.692)
follow-up VG-RVPO ≥-14.7 mV·ms	0.576 (0.457-0.695)
Δ VG-RVPO	0.626 (0.488-0.764)
Δ VG-RVPO ≥-24.9 mV·ms	0.570 (0.488-0.695)

Abbreviations: AUC, area under the curve; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

When evaluating diagnostic accuracy of the ΔVG-RVPO to detect residual PH for patients with normal vs abnormal indexed RV mass, using the VG-RVPO only in patients with a normal indexed RV mass, would not have improved the performance. Specificity would have been 36-55% and sensitivity 57-100 (**Table S1, Figure S1**). Only when using the cut-off for Δ VG-RVPO of <-24.9 mV·ms there would have been an indication to perform RHC in 78% of the patients with a normal indexed RV mass and none of the residual PH patients with a normal indexed RV mass would have been missed. However, as the CMR sub analysis could only be performed in 20 patients and the indexed RV mass post-PEA was abnormal in only 2 patients, power was very low and these results are highly uncertain.

Sensitivity analyses for the diagnostic accuracy of VG-RVPO

When using the new criteria to define pulmonary hypertension based on the 2022 ESC guideline, we saw similar results for the mean VG-RVPO measurement in patients with/without residual PH (**Table S2**). For the diagnostic performance of the VG-RVPO using the different cut-off values, specificity ranged between 20-51%% and sensitivity between 67-93%. Also, the need for RHC was minimized to 57-86%, but residual PH would have been missed in 7-33% of the patients with residual PH (**Table S3**). Overall predictive accuracy was moderate to poor (AUC ROC ranged 0.561-0.774; **Table S4**).

When excluding the 10 patients with an ECG >90 days after follow-up RHC, mean VG-RVPO and diagnostic accuracy showed similar results as the main analysis (**Table S5-S7**).

VG-RVPO measurements before and after PEA

At baseline, mean VG-RVPO was -5.14 mV·ms. Post-PEA, this was -11.2 mV·ms (**Table 4**). There was no clear difference in post-PEA VG-RVPO between patients with and without residual PH (-10.0 vs-12.1 mV·ms, respectively; mean difference 2.07, 95% CI -5.36 to 9.49). Overall, Δ VG-RVPO was -6.07 mV·ms, indicating a more negative VG-RVPO over time (i.e. more 'normal'). Patients with residual PH had a numerical lower Δ VG-RVPO compared to patients without residual PH (-2.36 vs -8.81 mV·ms, respectively; mean difference 6.46 mV·ms, 95% CI -2.28 to 15.2).

Table 4: VG-RVPO measurements

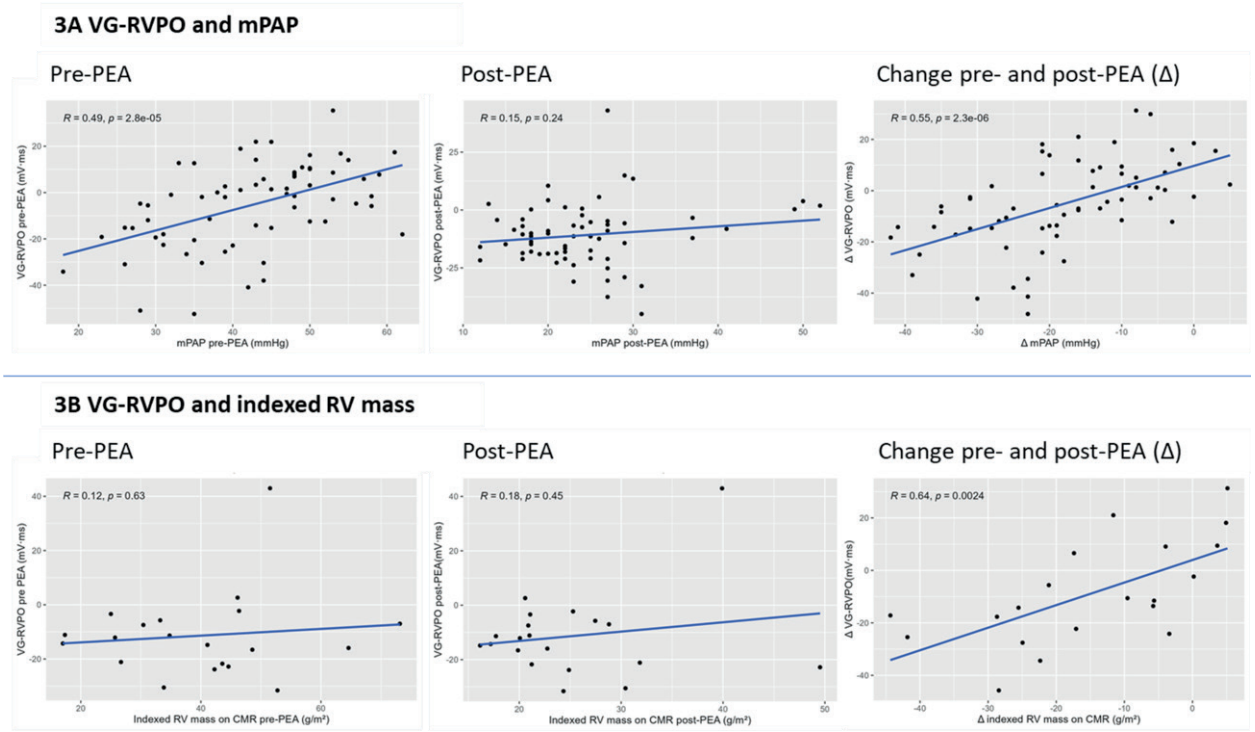
	All patients (n=66)	Patients without residual PH after PEA (n=38)	Patients with residual PH after PEA (n=38)	Mean difference (95%CI)
VG-RVPO at baseline (mV·ms), mean +- SD	-5.14 (18.2)	-3.28 (18.5)	-7.67 (17.8)	-4.39 (95% CI -13.4-4.62)
VG-RVPO during follow-up (mV·ms), mean +- SD	-11.2 (13.6)	-12.09 (9.55)	-10.0 (17.9)	2.07 (95% CI -5.36-9.49)
Δ VG-RVPO (between baseline and during follow up) (mV·ms), mean +- SD	-6.07 (17.8)	-8.81 (17.9)	-2.36 (17.3)	6.46 (95% CI -2.28-15.2)

Abbreviations: PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SD, standard deviation; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

Association VG-RVPO with mPAP and indexed RV mass

Figure 3a depicts the association between the VG-RVPO and the mPAP measured at RHC. Before PEA, a higher mPAP is correlated with a higher VG-RVPO (r=0.49, p<0.05). After PEA this correlation seems to dilute, as the correlation coefficient (r) is only 0.15 (p=0.24). However, when looking at Δ VG-RVPO and mPAP, a positive correlation was identified (r=0.55, p<0.05). **Figure 3b** depicts the correlation between VG-RVPO and indexed RV mass. There seems to be a positive correlation between VG-RVPO and indexed RV mass before PEA (r=0.12, p=0.63), after PEA (r=0.18, p=0.45), and over time (Δ; r=0.64, p<0.05).

Figure 3: relationship between VG-RVPO and mPAP or indexed RV mass



Abbreviations: CMR, cardiac magnetic resonance; mPAP, mean pulmonary artery pressure; PEA, pulmonary endarterectomy; RV, right ventricle; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

Association VG-RVPO with mPAP and indexed RV mass

Figure 3a depicts the association between the VG-RVPO and the mPAP measured at RHC. Before PEA, a higher mPAP is correlated with a higher VG-RVPO (r=0.49, p<0.05). After PEA this correlation seems to dilute, as the correlation coefficient (r) is only 0.15 (p=0.24). However, when looking at Δ VG-RVPO and mPAP, a positive correlation was identified (r=0.55, p<0.05).

Figure 3b depicts the correlation between VG-RVPO and indexed RV mass. There seems to be a positive correlation between VG-RVPO and indexed RV mass before PEA (r=0.12, p=0.63), after PEA (r=0.18, p=0.45), and over time (Δ; r=0.64, p<0.05).

DISCUSSION

The main goal of this study was to evaluate the diagnostic accuracy of the VG-RVPO for detecting residual PH in CTEPH patients post PEA. Unfortunately, the pre-PEA and Δ VG-RVPO significantly correlated with mPAP and indexed RV mass. However, the use of the VG-RVPO in detecting residual PH was limited as 36% of the CTEPH patients with residual PH had a normal VG-RVPO and 7% had a clear improvement of VG-RVPO over time. This suggests that relying solely on VG-RVPO for the detection of residual PH would result in overlooking a substantial portion of affected individuals.

Chronically increased pulmonary artery pressure resulting in RV pressure overload induces changes in action potential duration that can be detected using vector ECG. The VG-RVPO, a vector gradient optimized to detect RV pressure overload, operates on this principle. Given that VG-RVPO measurement is a non-invasive tool, we hypothesized its potential utility in detecting persistent increased pulmonary artery pressure (i.e. residual PH) in CTEPH patients following PEA. Indeed before PEA there was correlation between increased mPAP or indexed RV mass and the VG-RVPO. However, our study found that VG-RVPO did not perform adequately in excluding the presence of residual PH after PEA, likely due to remodelling of the heart after PEA.

One of the factors contributing to the underperformance of the VG-RVPO related to remodelling of the heart after PEA might be persistent RV hypertrophy. Following PEA there is a reduction in RV mass, although it does not fully normalize compared to healthy controls. [20] In some CTEPH patients, RV hypertrophy may persist despite normalization of pulmonary artery pressure post-PEA, leading to

an abnormal VG-RVPO. This could diminish the discriminative ability of the VG-RVPO in detecting residual PH. However, even in patients with a normalized RV mass, the diagnostic accuracy of the VG-RVPO for detecting residual PH was poor. Although it should be noted that the power of this analysis was severely limited due to the availability of CMR data in only 20 patients. Therefore, definitive conclusions regarding this sub-analysis cannot be drawn.

Given that the VG-RVPO was designed to detect electrophysiological changes in action potential duration rather than sole RV hypertrophy[8], it's crucial to consider other factors related to the remodelling of the heart after PEA that may impact its performance in discriminating residual PH. One such factor post-PEA could be the persistent abnormality in the composition of the heart. Despite the decrease in RV mass post-PEA, Braams and colleagues have demonstrated that the composition of the heart after PEA remains abnormal. [20] The persistent altered composition might lead to heterogeneity in action potential duration, thus influencing the ability of the VG-RVPO to detect increased pulmonary artery pressure. Therefore, beyond RV hypertrophy, the ongoing abnormality in the heart's composition post-PEA could contribute to the suboptimal performance of VG-RVPO in this context.

Overall, the VG-RVPO seems to effectively detect increased pulmonary artery pressure before PEA, which aligns with a previous study demonstrating that the VG-RVPO significantly correlated with increased mPAP in patients with suspected PH and effectively identifies PH in systemic sclerosis patients.8, 9 However, due to heart remodelling post-PEA, the additional value of the VG-RVPO in identifying residual pulmonary hypertension (PH) post-PEA is limited. A previous study also showed limited use of the VG-RVPO in the detection of CTEPH in acute PE survivors, possibly due to the diluting effect of persistent RV pressure overload in non-CTEPH acute PE survivors.[21] Whether the VG-RVPO could still contribute to the diagnostic of suspected PH in other patient categories remains unclear.

Our study has some limitations. First, ECG data before or after PEA was unavailable in a proportion of the CTEPH patients. While this missing data is likely random, the possibility of selection bias cannot be entirely ruled out. Second, there was a time gap between the ECGs and RHC, as it was not mandatory to conduct ECGs on the same day as the catheterization procedure. As a result in 10 patients, ECGs were conducted more than 90 days after right heart catheterization. However, we addressed this limitation by conducting a sensitivity analysis excluding these patients, which yielded similar results. Third, CMR data

was only accessible in 20 patients. As a result, the sub-analysis involving CMR is underpowered, and definitive conclusions cannot be drawn. Lastly, (residual) PH was defined as mPAP≥25 mmHg measured with RHC according to the current guideline at time of inclusion of this cohort. [16] Therefore applicability of our findings to CTEPH patients diagnosed using the 2022 definition of PH may be debatable. To address concerns regarding the applicability of the definition of residual PH, we conducted a sensitivity analysis classifying CTEPH patients with residual PH according to the 2022 definition, yielding similar results.

In conclusion, while we observed a correlation between VG-RVPO and increased pulmonary artery pressure in CTEPH patients before PEA, this correlation appears to diminish after PEA. The remodelling of the heart after PEA such as persistent abnormality in the composition of the heart or persistent RV hypertrophy despite normalization of the pulmonary artery pressure seems to clarify why our study did not demonstrate a relevant diagnostic value of VG-RVPO for detecting PH in CTEPH patients post-PEA. These findings suggest that the utility of VG-RVPO is limited in this context, highlighting the need for further research to explore alternative approaches to improve (non-invasive) follow-up of CTEPH patients post PEA.

REFERENCES

1. Delcroix M, Torbicki A, Gopalan D, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. *The European respiratory journal* 2020: 57(6): 2002828.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *The European respiratory journal* 2019: 54(3): 1901647.
3. Galiè N, Humbert M, Vachiery J-L, 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* 2015: 37(1): 67-119.
4. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. *Circulation* 2011: 123(16): 1788-1830.
5. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2013: 62(25 Suppl): D92-99.
6. Cannon JE, Su L, Kiely DG, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation* 2016: 133(18): 1761-1771.
7. Quadery SR, Swift AJ, Billings CG, et al. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2018: 52(3).
8. Kamphuis VP, Haeck MLA, Wagner GS, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. *Journal of Electrocardiology* 2014: 47(2): 175-182.
9. Meijer FMM, Kies P, Jongbloed MRM, et al. ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients. *Int J Cardiol* 2018: 273: 203-206.
10. Henkens IR, Mouchaers KTB, Vonk-Noordegraaf A, et al. Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging. *Am J Physiol Heart Circ Physiol* 2008: 294(5): H2150-H2157.
11. Meijer FMM, Hendriks SV, Huisman MV, et al. The prognostic value of ECG-derived ventricular gradient in early adverse events in acute pulmonary embolism patients. *Thrombosis Update* 2021: 2: 100033.
12. Meijer FMM, Hendriks SV, Huisman MV, et al. Lack of diagnostic utility of the ECG-derived ventricular gradient in patients with suspected acute pulmonary embolism. *J Electrocardiol* 2020: 61: 141-146.
13. Couperus LE, Vliegen HW, Henkens IR, et al. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. *J Electrocardiol* 2016: 49(1): 60-68.
14. Scherptong RWC, Henkens IR, Man SC, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J Electrocardiol* 2008: 41(6): 648-655.
15. Ruigrok D, Handoko ML, Meijboom LJ, et al. Noninvasive follow-up strategy after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *ERJ Open Res* 2022: 8(2).
16. Galie N, Humbert M, Vachiery JL, 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.
17. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011: 58(24): 2511-2519.
18. Draisma HHM, Swenne CA, van de Vooren H, et al. LEADS An interactive research oriented ECG/VCG analysis system. *Computers in cardiology* 2005: 515–518.
19. Draisma HHM, Schalij MJ, van der Wall EE, et al. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. *Heart Rhythm* 2006: 3(9): 1092-1099.
20. Braams NJ, Kianzad A, van Wezenbeek J, et al. Long-Term Effects of Pulmonary Endarterectomy on Right Ventricular Stiffness and Fibrosis in Chronic Thromboembolic Pulmonary Hypertension. *Circ Heart Fail* 2023: 16(10): e010336.
21. Luijten D, Meijer FMM, Boon G, et al. Diagnostic efficacy of ECG-derived ventricular gradient for the detection of chronic thromboembolic pulmonary hypertension in patients with acute pulmonary embolism. *J Electrocardiol* 2022: 74: 94-100.

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General discussion and summary

In this thesis we described studies that aimed to improve the management of pulmonary embolism (PE). **Chapter 1** gives a general introduction on the management of PE during the acute phase and during follow-up, along with an overview of the presented studies.

Chapter 2 describes four challenges presented in PE management where an expert opinion based on current literature was given. The first challenge is selecting patients with an indication for reperfusion treatment. There is a lack of randomized controlled trials demonstrating the superiority of reperfusion treatment over standard of care for hemodynamically stable acute PE patients with right ventricular (RV) dysfunction and myocardial injury (i.e. intermediate-high risk patient). Consequently, reperfusion is currently only recommended in these patients as a rescue treatment if anticoagulation fails to stabilize the patient.

Second, subsegmental PE may be left untreated in selected low risk patients, after proximal deep vein thrombosis has been ruled out, although this remains to be proven safe and has not yet been evaluated in a randomized controlled trial.

Third, previous studies have shown that selecting patients eligible for home treatment based on a risk stratification tool, such as the Hestia criteria or sPESI with clinical judgement, is safe. However, their applicability across all acute PE patients due to underrepresentation of certain subgroups in clinical trials, particularly those with RV dysfunction/pressure overload, is unknown. Adverse event rates in patients with a negative Hestia score or an sPESI score of 0 are low even in patients with signs of RV pressure overload, suggesting that home treatment may be safe for a broader group than currently recommended in guidelines. **Chapter 3** addresses this topic by presenting a large systematic review and individual patient data meta-analysis (IPDMA) on the safety of home treatment. Among 2,694 acute PE patients selected using predefined risk stratification, the rates of all-cause mortality and adverse events (i.e. combined endpoint of all-cause mortality, major bleeding an recurrent venous thromboembolism (VTE)) within 14 days were low (0.11% and 0.56%, respectively) when receiving home treatment (i.e. discharge within 24h). Cancer patients had a 3-5 fold higher incidence of 30-day mortality or adverse events. However, absolute numbers for mortality in cancer patients remains low (0.46%), and mortality was mostly due to underlying cancer. For other subgroups, including for patients with RV overload, there was no increased mortality risk. Overall these results suggest that validated triage tools such as Hestia or sPESI in combination with a negative clinical judgement, can be used in the emergency department to select acute PE

patients for home treatment. Moreover, the point estimates of the absolute risk of adverse events provide important evidence to perform clinical shared decision-making in daily practice.

Another subgroup evaluated in **Chapter 3** were older patients. Within the sPESI score, being 80 years or older results in a score of ≥1. Patients with a score of ≥1 are considered not at low risk for death and therefore guidelines advice to hospitalize these patients. Thus, older patients are, based on this approach, considered excluded from home treatment. However, in the IPDMA we observed no increased risk of adverse outcomes solely depending on age. This is supported by **Chapter 4**, where a retrospective cohort study showed that 25% of older PE patients (aged 70 years or older) could safely receive home treatment using the Hestia criteria, compared to only 3.9% if the sPESI score in combination with absence of signs of RV overload would have been used to select patients for home treatment. Given the benefits of home treatment, including higher patient satisfaction and lower healthcare costs[1, 2], using the Hestia criteria to select older patients who are eligible for home treatment appears to be a safe and more effective alternative than the sPESI score in combination with absence of RV overload. Additionally, on the other side of the severity spectrum, **Chapter 4** also examined the management of older patients presenting with a haemodynamically unstable PE (i.e. high risk PE). Among 20 high risk older patients, only eight received reperfusion treatment. Although reperfusion treatment is recommended for high risk patients, it was often withheld because hemodynamic instability was attributed to comorbidities other than PE. Comorbidities appear to significantly influence the evaluation of hemodynamically unstable older patients with acute PE, which raises questions about the applicability of the definition of high risk PE in older patients. Nonetheless, even if reperfusion treatment was administered, older patients in this category had a very poor outcome as over half of them died within 14-days. Finally, the European Society of Cardiology (ESC) risk classification and the Acute Presenting Older Patient (APOP) score both effectively predicted mortality risk, therefore we hypothesize that combining PE-specific and age-specific risk classifications may improve management decisions.

The final challenge presented in **Chapter 2** is the optimal approach to diagnose and treat the post-PE syndrome (PPES). **Chapter 5** provides an overview of the definition and treatment of PPES, covering chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic pulmonary disease (CTEPD)

without pulmonary hypertension (PH), post-PE cardiac impairment and post-PE functional limitations.

In post-PE functional impairment, the fear of recurrence and the reflex or even counselling to be cautious with performing exercise may lead to inactivity and deconditioning. Given the suggested benefits of early exercise training to prevent chronic functional impairment, **Chapter 6** evaluates the safety and physiological response to exercise 2-4 weeks post-PE diagnosis through cardiopulmonary exercise testing (CPET). This study, a sub-analysis of the ongoing PE@HOME trial, involved 100 acute PE patients undergoing CPET, with no PE-related adverse events when performing CPET. Despite persistent dyspnoea and functional limitations in all patients, CPET revealed that one out of seven patients displayed no signs of inefficient ventilation or insufficient cardiocirculatory reserve of which we conclude had an adequate cardiopulmonary response during exercise, meaning that not all post-PE dyspnoea and/or functional limitation can be explained by abnormalities observed during exercise, highlighting the multifactorial nature of PPES. Among the 66 patients with an abnormal cardiopulmonary limitation, 49 were still able to achieve a normal exercise capacity (74%). The absence of adverse events, the adequate cardiopulmonary response in one out of seven of the patients, and the fact that most patients with abnormalities still achieved normal exercise capacity underscores the potential safety of advising similar patients to resuming exercise soon after their PE diagnosis to prevent inactivity and deconditioning. However, as safety of resuming exercise was formally not investigated in this study and a selected group of acute PE patients was investigated, this remains to be proven. The ongoing PE@HOME trial will give us therefore more insight in the safety and efficacy of exercise resumption at home under the remote guidance of a physiotherapist.

If patients continue to experience incomplete recovery after three months of anticoagulant therapy, they should be evaluated for PPES, with a first focus on identifying CTEPH, the most severe and potentially deadly form. **Chapter 7** presents a systematic review and meta-analysis showing that only 2.7% of the acute PE survivors are ultimately diagnosed with CTEPH. This knowledge is crucial for designing and implementing algorithms to detect CTEPH post-PE. Moreover, those with recurrent VTE, unprovoked PE, and RV dysfunction at index PE have an increased risk of developing CTEPH. This emphasizes the principle known as acute-on-chronic CTEPH, where undiagnosed CTEPH patients experience an acute worsening of their condition. Subsequent imaging then reveals obstructed

pulmonary arteries, leading to a 'misclassification' of acute PE due to the absence of prior imaging.

Dedicated CTEPH follow-up algorithms are crucial for effective and timely identification of the 2.7% with CTEPH among all patients with incomplete recovery after PE. One algorithm designed to identify CTEPH early after acute PE is the InShape II algorithm.[13] According to the algorithm, patients with either a high-pretest probability of CTEPH, as assessed with the CTEPH prediction score, or suggestive symptoms of CTEPH are subjected to the "CTEPH rule-out criteria", consisting of electrocardiogram (ECG) reading for the presence of RV strain and NTproBNP measurement.[13-15] CTEPH is ruled out if both are normal, otherwise echocardiography is necessary. However, the InShape II algorithm may be further improved in terms of efficiency and safety. Therefore, in **Chapter 8** we evaluated the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) as a new rule-out criteria within the InShape II algorithm. Unfortunately, the VG-RVPO did not add value either as a standalone test for detecting CTEPH after acute PE or as a component within the InShape II algorithm. This may be explained by the fact that RV pressure overload can also occur in non-CTEPH acute PE patients, and temporary improvement of RV function can occur in acute-on-chronic CTEPH following the initiation of anticoagulation. [3-8]

Another potential improvement for CTEPH detection might be by using index PE CTPA scans, since at the index PE event there are specific signs on CTPA scans that are highly predictive of a future CTEPH diagnosis, which adheres to the principle of acute-on-chronic CTEPH. [3, 9-12] Since CTPA scans are routinely available for acute PE patients, utilizing detailed CTPA readings might enhance the performance of the InShape II algorithm. In **Chapter 9** we designed 12 hypothetical algorithms where detailed CTPA reading was incorporated in the InShape II algorithm, either as an additional test or by replacing one of the preexisting items. The best-performing algorithm was the InShape IV algorithm. This algorithm suggest perform echocardiography only in patients with 1) a positive index PE CTPA reading (≥3/6 signs of chronicity) or 2) symptomatic patients with signs of RV pressure strain on ECG or abnormal NT-proBNP levels; CTEPH is considered ruled in all others without further testing. Compared to InShape II, InShape IV improved the failure rate: one CTEPH patient in whom CTEPH was considered ruled out by InShape II based on negative rule-our criteria, had an echocardiography indication in InShape IV due to positive CTPA reading. However, this did not result in an overall improved CTEPH detection rate, as

echocardiography was negative for this particular patient six months post-PE, suggesting incident CTEPH. Nonetheless, InShape IV has several important improvements over InShape II. Firstly, the CTPA reading in InShape IV replaces the CTEPH prediction score in InShape II. The prediction score included factors without an obvious pathophysiological link to CTEPH, such as diabetes, thus eliminating the prediction score results in a better alignment with the pathophysiology of acute-on-chronic CTEPH. [13, 14] Secondly, the CTPA reading within InShape IV can be easily applied by also less experienced radiologist as is uses the presence of ≥3/6 signs of chronicity.[15] This reduces subjectivity and enhances applicability in various clinical settings. Thirdly, the algorithm in InShape IV allows CTEPH patients to undergo echocardiography directly without first requiring ECG reading or NTproBNP testing. This reduces the overall necessity for these tests from 43% in InShape II to 23% in InShape IV, potentially lowering costs. Furthermore, by efficiently identifying patients needing echocardiography, referrals to expert pulmonary hypertension centres can be expedited, minimizing diagnostic delays and improving outcomes.

Whether InShape IV really results in a cost-effective approach was subsequently evaluated in **Chapter 10**. This study included 11 different PE follow-up algorithms and one hypothetical scenario without a dedicated CTEPH follow-up, all analysed using a Markov model. The study found two key results. First, integrating any of the algorithms to detect CTEPH is preferred over not performing dedicated follow-up, resulting in an increase of 0.89-1.2 quality adjusted life year (QALY) at an incremental cost-effectiveness ratio (ICER) of €25,700-€46,300 per QALY, all below the Dutch threshold of €50,000 per QALY, indicating a cost-effective approach. Second, the InShape IV algorithm was the most cost-effective, with an ICER of €26,700 per QALY compared to the next best algorithm. Based on these results we concluded that implementing any dedicated follow-up algorithm is cost-effective compared to not performing one. The choice of algorithm should depend on local healthcare resources. If no specific preferences exist, the InShape IV algorithm may be considered as the optimal strategy as is proved to be the most cost-effective option.

In **Chapter 11**, we further discussed why some acute PE patients don't fully recover. Through a systematic review and meta-analysis, we explored the association between pulmonary perfusion defects or residual vascular obstruction and post-PE functional recovery. Our findings showed that 34% of acute PE patients had these abnormalities on imaging during follow-up. Among them, 48%

reported persistent symptoms, compared to 34% of patients with normal imaging results. Despite a moderate association (odds ratio of 2.2) between persistent defects and persistent symptoms, causality wasn't proven. Notably, half of the patients with defects fully recovered, and a significant proportion without defects also reported symptoms, suggesting that not all PPES can be explained solely by unresolved clots. Moreover, most studies didn't screen for CTEPH, possibly overestimating the association between defects and symptoms in non-CTEPH patients. Additionally, we found no correlation between persistent defects and altered haemodynamics (as measured by CPET), raising questions about a potential causal link with symptoms. Our finding support current guideline recommendations that propose to only perform imaging in cases showing signs of CTEPH (for example within the InShape IV algorithm those with an intermediate to high risk of PH on echocardiography) or signs of CTEPD without PH on CPET. Thus routine repeat imaging for symptomatic PE survivors isn’t recommended.

In **Chapter 12**, our focus shifted to the management of CTEPH, evaluating the diagnostic accuracy of the VG-RVPO in detecting residual PH post-pulmonary endarterectomy (PEA). We analysed data from 66 CTEPH patients who underwent PEA, assessing the VG-RVPO's diagnostic performance for residual PH detection and its potential to replace RHC. Results revealed significant correlations between pre-PEA and Δ VG-RVPO with mean pulmonary artery pressure or indexed RV mass. However, relying solely on VG-RVPO for residual PH detection had limitations; 36% of patients with residual PH had normal VG-RVPO and 7% showed improvement over time. This suggests using VG-RVPO alone may misclassify a substantial number of cases. Persistent RV hypertrophy and ongoing cardiac abnormalities post-PEA may contribute to VG-RVPO's suboptimal performance. Altogether the VG-RVPO has limited utility in this context.

Future perspective

This thesis discusses the management of PE during the acute episode, as well as the detection of chronic complications. Decisions made during the acute phase can impact the risk of developing chronic complications. For post-PE patients, the fear of recurrence and the instinct, or even medical advice, to avoid physical activity may lead to inactivity and deconditioning, potentially causing long-term limitations. Providing clear and adequate guidance on safely resuming physical activity during the acute phase can help prevent this negative cycle. However, given the large amount of information patients receive during this phase, both the content and delivery of this information are critical factors that may influence patient satisfaction and outcomes after PE. Therefore, effective communication in the acute phase is essential. The Scientific and Standardization Committee on Predictive and Diagnostic Variables in Thrombotic Disease of the International Society of Thrombosis and Haemostasis is developing an information toolbox to guide physicians on key topics to discuss with patients after acute PE. While this initiative is a crucial first step in improving patient communication, future research should investigate its impact in daily practice. A pre- and post-implementation study could evaluate the influence of this toolkit on patient satisfaction and the incidence of PPES.

PE-specific rehabilitation or remote guidance by a physiotherapist may also aid recovery after PE, but a randomized study on the safety and efficacy of such programs shortly after diagnosis in a selected group of patients is lacking. Additionally, it remains unclear if patients with abnormal cardiovascular limitations shortly after diagnosis continue to experience limitations and symptoms during follow-up, and the impact of exercise training programs on post-PE syndrome remains uncertain. The ongoing PE@HOME study addresses these questions and will hopefully provide further clarity.

Finally better systematic follow-up for PE is needed. Despite existing algorithms to detect CTEPH, the diagnostic delay remains around 15 months.[17] This delay may be due to unclear follow-up procedures for acute PE, including the need for a comprehensive algorithm that covers all PPES entities. In **Chapter 5**, we proposed an algorithm including CPET to detect persistent clots causing symptoms. Although CPET is comprehensive and there are guidelines for interpreting results, clear CPET algorithms identifying patterns of PPES and subsequent management strategies are lacking. [18]

When evaluating CPET, predicted values for CPET parameters are calculated first, with abnormalities defined as values below or above a certain percentage of the predicted value. Various efforts for standardization of normal values and interpretating strategies and have been developed. However, general consensus on calculating predicted values and target thresholds is lacking. The SHIP cohort, which included 616 healthy individuals, aimed to develop improved predictive values. [19] However, asymptomatic post-PE patients without CTEPD might not classify as healthy, and different reference values may apply. Moreover, reduced exercise performance on CPET post-PE may result from various pathophysiological factors but also from suboptimal effort. Differentiating these causes is crucial but challenging without a gold standard for defining maximal effort. Finally, there is no agreement on the importance and combination of abnormal parameters needed to classify post-PE patterns, with factors like beta blockers use, comorbidities or submaximal effort influencing results.

Future efforts should clarify these issues and provide better guidance on interpreting CPET results for persistent symptoms post-PE. A systematic review summarizing all CPET tests post-PE could elucidate mean values of CPET variables in CTEPH, CTEPD without PH, symptomatic, and asymptomatic post-PE patients. An IPDMA could then determine 'normal values' for these populations based on mean values and the distribution within the asymptomatic post-PE group. The diagnostic accuracy of these variables and cut-off values can subsequently be tested by comparing different groups. These findings can inform a Delphi study among CPET and PE experts to determine for post-PE patients: (1) how to best determine predicted values, (2) the acceptable reference range, (3) the combination of abnormal variables indicating an ‘abnormal’ CPET, and (4) subsequent steps for an ‘abnormal’ CPET, such as performing a CTPA. Overall, these efforts should increase awareness of PPES and improve follow-up care for PE patients.

REFERENCES

1. Bledsoe JR, Woller SC, Stevens SM, et al. Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. *Chest* 2018: 154(2): 249-256.
2. Hendriks SV, van den Hout WB, van Bemmel T, et al. Home Treatment Compared to Initial Hospitalization in Normotensive Patients with Acute Pulmonary Embolism in the Netherlands: A Cost Analysis. *Thromb Haemost* 2022: 122(3): 427-433.
3. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, 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): 731-738.
4. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. *Thromb Haemost* 2014: 112(3): 598-605.
5. Klok FA, Couturaud F, Delcroix M, et al. Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *The European respiratory journal* 2020: 55(6).
6. Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017: 26(143): 160112.
7. Lang IMandMadani M. Update on chronic thromboembolic pulmonary hypertension. *Circulation* 2014: 130(6): 508-518.
8. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. *AJR Am J Roentgenol* 2020: 215(4): 800-806.
9. Boon G, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. *Eur Radiol* 2021.
10. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. *Eur J Intern Med* 2021: 93: 64-70.
11. Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. *Eur Respir J* 2021.
12. Barco S, Mavromanoli AC, Kreitner K-F, et al. Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism. *CHEST*.
13. Klok FA, Surie S, Kempf T, 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): 21-26.
14. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost* 2016: 14(1): 121-128.
15. Boon G, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. *Eur J Intern Med* 2021.
16. Roh HandPark KH. A Scoping Review: Communication Between Emergency Physicians and Patients in the Emergency Department. *J Emerg Med* 2016: 50(5): 734-743.
17. Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. *The European respiratory journal* 2018: 52(6): 1801687.

18. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev* 2019: 28(154): 180101.
19. Gläser S, Ittermann T, Schäper C, et al. [The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing]. *Pneumologie* 2013: 67(1): 58-63.

14

Nederlandse samenvatting

In dit proefschrift beschrijven we studies die zich richten op het verbeteren van de behandeling van longembolie patiënten. **Hoofdstuk 1** geeft een inleiding over de behandeling van een longembolie tijdens de acute fase en gedurende de nazorg. Ook geeft **Hoofdstuk 1** een overzicht van de gepresenteerde studies.

Hoofdstuk 2 beschrijft vier uitdagingen waarmee een arts in aanraking komt bij het behandelen van een longembolie. Per uitdaging wordt een *expert opinion* op basis van de huidige literatuur gegeven. De eerste uitdaging is het selecteren van patiënten met een indicatie voor reperfusiebehandeling. Er is een gebrek aan gerandomiseerde studies die de superioriteit van reperfusiebehandeling aantonen ten opzichte van de standaardzorg als primaire behandeling voor hemodynamisch stabiele acute longembolie patiënten met rechterventrikel (RV) dysfunctie en myocardiale schade (oftewel patiënten met een intermediair-hoog risico longembolie). Reperfusie wordt momenteel alleen aanbevolen als optie, wanneer antistolling als primaire behandeling faalt. Dit is het geval bij hemodynamische verslechtering of het uitblijven van herstel van bedreigde vitale parameters, zoals een verhoogde hartslag of een lage saturatie.

De tweede uitdaging betreft de mogelijkheid om subsegmentele longembolieën onbehandeld te laten bij geselecteerde laagrisicopatiënten, nadat proximale diepe veneuze trombose is uitgesloten. Verschillende observationele studies hebben patiënten met een geïsoleerde subsegmentele longembolie onbehandeld gelaten, waarbij de incidentie van symptomatische recidiverende veneuze trombose laag bleef. De veiligheid hiervan is echter nog niet bewezen met een gerandomiseerde studie.

Ten derde, eerdere studies hebben aangetoond dat het selecteren van patiënten die in aanmerking komen voor thuisbehandeling op basis van een beslisinstrument zoals de Hestia-criteria of sPESI met klinisch oordeel, veilig is. Echter, er is discussie over de toepasbaarheid van deze beslisinstrumenten bij bepaalde subgroepen van patiënten met acute longembolie door de ondervertegenwoordiging van deze subgroepen in klinische studies. Met name patiënten met RV-overbelasting zijn hier ondervertegenwoordigd. Het aantal patiënten met een negatieve Hestia-score of een sPESI-score van 0 die overlijden, een recidief trombose ontwikkelen of een ernstige bloeding hebben in de eerste weken na diagnose is laag, zelfs bij patiënten met tekenen van RV-overbelasting. Dit suggereert dat thuisbehandeling mogelijk veilig is voor een bredere groep dan momenteel wordt aanbevolen in de Europese richtlijn. **Hoofdstuk 3** onderzoekt dit onderwerp verder door het presenteren van een grote systematische review

en een individuele patiënten data meta-analyse (IPDMA) over de veiligheid van thuisbehandeling. Onder de 2.694 patiënten met een acute longembolie, geselecteerd met behulp van een op voorhand gedefinieerd beslisinstrument, waren de percentages voor sterfte en nadelige uitkomsten (d.w.z. het gecombineerde eindpunt van sterfte, ernstige bloedingen en recidiverende veneuze trombose) binnen 14 dagen laag wanneer zij thuis behandeld werden, gedefinieerd als ontslag binnen 24 uur: 0.11% en 0.56% respectievelijk. Kankerpatiënten hadden een 3-5 keer hogere incidentie van 30-dagen sterfte of nadelige uitkomsten. De absolute cijfers voor sterfte bij kankerpatiënten blijven echter laag (0.46%) en sterfte werd meestal veroorzaakt door de onderliggende kanker. Voor andere subgroepen, waaronder patiënten met RV-overbelasting, is er geen verhoogd sterfterisico aangetoond. Deze resultaten suggereren dat gevalideerde beslisinstrumenten zoals Hestia of de sPESI in combinatie met een negatief klinisch oordeel, inderdaad kunnen worden gebruikt op de spoedeisende hulp om patiënten met een acute longembolie te selecteren voor thuisbehandeling. Bovendien bieden de puntschattingen van het absolute risico op nadelige uitkomsten belangrijk bewijs voor gedeelde besluitvorming in de dagelijkse praktijk.

Een andere subgroep die werd geëvalueerd in **Hoofdstuk 3** waren oudere patiënten. Alle patiënten met een leeftijd van 80 jaar of ouder hebben een sPESI score van ≥1. Patiënten met een score van ≥1 worden beschouwd als het hebben van een niet-laag risico op sterfte en daarom adviseren de Europese richtlijnen om deze patiënten op te nemen in het ziekenhuis. Op basis van deze aanpak worden oudere patiënten dus uitgesloten van thuisbehandeling. In de IPDMA zagen we echter dat het uitsluitend hebben van een hogere leeftijd niet geassocieerd is met een verhoogd risico op nadelige uitkomsten. Dit wordt ondersteund door **Hoofdstuk 4,** waarin een retrospectieve cohortstudie aantoont dat 25% van de oudere patiënten met een longembolie (70 jaar of ouder) veilig thuis kon worden behandeld wanneer gebruik wordt gemaakt van de Hestia-criteria. Ter vergelijking: slechts 3.9% van deze patiënten zou voor thuisbehandeling in aanmerking komen als selectie had plaatsgevonden op basis van de sPESI-score in combinatie met de afwezigheid van tekenen van RV-overbelasting. Gezien de voordelen van thuisbehandeling, waaronder hoge patiënttevredenheid en lagere zorgkosten, lijkt het gebruik van de Hestia-criteria om oudere patiënten te selecteren die in aanmerking komen voor thuisbehandeling een veilige en

efficiëntere optie dan de sPESI-score in combinatie met afwezigheid van RV-overbelasting.

Gekeken naar ernstigere vormen van een longembolie werd in **Hoofdstuk 4** ook de behandeling van oudere patiënten met een hemodynamisch instabiele longembolie (ook wel hoog risico longembolie genoemd) onderzocht. Onder 20 oudere patiënten met een hoog risico longembolie kregen slechts 8 patiënten een reperfusiebehandeling. Hoewel reperfusiebehandeling wordt aanbevolen voor patiënten met een hoog risico longembolie, werd dit achterwege gelaten omdat de hemodynamische instabiliteit werd toegeschreven aan andere acute ziektebeelden zoals sepsis in plaats van de longembolie. Deze ziektebeelden lijken een aanzienlijke invloed te hebben op de evaluatie van hemodynamisch instabiele oudere patiënten met acute longembolie, wat vragen oproept over de toepasbaarheid van de definitie van een hoog risico longembolie bij oudere patiënten. Zelfs als reperfusiebehandeling werd toegediend, hadden oudere patiënten in deze categorie een zeer slechte prognose: meer dan de helft van hen overleed binnen 14 dagen. Tot slot voorspelden zowel de European Society of Cardiology (ESC) risicoclassificatie als de Acute Presenting Older Patient (APOP)-score effectief het sterfterisico. Dit werpt de veronderstelling op dat het combineren van longembolie specifieke en leeftijdsspecifieke risicoclassificaties de behandeling van oudere longembolie patiënten mogelijk kan verbeteren.

Terugkomend op de uitdagingen beschreven in **Hoofdstuk 2**, betreft de laatste uitdaging de optimale aanpak voor het diagnosticeren en behandelen van het post-longembolie syndroom (*post pulmonary embolism syndrome*; PPES). **Hoofdstuk 5** biedt een overzicht van de definitie en behandeling van PPES, inclusief chronische trombo-embolische pulmonale hypertensie (CTEPH), chronische trombo-embolische pulmonaire ziekte (CTEPD) zonder pulmonale hypertensie (PH), post-PE hartdysfunctie en post-PE functionele beperkingen. Bij post-PE functionele beperkingen kan de angst voor een recidief en het advies om voorzichtig te zijn met lichamelijke inspanning leiden tot inactiviteit en deconditionering. Op grond van de veronderstelling dat vroege fysieke training mogelijk chronische functionele beperkingen kan voorkomen, wordt in **Hoofdstuk 6** de veiligheid en fysiologische respons op lichaamsbeweging 2-4 weken na de diagnose van een longembolie door middel van cardiopulmonaire inspanningstesten (*cardiopulmonary exercise test*; CPET) geëvalueerd. Deze studie, een sub analyse van de lopende PE@HOME-trial, omvatte 100 patiënten met een acute longembolie die CPET ondergingen, zonder dat er longembolie gerelateerde

nadelige uitkomsten plaatsvonden tijdens en kort na de uitvoering van CPET. Ondanks aanhoudende dyspneu en functionele beperkingen bij alle patiënten, toonde CPET aan dat één op de zeven patiënten geen tekenen van inefficiënte ventilatie of onvoldoende cardioreserve vertoonde, wat betekent dat niet alle post-longembolie dyspneu en/of functionele beperkingen verklaard kunnen worden door de gemeten afwijkingen tijdens inspanning. Van de 66 patiënten met een abnormale cardiopulmonaire beperking had 74% nog steeds een normale inspanningscapaciteit. Het uitvoeren van de CPET zonder problemen bij onze patiënten, de adequate cardiopulmonale respons bij één op de zeven patiënten, en het feit dat de meeste patiënten met afwijkingen nog steeds een normale inspanningscapaciteit hadden, benadrukt de veiligheid van het adviseren van soortgelijke patiënten om snel na de diagnose van de longembolie de fysieke activiteit te hervatten om inactiviteit en deconditionering te voorkomen.

Als patiënten na drie maanden antistollingstherapie nog steeds een onvolledig herstel ervaren, moeten zij worden geëvalueerd op PPES. Hierbij ligt de eerste focus op het identificeren van CTEPH, de meest ernstige en mogelijk dodelijke vorm van PPES. **Hoofdstuk 7** presenteert een systematische review en meta-analyse die laat zien dat slechts 2.7% van de overlevenden van een acute longembolie uiteindelijk wordt gediagnosticeerd met CTEPH. Deze kennis is cruciaal voor het ontwerpen en implementeren van algoritmen om CTEPH na een longembolie op te sporen. Patiënten met een recidiverende veneuze trombose, niet-uitgelokte longembolie en RV-overbelasting ten tijde van de acute longembolie diagnose hebben een verhoogd risico op het ontwikkelen van CTEPH. Dit benadrukt het principe van acute-op-chronische CTEPH, waarbij niet-gediagnosticeerde CTEPH-patiënten een acute verslechtering van hun toestand ervaren. Het vervolgens uitvoeren van beeldvorming toont trombose in de longslagaders aan, wat wordt ‘gemisclassificeerd’ als een acute longembolie vanwege het ontbreken van eerdere beeldvorming.

Toegewijde CTEPH-opvolgalgoritmes zijn cruciaal voor een effectieve en tijdige identificatie van de 2.7% met CTEPH onder alle patiënten met een onvolledig herstel na een longembolie. Een algoritme dat is ontworpen om CTEPH vroegtijdig na een acute longembolie te identificeren is het InShape II-algoritme. Volgens dit algoritme worden patiënten met een hoge vooraf kans op de CTEPH, beoordeeld middels de CTEPH voorspellingsscore, of symptomen suggestief voor CTEPH, onderworpen aan de "CTEPH uitsluitcriteria". Deze uitsluitcriteria bestaan uit een elektrocardiogram (ECG) om te kijken naar tekenen van RV-overbelasting en een

NTproBNP-meting. CTEPH wordt uitgesloten als beide normaal zijn; anders is een echocardiografie noodzakelijk. Echter, het InShape II-algoritme kan mogelijk verder worden verbeterd op het gebied van efficiëntie en veiligheid. Daarom hebben we in **Hoofdstuk 8** de ECG-afgeleide 'ventriculaire gradiënt geoptimaliseerd voor RV-overbelasting' (VG-RVPO) geëvalueerd als een nieuw uitsluitcriterium binnen het InShape II-algoritme. Het bleek dat de VG-RVPO geen diagnostische waarde toevoegde, noch als op zichzelf staande test voor het detecteren van CTEPH na een acute longembolie, noch als onderdeel van het InShape II-algoritme. Dit kan worden verklaard door het feit dat RV-overbelasting ook kan optreden bij niet-CTEPH acute longembolie patiënten, en dat tijdelijke verbetering van RV-functie kan optreden bij acute-op-chronische CTEPH na het starten van antistollingsmiddelen.

Mogelijk kunnen CT-pulmonale angiografie-scans (CTPA), welke gemaakt worden om de acute longembolie te diagnosticeren, ook gebruikt worden in de detectie van CTEPH, omdat bepaalde kenmerken op CTPA-scans sterk voorspellend zijn voor een toekomstige diagnose van CTEPH. Dit sluit aan bij het principe van acute-op-chronische CTEPH. Aangezien CTPA-scans routinematig beschikbaar zijn voor acute longembolie patiënten, kan het gebruik maken van gedetailleerde CTPA-beoordelingen mogelijk de prestaties van het InShape II-algoritme verbeteren. In **Hoofdstuk 9** hebben we 12 hypothetische algoritmes ontworpen waarin gedetailleerde CTPA-beoordeling werden opgenomen in het InShape II-algoritme, als een aanvullende test of door een van de bestaande onderdelen te vervangen. Het best presterende algoritme was het InShape IV-algoritme. Dit algoritme stelt voor om echocardiografie alleen uit te voeren bij patiënten met 1) een positieve index longembolie CTPA-beoordeling (≥3/6 tekenen van chronische ziekte) of 2) symptomatische patiënten met tekenen van RV-overbelasting op ECG of abnormale NTproBNP-waarden. CTEPH wordt bij alle andere patiënten als afwezig beschouwd zonder verdere testen. Vergeleken met InShape II verbeterde InShape IV de foutmarge: een CTEPH-patiënt waarbij CTEPH als afwezig werd beschouwd door InShape II, had een echocardiografie-indicatie in InShape IV. Daarnaast heeft InShape IV verschillende belangrijke verbeteringen ten opzichte van InShape II. Ten eerste vervangt de CTPA-beoordeling in InShape IV de CTEPH-voorspellingsscore in InShape II. De voorspellingsscore bevatte factoren zonder een voor de hand liggende pathofysiologische link met CTEPH, zoals diabetes, waardoor het elimineren van de voorspellingsscore resulteert in een betere afstemming op de pathofysiologie van acute-op-chronische CTEPH.

Ten tweede kan de CTPA-beoordeling binnen InShape IV gemakkelijk worden toegepast door minder ervaren radiologen, aangezien het gebruik maakt van de aanwezigheid van ≥3/6 tekenen van chronische ziekte. Dit vermindert de subjectiviteit en verbetert de toepasbaarheid in verschillende klinische omstandigheden. Ten derde maakt het algoritme in InShape IV het mogelijk dat CTEPH-patiënten direct een echocardiografie ondergaan zonder eerst een ECG of NTproBNP-test uit te voeren. In InShape II moest 43% van de patiënten een ECG en NTproBNP-test ondergaan, terwijl dit maar 23% was in InShape IV, wat een mogelijke kostenvermindering met zich meebrengt. Bovendien kan door efficiënt patiënten te identificeren die echocardiografie nodig hebben, verwijzingen naar expertcentra voor PH worden versneld, waardoor diagnostische vertragingen worden geminimaliseerd en de uitkomsten mogelijk verbeteren.

Of InShape IV werkelijk leidt tot een kosteneffectieve aanpak, werd vervolgens geëvalueerd in **Hoofdstuk 10**. Deze studie omvatte 11 verschillende longembolie opvolgalgoritmes en één hypothetisch scenario zonder een toegewijd CTEPH-opvolgalgoritme, die werden geanalyseerd met behulp van een Markov-model. De studie had twee belangrijke resultaten. Ten eerste heeft het integreren van een van de algoritmes om CTEPH te detecteren de voorkeur boven het niet uitvoeren van een toegewijd opvolgalgoritme, aangezien de algoritmes resulteerde in een toename van 0.89-1.2 kwaliteit aangepaste levensjaren (*quality adjusted life years*; QALY) tegen een incrementele kosteneffectiviteitsratio (*incremental cost-effectiveness ratio*; ICER) van €25.700-€46.300 per QALY. Dit ligt allemaal onder de Nederlandse drempel van €50.000 per QALY, wat aangeeft dat het een kosteneffectieve aanpak is. Ten tweede bleek het InShape IV-algoritme het meest kosteneffectief, met een ICER van €26.700 per QALY. Op basis van deze resultaten concludeerden we dat het implementeren van een toegewijd opvolgalgoritme kosteneffectief is in vergelijking met het niet uitvoeren van een dergelijk algoritme. De keuze voor een algoritme moet echter afhangen van de lokale mogelijkheden en organisatie van de zorg. Als er geen specifieke voorkeuren zijn, kan het InShape IV-algoritme worden beschouwd als de optimale strategie, aangezien het de meest kosteneffectieve optie is.

In **Hoofdstuk 11** gingen we verder in op waarom sommige acute longembolie patiënten niet volledig herstellen. Via een systematische review en meta-analyse onderzochten we het verband tussen persisterende pulmonaire perfusie-defecten of resterende vasculaire obstructie en functioneel herstel na longembolie. Wij toonden aan dat 34% van de acute longembolie patiënten deze afwijkingen had

op beeldvorming tijdens de opvolging. Van hen rapporteerde 48% aanhoudende symptomen, vergeleken met 34% van de patiënten met normale beeldvorming. Ondanks een matige associatie (odds ratio van 2.2) tussen aanhoudende defecten en aanhoudende symptomen, achten wij causaliteit niet bewezen. Opmerkelijk is dat de helft van de patiënten met defecten volledig herstelde en een aanzienlijk deel zonder defecten ook symptomen rapporteerde. Dit suggereert dat niet alle PPES verklaard kan worden door persisterende trombose. Daarnaast werden patiënten met CTEPH niet uitgezonderd van studiedeelname, wat mogelijk de associatie tussen defecten en symptomen bij niet-CTEPH-patiënten overschat. Ook vonden we geen correlatie tussen aanhoudende defecten en een veranderde hemodynamiek (gemeten met CPET), wat vragen oproept over een mogelijke causale link met symptomen. Onze bevindingen ondersteunen de huidige richtlijnen die voorstellen om alleen beeldvorming uit te voeren in gevallen met tekenen van CTEPH op echocardiografie of tekenen van CTEPD zonder PH op CPET. Het routinematig herhalen van beeldvorming voor patiënten met een longembolie gedurende poliklinische controles wordt daarom afgeraden.

In **Hoofdstuk 12** verlegden we onze focus naar het behandelen van CTEPH, waarbij we de diagnostische nauwkeurigheid van de VG-RVPO evalueerden bij het detecteren van resterende PH na pulmonale endarteriëctomie (PEA). We analyseerden gegevens van 66 CTEPH-patiënten die een PEA hadden ondergaan, waarbij we de diagnostische prestaties van de VG-RVPO beoordeelden voor de detectie van resterende PH. De resultaten toonden aan dat er correlaties waren pre-PEA tussen Δ VG-RVPO en de gemiddelde pulmonale arteriële druk of de geïndexeerde RV-massa gemeten op cardiale MRI. Echter, het gebruik maken van alleen de VG-RVPO voor het detecteren van resterende PH had beperkingen; 36% van de patiënten met resterende PH had een normale VG-RVPO en 7% toonde verbetering in de tijd. Dit suggereert dat het gebruiken van alleen de VG-RVPO mogelijk een aanzienlijk aantal gevallen verkeerd classificeert. Aanhoudende RV-hypertrofie en blijvende hartafwijkingen na PEA ondanks normalisatie van de pulmonaal drukken kunnen bijdragen aan de suboptimale prestaties van VG-RVPO. Concluderend heeft de VG-RVPO beperkte bruikbaarheid in deze context.

Toekomstperspectief

Dit proefschrift bespreekt de behandeling van een longembolie tijdens de acute episode, evenals de detectie van chronische complicaties. Beslissingen die tijdens de acute fase worden genomen, kunnen invloed hebben op het risico van

chronische complicaties. Voor patiënten na een longembolie kan de angst voor herhaling, samen met het instinct of zelfs medisch advies om fysieke activiteit te vermijden, leiden tot inactiviteit en deconditionering. Dit kan uiteindelijk resulteren in langdurige beperkingen. Het geven van duidelijke en adequate begeleiding over het veilig hervatten van fysieke activiteit tijdens de acute fase kan helpen deze negatieve cyclus te doorbreken. Gezien de grote hoeveelheid informatie die patiënten in deze fase ontvangen, zijn zowel de inhoud als de wijze van het overbrengen van deze informatie cruciaal voor de patiënttevredenheid en de uitkomsten na een longembolie. Daarom is effectieve communicatie in de acute fase essentieel. De Wetenschappelijke en Standaardisatiecommissie (SSC) voor Voorspellende en Diagnostische Variabelen bij Trombotische Ziekten van de Internationale Vereniging voor Trombose en Hemostase (ISTH) ontwikkelt een informatiewijzer om artsen te begeleiden bij de belangrijkste onderwerpen die zij met patiënten moeten bespreken na een acute longembolie. Hoewel dit initiatief een belangrijke eerste stap is in het verbeteren van de communicatie met patiënten, moet toekomstig onderzoek de impact hiervan in de dagelijkse praktijk evalueren. Een voor- en na-implementatiestudie zou de invloed van deze informatiewijzer op de patiënttevredenheid en de incidentie van PPES kunnen evalueren.

Longembolie specifieke revalidatie of begeleiding op afstand door een fysiotherapeut kan ook bijdragen aan het herstel na een longembolie. Wat hier echter nog ontbreekt is een gerandomiseerde studie over de veiligheid en effectiviteit van dergelijke programma's kort na de diagnose bij een geselecteerde groep patiënten. Bovendien is het onduidelijk of patiënten met abnormale cardiovasculaire beperkingen kort na de diagnose tijdens de opvolging nog steeds beperkingen en symptomen ervaren. Ook blijft de impact van trainingsprogramma's op PPES onzeker. De lopende PE@HOME-studie onderzoekt deze vraagstukken en zal hopelijk verdere duidelijkheid verschaffen.

Tot slot is er een betere systematische opvolging voor patiënten met een longembolie nodig. Ondanks dat er verschillende algoritmes om CTEPH te detecteren bestaan, duurt het nog steeds gemiddeld 15 maanden voordat een acute longembolie patiënt met CTEPH wordt gediagnosticeerd. Dit komt door onduidelijke en niet gestandaardiseerde opvolgingsprocedures voor acute longembolieën, inclusief het ontbreken van een allesomvattend algoritme dat alle PPES-entiteiten omvat. In **Hoofdstuk 5** hebben we een algoritme voorgesteld inclusief CPET om oude longembolie resten te detecteren die symptomen

veroorzaakt. Hoewel CPET uitgebreid is en er richtlijnen zijn voor het interpreteren van de resultaten, ontbreken er duidelijke CPET-algoritmes om patronen van PPES te identificeren en daaropvolgende behandelstrategieën vast te stellen. Bij de evaluatie van CPET worden eerst de voorspelde waarden voor CPET-parameters berekend, waarbij afwijkingen worden gedefinieerd als waarden onder of boven een bepaald percentage van deze voorspelde waarde. Er zijn verschillende pogingen gedaan voor de standaardisatie van normale waarden en interpretatiestrategieën. Er is echter geen algemene consensus over het berekenen van voorspelde waarden en streefwaarden. De SHIP-cohortstudie, waarin 616 gezonde individuen werden onderworpen aan CPET, had als doel verbeterde voorspellende waarden te ontwikkelen. Echter, asymptomatische post-longembolie-patiënten zonder CTEPD kunnen mogelijk niet als gezond worden geclassificeerd. Hierdoor kunnen andere referentiewaarden van toepassing zijn. Bovendien kan een verminderde inspanning bij CPET na longembolie het gevolg zijn van verschillende pathofysiologische factoren, waaronder suboptimale inspanning. Het onderscheiden van deze oorzaken is cruciaal maar ook uitdagend bij gebrek aan een gouden standaard voor het definiëren van maximale inspanning.

Toekomstig onderzoek moeten deze kwesties verduidelijken en betere richtlijnen bieden voor het interpreteren van CPET-resultaten voor aanhoudende symptomen na longembolie. Een systematische review die alle CPET-testen na longembolie samenvat, zou gemiddelde waarden van CPET-variabelen in CTEPH, CTEPD zonder PH, symptomatische en asymptomatische post-longembolie-patiënten kunnen verduidelijken. Een IPDMA zou vervolgens ‘normale waarden’ voor deze populaties kunnen vaststellen op basis van gemiddelde waarden en de verdeling binnen de asymptomatische post-longembolie-groep. De diagnostische nauwkeurigheid van deze variabelen en afkapwaarden kunnen vervolgens worden getest door verschillende groepen te vergelijken. Deze bevindingen kunnen een Delphi-studie onder CPET- en longembolie experts informeren om te bepalen: (1) hoe de voorspelde waarden het beste kunnen worden bepaald, (2) de acceptabele referentiewaarden, (3) de combinatie van abnormale variabelen die een ‘abnormale’ CPET aanduiden, en (4) de vervolgstappen voor een ‘abnormale’ CPET, zoals het uitvoeren van een CTPA. Deze inspanningen kunnen mogelijk het bewustzijn van PPES vergroten en de nazorg voor longembolie patiënten verbeteren.

A

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Klok FA, … Luijten D, et al. Optimising communication to patients with venous thromboembolism: development of a provider toolkit. Lancet Haematol. 2025 Jun;12(6):e411-e412.

Mishra S, … Luijten D, et al. An assessment of evidence to inform best practice for the communication of acute venous thromboembolism diagnosis: a scoping review. Res Pract Thromb Haemost. 2025 Mar 23;9(3):102835.

Luijten D, van Es J, Abbink JJ, et al.Cardiopulmonary exercise testing in dyspnoeic persons with a recent acute pulmonary embolism. CHEST Pulmonary. 2025 March 18; Epub ahead of print

Luijten D, Rodenburg T, Bogaard HJ, et al. The value of vector ECG in predicting residual pulmonary hypertension in CTEPH patients after pulmonary endarterectomy. PLoS One. 2025 Feb 26;20(2):e0317826.

Luijten D, van den Hout WB, Boon GJAM, et al. Cost-effectiveness of follow-up algorithms for chronic thromboembolic pulmonary hypertension in pulmonary embolism survivors. ERJ Open Res. 2025 Jan 13;11(1):00575-2024.

Luijten D, Abbel D, Cannegieter SC, et al. Risk assessment and management strategies in older patients with acute pulmonary embolism. J Thromb Haemost. 2025 Feb;23(2):588-599.

Klok FA, … Luijten D, et al. Incidence and clinical course of chronic thromboembolic pulmonary hypertension with or without a history of venous thromboembolism in Denmark. J Thromb Haemost. 2024 Dec;22(12):3562-3571

Cimini CA & Luijten D, Barco S et al. Pulmonary perfusion defects or residual vascular obstruction and persistent symptoms after pulmonary embolism: a systematic review and meta-analysis. ERJ Open Res. 2024 Jul 29;10(4):01010-2023

Luijten D, Douillet D, Luijken K, et al. Safety of treating acute pulmonary embolism at home: an individual patient data meta-analysis. Eur Heart J. 2024 Jul 12:ehae378.

Luijten D, Valerio L, Boon GJAM, et al.. Optimisation of detecting chronic thromboembolic pulmonary hypertension in acute pulmonary embolism survivors: the InShape IV study. Eur Respir J. 2024 Jun 27:2400544.

Burggraaf-van Delft JLI, … Luijten D at al. Tailored anticoagulant treatment after a first venous thromboembolism: protocol of the Leiden Thrombosis Recurrence Risk Prevention (L-TRRiP) study - cohort-based randomised controlled trial. BMJ Open. 2024 Mar 23;14(3):e078676.

Casey SD, … Luijten D, et al. Addressing the rising trend of high-risk pulmonary embolism mortality: Clinical and research priorities. Acad Emerg Med. 2024 Mar;31(3):288-292.

Luijten D, Talerico R, Barco S, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. Eur Respir J. 2023 Jul 7;62(1):2300449.

Luijten D, Klok FA, van Mens TE, Huisman MV. Response to letter to the editor: "Clinical controversies in the management of acute pulmonary embolism: evaluation of four important but controversial aspects of acute pulmonary embolism management that are still subject of debate and research". Expert Rev Respir Med. 2023 May 19:1-2.

Luijten D, Klok FA, van Mens TE, Huisman MV. Clinical controversies in the management of acute pulmonary embolism: evaluation of four important but controversial aspects of acute pulmonary embolism management that are still subject of debate and research. Expert Rev Respir Med. 2023 Mar;17(3):181-189.

Abedian Kalkhoran ... Luijten D, et al. A text-mining approach to study the real-world effectiveness and potentially fatal immune-related adverse events of PD-1 and PD-L1 inhibitors in older patients with stage III/IV non-small cell lung cancer. BMC Cancer. 2023 Mar 14;23(1):247.

Luijten D, Meijer FMM, Boon GJAM, et al. Diagnostic efficacy of ECG-derived ventricular gradient for the detection of chronic thromboembolic pulmonary hypertension in patients with acute pulmonary embolism. J Electrocardiol. 2022 Sep-Oct;74:94-100

Luijten D, de Jong CMM, Ninaber MK, Spruit MA, Huisman MV, Klok FA. Post-Pulmonary Embolism Syndrome and Functional Outcomes after Acute Pulmonary Embolism. Semin Thromb Hemost. 2022 Jul 12.

Luijten D, de Jong CMM, Klok FA. Post Pulmonary Embolism Syndrome. Arch Bronconeumol. 2022 Jul;58(7):533-53

Luijten D, Vreeswijk MPG, Boere I and Kroep J. (2018) Current and Future Developments of PARP Inhibitors in the Treatment of Breast and Ovarian Cancer. J Cancer Sci Ther 10: 178-189.

Appendices Dankwoord

De afgelopen jaren hebben vele fantastische mensen onderdeel uitgemaakt van mijn leven, en door hun directe en indirecte steun is dit proefschrift tot stand gekomen. Hiervoor wil ik iedereen enorm bedanken. Graag noem ik een aantal personen in het bijzonder.

Allereerst wil ik alle patienten bedanken voor hun deelname in de onderzoeken.

Prof. dr. F.A. Klok, Erik, jouw kennis en enthousiasme voor de wetenschap en vasculaire geneeskunde zijn inspirerend. Als ik een fractie hiervan kan meenemen in mijn verdere carriere, denk ik dat dit me ver kan brengen. Bedankt voor je begeleiding de afgelopen jaren en voor de kansen welke je me hebt aageboden om me te ontwikkelen tot arts en onderzoeker.

Prof. dr. M.V. Huisman en dr. M. Ninaber, Menno en Maarten, ook jullie wil ik bedanken voor de begelding de afgelopen jaren. Menno, jouw ervaring in de wetenschap is bewonderenswaardig, bedankt dat ik onderdeel van deze succesvolle onderzoeksgroep mocht zijn. Maarten, bedankt voor de kansen binnen de longgeneeksunde, ik kijk uit naar de rest van de opleiding tot longarts.

Daarnaast wil ik alle onderzoekers bedanken met wie ik heb mogen samenwerken binnen de PE@HOME studie en in het bijzonder Josien, Coen, Anton, Ivo, Marjo, Marieke, Yvonne, Mart, Annemarie, Ronald, Bas, Saskia, Marion, Rosalie, Ties, Robert en Dorianne. Dank voor de fijne samenwerking de afgelopen jaren, ik heb veel van jullie mogen leren.

Ook zou ik alle collega's op C7 willen bedanken inclusief alle basale onderzoekers, epidemiologen en klinici van de vasculaire. Alhoewel ik niet bij de basale onderzoekers of epidemiologen op kantoor heb gewerkt, ben ik erg blij dat ik zoveel met jullie heb mogen samenwerken. Alle lunchpauzes/koffies/reizen/congressen/uitjes/borrels zijn een verreiking geweest van mijn promotie. In het specifiek de klinische stollers: Milou, Fleur, Cindy, Emily, Sabine, Linde, Jurjen, Sophie, Jamilla en Rosa. Het was fantatisch deze ervaringen met jullie te mogen delen. Door jullie is het een onvergetenlijke tijd geworden.

Ik wil al mijn lieve vrienden zowel uit Leiden/Den Haag als uit Boxtel en omgeving bedanken voor hun vriendschap, gezelligheid en de fijne momenten die we samen hebben gehad. Er is meer in het leven dan alleen werk en ik ben gelukkig dat ik een leven heb met zoveel bijzondere mensen om mij heen die mijn leven verreiken.

Lief rijtje, wat ben ik blij dat ik jullie heb leren kennen. Leiden werd thuis en ik kreeg er vrienden bij die ik als familie zie. Bedankt dat jullie mijn vriendinnen zijn en al mijn verhalen over de perikelen van promoveren hebben willen aanhoren de afgelopen jaren. Ik weet zeker dat jullie de rest van mijn leven een belangrijke rol gaan spelen.

Lieve schoonfamilie: Angeliek en Dick. Bij jullie thuis is het warm en gezellig, niet alleen door de inrichting, maar vooral door jullie persoonlijkheden. Ook jullie steun de afgelopen jaren en oprechte interesse in al mijn medische verhalen heb ik enorm gewaardeerd.

Lieve pap en mam, ik ben er van overtuigd dat de kansen die je in het leven krijgt worden beinvloed door waar je wieg staat en wat prijs mezelf ik gelukkig dat mijn wieg op de Kuiper stond en jullie mijn ouders zijn. Jullie staan altijd voor me klaar en jullie harde werk is een voorbeeld voor me. Bedankt voor alles, niet alleen tijdens deze promotie tijd, maar ook alle jaren ervoor. Ik kijk uit naar de zomers waar we samen kunnen genieten in de Bourgogne met lekker eten maar vooral met heel fijn gezelschap.

Lieve Cindy en Lotte, bedankt dat jullie mijn paranimfen wilde zijn en een bijzondere rol wilde spelen deze dag. Cin, als ik terug denk aan onze promotie tijd kan ik alleenmaar glimlachen, van de feestjes, tot de gedeelde liefde voor Froukje, tot die keer dat ik onze wekker veelste vroeg had gezet. Bedankt voor alle gezelligheid en steun, ik mis de tijden van de bureaus tegenover elkaar. Lot, bedankt dat ik altijd bij je terrecht kan voor advies of gewoon om te vertellen wat ik die dag heb meegemaakt. Ik waardeer je enorm en ben heel trots dat je mijn zus bent, hoe je er altijd voor ons gezin bent, je werkt als een girlboss en hoe je een samen met Niels fantastische ouders bent voor de lieve Fiene.

Tot slot, lieve Nick. Je maakt me soms gek, maar ik ben zo ongelofelijk gek op jou. Zonder jouw steun was ik dit avontuur niet aangegaan. Bedankt voor alles, meer hoeft ik niet te zeggen. Ik kijk uit naar alle mooie momenten die nog gaan komen, want met jou is het leven zo veel leuker.

Appendices Curriculum vitae

Dieuwke Luijten werd geboren op 18 augustus 1996 te ‘s-Hertogenbosch. In 2014 behaalde zij haar Atheneum diploma aan het Jacob-Roelandslyceum te Boxtel. In datzelfde jaar startte zij met de studie Geneeskunde aan de Universiteit Leiden. Tijdens haar bachelor behaalde ze gelijktijdig haar honours-diploma waarvoor zij vakken van biomedische wetenschappen volgde. De eerste wetenschappelijke ervaringen met wetenschappelijk onderzoek werden ook opgedaan tijdens het honours-traject waar ze een review schreef voor de medische oncologie over borst kanker.

Na afronden van haar bachelor heeft ze buitenland ervaring opgedaan door op exchange naar Caen (Frankrijk) te gaan, waar zij een maand als coassistent op de oncologie afdeling heeft gewerkt. In 2018 startte ze aan haar coschappen waar ze als keuzecoschappen Radiologie in het Haaglanden Medisch Centrum en Geriatrie in het Laurens Antonius Binnenweg te Rotterdam heeft gevolgd. Afrondend deed ze haar semiarts stage en wetenschapsstage bij de Longgeneeskunde in het Haga ziekenhuis. In 2021 behaalde zij het artsenexamen, waarna zij werkzaam was als art-assistent niet in opleiding tot specialis op de afdeling longgeneeskunde in het Haga ziekenhuis.

Mid 2021 begon zij aan wetenschappelijk onderzoek op de afdeling Trombose en Hemostase van het Leids Universitair Medisch Centrum onder begeleiding van prof. dr. F.A. Klok, prof. dr. M.V. Huisman en dr. M. Ninaber, waarvan de resultaten zijn beschreven in dit proefschrift.

Sinds augustus 2024 is zij in opleiding tot longarts in het Leids Universitair Medisch Centrum.