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

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Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study

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ABSTRACT

Background: The current diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE) is unacceptably long causing loss of quality-adjusted life years and excess mortality. Validated screening strategies for early CTEPH diagnosis are lacking. Echocardiographic screening among all PE survivors is associated with overdiagnosis and cost-ineffectiveness. We aimed to validate a simple screening strategy for excluding CTEPH early after acute PE limiting the number of performed echocardiograms.

Methods: In this prospective, international, multicentre management study, consecutive patients were managed according to a screening algorithm starting three months after acute PE to determine whether echocardiographic evaluation of PH was indicated. If the 'CTEPH prediction score' indicated high pre-test probability or matching symptoms were present, the 'CTEPH rule-out criteria' were applied, consisting of ECG reading and NT-proBNP. Only if these results could not rule out possible PH, patients were referred for echocardiography.

Results: 424 patients were included. Based on the algorithm, CTEPH was considered absent in 343 (81%) patients, leaving 81 patients (19%) referred for echocardiography. During two-year follow-up, one patient in whom echocardiography was deemed unnecessary by the algorithm was diagnosed with CTEPH, reflecting an algorithm failure rate of 0.29% (95%CI 0-1.6%). Overall CTEPH incidence was 3.1% (13/424), of whom 10 patients were diagnosed within 4 months after the PE presentation.

Conclusions: The InShape II algorithm accurately excluded CTEPH, without the need for echocardiography in the overall majority of patients. CTEPH was identified early after acute PE, resulting in a substantially shorter diagnostic delay than in current practice.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by persistent obstruction of the pulmonary arteries by organized fibrotic thrombi with secondary microvascular remodelling, leading to increased pulmonary vascular resistance, pulmonary hypertension (PH), right heart failure and ultimately, if proper and timely treatment is not initiated, death.[1-5] While this rare disease is the most feared long-term complication of acute pulmonary embolism (PE), its early diagnosis remains an important clinical challenge.[6,7] Indeed, the current diagnostic delay of CTEPH after PE is unacceptably long exceeding 1 year, causing loss of quality-adjusted life years and excess mortality.[8-11]

Until recently, there were no clear recommendations for specific follow-up programs after PE for early detection of CTEPH.[12,13] Subjecting all acute PE survivors to transthoracic echocardiography, which is the recommended screening tool for suspected PH, has been shown to have a low diagnostic yield, results in overdiagnosis and is cost-ineffective.[14] An active screening algorithm was suggested for the first time in the 2019 ESC/ERS guidelines on PE, and involved the recommendation to apply echocardiography 3 to 6 months after PE diagnosis in all patients with persistent dyspnoea and/or predisposing conditions for CTEPH.[15] Given the fact that 50% of PE patients report persistent dyspnoea to some degree, a considerable number of patients will require echocardiography according to this guideline, and sufficient resources may not be available around the globe.[16-18]

We have developed a non-invasive screening algorithm aimed at timely exclusion of CTEPH in patients recently diagnosed with PE while limiting the number of required echocardiograms. The stepwise approach of the algorithm starts with application of the 'CTEPH prediction score'. In case this score indicates a high pre-test probability of CTEPH, or if symptoms suggestive of CTEPH are present, ECG reading and an NT-proBNP assessment are performed as part of the 'CTEPH rule-out criteria'.[19-21] Only if these criteria cannot rule out possible PH, patients are referred for echocardiography, and further diagnostic testing if necessary. Retrospective evaluation among CTEPH patients revealed that 91% of these patients would indeed have been identified correctly and early by the screening algorithm.[22] In the InShape II study, we aimed to prospectively validate the safety of this algorithm for excluding CTEPH early after acute PE.

METHODS

Study design and patients

The InShape II study was a prospective, international, multicentre management study comprising consecutive patients diagnosed with acute PE in five academic hospitals and one teaching hospital in the Netherlands, Belgium and Poland (NCT02555137). All participating hospitals have a dedicated and expert outpatient clinic for PH care. Patients were eligible for inclusion if they 1) were aged 18 years or older; 2) had a CT pulmonary angiography (CTPA) proven diagnosis of first or recurrent symptomatic acute PE; 3) and had been treated with therapeutically dosed anticoagulant therapy for at least three months according to current guidelines. Exclusion criteria were known CTEPH or PH, NYHA class III or IV chronic heart failure (echocardiographically confirmed left ventricular systolic or diastolic dysfunction), or severe renal failure (eGFR <15 ml/min or renal replacement therapy). Also, patients with medical or psychological conditions not permitting study completion, non-compliance or inability to adhere to treatment or to follow-up visits, were excluded. The study protocol was approved by all institutional review boards of the participating hospitals and all patients provided written informed consent before the start of any study procedure.

Procedures

Baseline study procedures

All study participants were managed according to the predefined screening algorithm (**Figure 1; Appendix A**), initiated during patient's routine visit to the outpatient clinic three months after their diagnosis of acute PE. At that time, pre-test probability of CTEPH was assessed by calculating the 'CTEPH prediction score' (**Appendix B**) and symptoms suggestive of CTEPH were evaluated (i.e. dyspnoea on exertion, oedema, newly developed palpitations, syncope or chest pain).[19] Only patients with a high pre-test probability (>6 points) or those with symptoms that might be associated with CTEPH were subjected to the CTEPH rule-out criteria, i.e. assessment of the presence of any of the 3 ECG criteria of right ventricular (RV) pressure overload, or an abnormal age- and gender dependent NT-proBNP level (**Appendix C**).[20] If at least one of the CTEPH rule-out criteria could not preclude the presence of RV pressure overload according to the judgement of the local investigator, patients were referred for transthoracic echocardiography, performed according to the 2015 ESC/ERS guidelines on PH.[12] As such, patients were divided into low, intermediate or high echocardiographic probability of PH. CTEPH was considered to be ruled out in patients with low probability of PH. Those with intermediate or high probability of PH were referred for further diagnostic work-up of suspected CTEPH following the standard of care. A diagnosis of

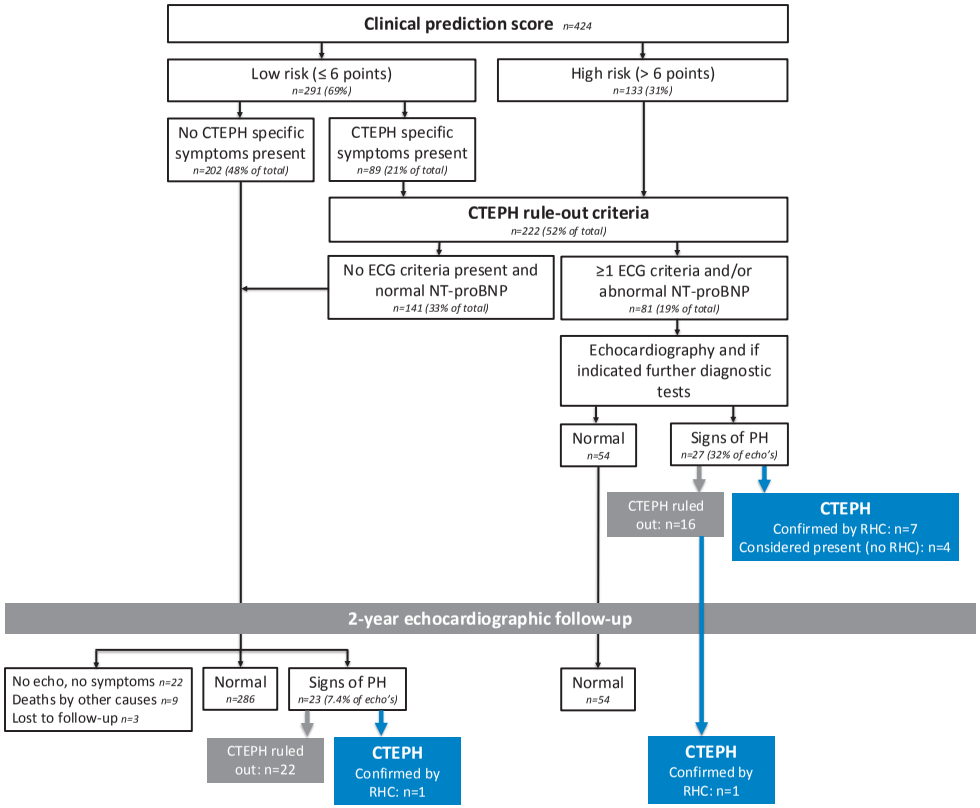

Figure 1: Results of 2-year follow-up after completing the InShape II study algorithm

Note: The ECG criteria of RV pressure overload are: 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°. "Signs of PH" relate to echocardiographically determined intermediate or high probability of PH according to the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH'.[12] *Abbreviations:* ECG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; RHC, right heart catheterization; RV, right ventricular.

CTEPH was established in a CTEPH expertise centre if strict diagnostic criteria, obtained after ≥3 months of adequate therapeutic anticoagulation, were met: 1) ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning; 2) mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest measured by invasive right heart catheterization (RHC); 3) pulmonary artery wedge pressure ≤15 mmHg.[12] All results were discussed by an independent interdisciplinary working group of PH specialists to ensure optimal diagnostic management. If CTEPH was confirmed, they received state-of-the-art treatment, preferably pulmonary endarterectomy (PEA). Management of confirmed CTEPH was not part of this study protocol.

Study procedures during 2-year follow-up

All patients without confirmed CTEPH were followed for two years after the index PE diagnosis. During this follow-up period, routine medical care was continued by the treating physician, allowing diagnostic tests if deemed necessary. At two years, patients were subjected to a follow-up echocardiography to evaluate the presence of CTEPH. As with the baseline echocardiogram, further CTEPH-targeted diagnostic tests were performed in case of intermediate or high probability of PH.

Objectives

The primary objective was to determine the failure rate of the screening algorithm, defined as the 2-year incidence of confirmed CTEPH in PE patients in whom echocardiography was deemed unnecessary by the algorithm at baseline. Main secondary objectives of the study were to evaluate 1) the incidence of CTEPH in the studied population; and 2) the feasibility of the screening algorithm (i.e. both the number of necessary echocardiograms at baseline and their results including false positive and incidental findings). A false positive echocardiogram was defined as indicating intermediate or high probability of PH, that was not confirmed upon RHC.

Statistical analysis

The sample size calculation was based on the assumption that the point estimate of the incidence of CTEPH two years after the diagnosis of acute PE in patients that do not need referral for echocardiography according to the screening algorithm is ≤1.0%, which represents a sensitivity ≥92% assuming a 4.0% CTEPH incidence.[6,23] Accordingly, we determined that a sample of 268 patients would provide 80% power to reject the null hypothesis, i.e. that the point estimate of the CTEPH rate in those patients would be >1.0%, at an overall one-sided significance level of 0.05. Assuming that echocardiography would be avoided in 75% of patients by the screening algorithm, and taking a 5% loss to follow-up into account, we aimed to include 375 patients.

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range (IQR). The diagnostic failure rate of the algorithm and the incidence of CTEPH was calculated with corresponding 95% confidence interval (95%CI). Feasibility was predetermined to be accomplished if 30% of patients or less would require referral for echocardiography, which is the conservative estimation of the required number of echocardiograms necessary if performed in all patients with persistent symptoms.[16,24,25] All statistical tests were performed using SPSS Statistics software (version 23.0, IBM).

RESULTS

Study patients

From February 2016 to October 2017, a total of 424 consecutive patients with a diagnosis of acute PE were included in 6 hospitals in the Netherlands, Belgium and Poland after excluding 162 patients (26%) for various reasons, in line with the predefined exclusion criteria (**Appendix D**). The baseline characteristics of the study patients are summarized in **Table 1**: 49% was male, mean age was 56 years (SD 16) and 19% had a prior history of venous thromboembolism (VTE).

Baseline study procedures

The algorithm was started at a mean of 4.3 months (SD 1.9) after the index PE diagnosis. CTEPH was considered absent in 343/424 patients (81%) without performing echocardiography. This was based on both a low CTEPH prediction score (≤6 points) and the absence of symptoms in 202 patients (48% of total), and because the rule-out criteria did not indicate presence of PH in 141 of the 222 remaining patients (33% of total; **Figure 1**). Hence, 81 patients (19% of total) were referred for echocardiography at baseline.

Follow-up study procedures

Of the 343 patients in whom CTEPH was considered absent according to the algorithm, one patient was diagnosed with CTEPH 11 months after the PE diagnosis, for a diagnostic failure rate of 0.29% (95%CI 0.05-1.6). This patient with persistent dyspnoea had no relevant medical history and a CTEPH prediction score of 3 points (**Table 2**: patient number 13). The CTEPH rule-out criteria precluded the possibility of PH. Echocardiography was eventually performed 6 months after the PE diagnosis because of persistent dyspnoea. A normal peak tricuspid regurgitation gradient (TRPG; 26 mmHg) was found, accompanied by borderline values of inferior vena cava diameter (21 mm with normal collapse at inspiration, normal <22 mm) and end-systolic right atrial

Table 1: Baseline characteristics of the included patients

	All PE patients (n=424)
Age (years, mean ±SD)	56 (16)
Male gender (n, %)	208 (49)
BMI (kg/m^2), mean ±SD)	28 (5.8)
Unprovoked PE *(n, %)*	246 (58)
High-risk PE *(n, %)*	9 (2.2)
Previous VTE (n, %)	82 (19)
Comorbidities (n, %)	
Anaemia	74 (18)
COPD / asthma	48 (11)
Active malignancy	33 (7.8)
Diabetes mellitus	32 (7.6)
Coronary artery disease	25 (5.9)
Rheumatic disease	20 (4.7)
Hypothyroidism	19 (4.5)
Interstitial lung disease	5 (1.2)
Inflammatory bowel disease	4 (0.9)
Known antiphospholipid antibodies	3 (0.7)
Major vasculitis syndromes	2 (0.5)
Prior infected pacemaker leads	1 (0.2)
Splenectomy	1 (0.2)
Anticoagulant treatment at 3-month follow-up visit (n, %)	
DOAC	302 (71)
VKA	100 (24)
LMWH	35 (8.3)

Note: 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.
Abbreviations: 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 anticoagulant. Anaemia was defined as: males <8.5 mmol/L or <13.5 g/dL; females <7.5 mmol/L or <12.0 g/dL.

area (18 cm^2, normal <19 cm^2), consistent with a 'low probability of PH' classification. The patient's progressive exertional dyspnoea over time however initiated further diagnostic tests, upon which ultimately a ventilation/perfusion (V/Q) scan performed 2 months after the echocardiography showed persistent bilateral perfusion defects in five lung segments. RHC confirmed CTEPH, although with a slightly elevated mPAP of 26 mmHg. Notably, the pulmonary vascular resistance (PVR) was normal (133 dynes·sec·cm^{-5}) as were cardiac index (3,7 L/min/m^2) and wedge pressure (13 mmHg).

Of all patients in whom CTEPH was considered absent at baseline, echocardiography with or without V/Q scan and RHC ruled out CTEPH in 308 patients at the 2-year

Table 2: Patients diagnosed with CTEPH

Baseline		**Follow-up**						**Adjudication and timing of CTEPH diagnosis (in months after index PE diagnosis)**
	Chronic thrombi and/or signs of PH present at index CTPA	*Symptoms suggestive of CTEPH present*	*CTEPH prediction score*	*CTEPH rule-out criteria*	*Echocardiography results^*	*Results of immediate further diagnostic work-up*	*Results and timing of repeat testing (in months after index PE diagnosis)*	
No. 1	Yes	Yes	11	NT-proBNP elevated, 1 ECG criterium	High probability of PH: TRPG 57	- V/Q: multiple perfusion defects - Pulmonary angiography: multiple chronic thrombi- RHC: mPAP 32, wedge 8, CO 4.0, PVR 840	*N.A.*	CTEPH confirmed by RHC after 4 mo
No. 2	Yes	Yes	11	1 ECG criterium	Intermediate probability of PH: TRPG 40	- V/Q: multiple perfusion defects - Pulmonary angiography: multiple chronic thrombi - RHC: mPAP 33, wedge 10, CO 7.8, PVR 235	*N.A.*	CTEPH confirmed by RHC after 4 mo
No. 3	Yes	Yes	11	1 ECG criterium	Intermediate probability of PH: TRPG 35, secondary signs of PH	- CTPA with perfusion images: multiple perfusion defects - RHC: mPAP 30, wedge 8, CO 8.1, PVR 193	*N.A.*	CTEPH confirmed by RHC after 14 mo
No. 4	Yes	Yes	11	1 ECG criterium	Intermediate probability of PH: TRPG 35, secondary signs of PH	- RHC: mPAP 34, wedge 12, CO 4.3, PVR 419	*N.A.*	CTEPH confirmed by RHC after 4 mo

Table 2: Patients diagnosed with CTEPH *(continued)*

Baseline		**Follow-up**						**Adjudication and timing of CTEPH diagnosis (in months after index PE diagnosis)**
	Chronic thrombi and/or signs of PH present at index CTPA	*Symptoms suggestive of CTEPH present*	*CTEPH prediction score*	*CTEPH rule-out criteria*	*Echocardiography results^*	*Results of immediate further diagnostic work-up*	*Results and timing of repeat testing (in months after index PE diagnosis)*	
No. 5	Yes	No	8	1 ECG criterium	High probability of PH: TRPG 85, secondary signs of PH, patent ductus arteriosus	- CTPA: chronic thrombi - V/Q: no clear perfusion defects - RHC: mPAP 46, wedge 12, CO 5.5, PVR 496	*N.A.*	CTEPH confirmed by RHC after 4 mo
No. 6	Yes	Yes	2	Elevated NT-proBNP	High probability of PH: TRPG 55, secondary signs of PH	- CTPA: chronic thrombi - RHC: mPAP 29, wedge 11, CO 5.6, PVR 255	*N.A.*	CTEPH confirmed by RHC after 4 mo
No. 7	Yes	Yes	11	Elevated NT-proBNP	Intermediate probability of PH: TRPG 35	- Pulmonary angiography: multiple chronic thrombi, decreased flow - RHC: mPAP 32, wedge 14, CO 5.4, PVR 317	*N.A.*	CTEPH confirmed by RHC after 4 mo
No. 8	Yes	Yes	9	Elevated NT-proBNP, 1 ECG criterium	High probability of PH: TRPG 80, secondary signs of PH	- CTPA: chronic thrombi - *RHC not performed*	*N.A.*	CTEPH considered present * after 3 mo
No. 9	No	Yes	2	Elevated NT-proBNP	Intermediate probability of PH: TRPG 35, secondary signs of PH	*Not performed*	*N.A.*	CTEPH considered present * after 3 mo

Table 2: Patients diagnosed with CTEPH *(continued)*

Baseline		**Follow-up**						**Adjudication and timing of CTEPH diagnosis (in months after index PE diagnosis)**
	Chronic thrombi and/or signs of PH present at index CTPA	*Symptoms suggestive of CTEPH present*	*CTEPH prediction score*	*CTEPH rule-out criteria*	*Echocardiography results^*	*Results of immediate further diagnostic work-up*	*Results and timing of repeat testing (in months after index PE diagnosis)*	
No. 10	No	Yes	5	Elevated NT-proBNP, 1 ECG criterium	Intermediate probability of PH: TRPG not measurable, secondary signs of PH	*Not performed*	*N.A.*	CTEPH considered present * after 4 mo
No. 11	Yes	No	8	3 ECG criteria	Intermediate probability of PH: TRPG 38, secondary signs of PH	- CTPA: chronic thrombi and signs of PH - RHC: mPAP 19, wedge 4, CO 6.3, PVR 190	- Echo at 20 mo; intermediate probability of PH: TRPG 45, secondary signs of PH - CTPA: increase in chronic thrombi and signs of PH - RHC: mPAP 33, wedge 13, CO 6.6, PVR 242	CTEPH confirmed by RHC after 26 mo
No. 12	Unknown	Yes	8	Elevated NT-proBNP, 1 ECG criterium	Intermediate probability of PH: TRPG 26, secondary signs of PH	- V/Q: multiple perfusion defects *(additional imaging tests and RHC were refused)*	- Echo at 39 mo; high probability of PH: TRPG 55, secondary signs of PH	CTEPH considered present * after 4 mo

Table 2: Patients diagnosed with CTEPH *(continued)*

Baseline		**Follow-up**						**Adjudication and timing of CTEPH diagnosis (in months after index PE diagnosis)**
	Chronic thrombi and/or signs of PH present at index CTPA	*Symptoms suggestive of CTEPH present*	*CTEPH prediction score*	*CTEPH rule-out criteria*	*Echocardiography results^*	*Results of immediate further diagnostic work-up*	*Results and timing of repeat testing (in months after index PE diagnosis)*	
No. 13	Yes	Yes	3	None	N.A.	-	- Echo at 6 mo; low probability of PH: TRPG 26 - CTPA with perfusion images: multiple perfusion defects - RHC: mPAP 26, wedge 13, CO 7.2, PVR 133	CTEPH confirmed by RHC after 11 mo

Note:

^ Secondary echocardiographic signs suggesting PH used to assess the probability of PH in addition to tricuspid regurgitation velocity measurements in the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH'. Those relate to: right ventricle/left ventricle basal diameter ratio >1.0, flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole), right ventricular outflow doppler acceleration time <105 msec and/or midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec, pulmonary artery diameter >25 mm, inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), Right atrial area (end-systole) >18 cm^2.[12]

* These patients are considered to very likely have CTEPH despite not performing a RHC because of several reasons, and are described in detail in **Table 3**.

Abbreviations: ECG, electrocardiography; CTPA, computed tomography pulmonary angiography; CO, cardiac output (displayed in L/min); IVC, inferior vena cava; mPAP, mean pulmonary artery pressure (displayed in mmHg); mo, months; N.A., not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; PH, pulmonary hypertension; PVR, pulmonary vascular resistance (displayed in dynes·sec·cm^{-5}); RA, right atrium; RHC, right heart catheterization; RV, right ventricle; TRPG, tricuspid regurgitation peak gradient (displayed in mmHg); V/Q, ventilation/perfusion scan.

follow-up visit. Nine patients died of other causes than CTEPH before the scheduled follow-up echocardiography could be performed (9/424, 2.1%; **Appendix E**), and echocardiography was not performed in 22 patients (22/424, 5.2%) for various reasons (**Appendix F**). None of these latter 22 patients had reported symptoms suggestive of CTEPH during the 2-year follow-up visit. Three patients were lost to follow-up (3/424, 0.71%). Recurrent VTE was diagnosed in 14 patients during follow-up; CTEPH was ruled out by echocardiography at the 2-year follow-up visit in all of them.

Secondary outcomes

Of the 81 patients with echocardiography performed at baseline, 27 (33%) had findings consistent with intermediate or high probability of PH. Of these, CTEPH was ruled out in 16 patients by normal RHC. CTEPH was confirmed by RHC soon after echocardiography in seven patients. In four patients, CTEPH was considered present even though an RHC could not be performed due to severe comorbidities (**Figure 1, Table 3**).

In addition to the 11 patients with CTEPH diagnosed at baseline and the patient missed by the algorithm, one more patient developed CTEPH. At baseline, the patient had an abnormal echocardiogram and V/Q scan but a normal RHC (mPAP 19 mmHg and PVR 190 dynes·sec·cm^{-5}) which proved to have progressed to CTEPH two years later (mPAP 33 mmHg and PVR 242 dynes·sec·cm^{-5}). Altogether, CTEPH was confirmed or considered present in 13 patients (**Table 2**). This accumulates to a 3.1% (95%CI 1.8-5.2) 2-year incidence of CTEPH. CTEPH was diagnosised within four months after the index PE diagnosis in ten of 13 patients (77%).

The predetermined definition of 'feasibility' of the screening algorithm was met since 19% of patients were referred for echocardiography. At baseline, 16 (20%) of all performed echocardiograms were judged false positive after RHC. Two patients (2.5%) had incidental findings (patent ductus arteriosus and diastolic dysfunction) without therapeutic consequences. During the follow-up study procedures, echocardiography was false positive in 22 patients (7.1% of all performed echocardiograms). Twelve patients (3.9%) had incidental findings: atrial fibrillation (n=1), dilated aorta (n=7), hypertrophic cardiomyopathy (n=1), dilated left atrium (n=2), and diastolic dysfunction (n=1).

DISCUSSION

The InShape II study was a prospective international single-arm management study in which we demonstrated that our simple, non-invasive screening algorithm accurately and early excluded CTEPH after acute PE, while avoiding echocardiography in 81% of patients. Importantly, the vast majority of patients developing CTEPH were diagnosed

Table 3: Details of patients considered to have CTEPH in whom RHC was not performed despite abnormal baseline echocardiogram

	Medical history	Result of baseline echocardiography	Additional imaging results	Reason for not performing RHC
No. 1	COPD GOLD IV with use of oxygen therapy with severe functional limitations	High probability of PH: ▪ TRPG 80 ▪ Secondary signs of PH	CTPA: multiple signs of RV pressure overload, chronic thrombi and severe emphysema	Died of progressive respiratory failure presumably due to CTEPH within 1 year after PE
No. 2	Sarcoma with chemotherapy treatment	High probability of PH: ▪ TRPG 35 ▪ Secondary signs of PH	N.A. (refrained from further diagnostic work-up or treatment because of progressive sarcoma)	Died of advanced sarcoma, 1.5 year after the index PE
No. 3	Ischemic cardiomyopathy	Intermediate probability of PH: ▪ TRPG not measurable ▪ Secondary signs of PH	N.A. (further diagnostic work-up was planned but declined after a carcinoma of unknown primary origin was diagnosed)	Died of carcinoma of unknown primary origin within 1.5 year after the PE
No. 4	Atrial fibrillation, hypertension	Intermediate probability of PH: ▪ TRPG 26 ▪ Secondary signs of PH	- V/Q: multiple perfusion defects - Echo at 39 mo; high probability of PH: ▪ TRPG 55 ▪ Secondary signs of PH	Patient refrained from RHC despite increase in TRPG and progressive exertional dyspnoea

Note:

‡ Secondary echocardiographic signs suggesting PH used to assess the probability of PH in addition to tricuspid regurgitation velocity measurements in the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH'.

Abbreviations: COPD, chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; GOLD, Global Initiative for Obstructive Lung Disease Criteria for COPD; N.A., not applicable; PA, pulmonary artery; PH, pulmonary hypertension; TRPG, tricuspid regurgitation peak gradient; RHC, right heart catheterization; RV, right ventricle.

within four months after the index PE diagnosis, which is substantially earlier than the 12-24 months diagnostic delay reported from current clinical practice.[9,11] The InShape II study is the first management study to successfully validate a dedicated CTEPH screening tool among PE patients.

Only one patient (failure rate 0.29%) was missed by the algorithm; echocardiography had not been performed because the CTEPH rule-out criteria did not identify signs of PH. Although the mPAP was abnormal (26 mmHg, normal <25 mmHg), meeting the criteria for CTEPH, the PVR was within normal limits (133 dynes·sec·cm^{-5}, normal <240 dynes·sec·cm^{-5}) which excludes pulmonary arterial hypertension. It is therefore questionable whether this patient actually had CTEPH. Earlier studies have indeed demonstrated that the rule-out criteria had a 90-95% sensitivity for early stage (or mild) CTEPH, in comparison with a 100% sensitivity for more severe CTEPH.[20,22] This lower sensitivity for early stage CTEPH is presumably explained by the initial adaptation of the right ventricle to increased RV afterload by enhancing its contractility and thickening the RV muscle wall ("coupling"). Since RV dilatation mostly occurs in late stages of pressure

overload ("uncoupling"), as does hypertrophy, the ECG and biomarkers of myocyte stress may remain normal in the early stages of disease. As such, echocardiography may not be a sensitive parameter to identify an early disease state either, as was the case in this patient in whom echocardiography 2 months before the final CTEPH diagnosis indicated low risk of PH.[26] Of note, two other CTEPH cases also had a normal PVR and therefore do not meet the current criteria of the updated PH definition incorporating an elevated PVR. Even so, according to the guidelines that were valid at the time of our study and that were applied in the historical literature on CTEPH to which we compare our findings, the diagnosis was correct. One could argue that the evolving definition of PH from a mPAP of 25 to 20 mmHg may further increase the number of missed cases by both the InShape II algorithm as well as routine use of echocardiography.[27] This remains to be evaluated in future studies.

The overall CTEPH incidence in our cohort was estimated to be 3.1% (95%CI 1.8-5.2%), which is in line with historical literature (3.2% in PE survivors), providing external validity to our study.[6] Importantly, RHC had not been performed in 4 cases due to clinical circumstances. For the sake of the study, we have considered these patients to have CTEPH anyway to make sure our definition of the primary outcome was as sensitive as possible. It has been argued that CTEPH may be a prevalent rather than an incident diagnosis among patients with acute PE. The main argument for this hypothesis comes from two studies demonstrating that typical radiological CTEPH characteristics often were present on the index CTPA performed to diagnose acute PE in patients diagnosed with CTEPH during follow-up.[4,28-31] Our study adds to this discussion by demonstrating that CTEPH may be either an incident or a prevalent disease in the clinical course of acute PE. In total, 10 of 13 CTEPH patients were diagnosed early after their PE diagnosis and 8 of them had signs of CTEPH on the index CTPA, which is suggestive of CTEPH appearing in disguise of acute PE. Still, CTEPH had clearly developed over time in at least one patient (**Table 2**). This emphasizes the importance of remaining vigilant for CTEPH if new-onset dyspnoea develops in the early years after an acute PE diagnosis, independent of diagnostic tests shortly after the PE.

Although the results of this study support the use of the CTEPH prediction score, we acknowledge that the score itself has limitations inherent to its derivation.[19] Because the study population used to construct the score included a limited number of patients with proven CTEPH, variables not considered causally related to CTEPH emerged as predictors -and thus score variables-, notably diabetes and thrombolysis. Considering the absence of other validated methods to assess pre-test probability of CTEPH in PE patients, this score nonetheless remains the best studied tool. A straightforward way to improve the accuracy of the CTEPH prediction score would be substituting the current CTPA RV/LV ratio assessment with more extensive CTPA evaluation for signs of CTEPH. Of note, 2 patients diagnosed with CTEPH at baseline had no symptoms, but were

'detected' by the score. This underlines the strength of combining a symptom-based with a pre-test probability based assessment in this setting and supports the 2019 ESC/ERS guideline recommendations to apply a CTEPH screening algorithm based on symptoms combined with estimation of the pre-test probability in all PE survivors.[15]

What are the clinical implications of our findings? Our study shows that dedicated follow-up of PE leads to early detection of CTEPH, which is by itself associated with better prognosis.[10,15] We provide an alternative to (but do not suggest to replace) the follow-up algorithm as proposed by the guideline which can be easily applied in several healthcare settings, including primary care. Notably, even though only 19% of patients was subjected to echocardiography at baseline, we still observed a considerable rate of false positive test results and incidental findings, emphasizing the potential overdiagnosis when echocardiography would be used as first-line screening test. This is in line with a large meta-analysis including 27 studies that performed both echocardiography and right heart catheterization, in which a suboptimal specificity of 74% (95%CI 64-81) was found.[32] The associated considerable number of false positive test results necessitates performing additional -frequently expensive and invasive- diagnostic tests that might be avoided by applying the strategy evaluated in the current study. Importantly, our algorithm was aimed at excluding CTEPH early after the PE diagnosis with optimal use of healthcare resources, but not at explaining symptoms of incomplete recovery after PE.[33] Importantly, echocardiography remains the diagnostic test of choice in patients with clinically suspected PH. Further, even if our algorithm indicates absence of CTEPH given normal rule-out criteria, echocardiography may still be indicated in symptomatic patients to evaluate the presence of other heart disease. In particular, evaluating the presence of chronic thromboembolic pulmonary disease (CTEPD) is relevant in patients with persistent dyspnoea in the course of PE, but was not covered by the algorithm. Importantly, we only focussed on CTEPH and not on CTEPD since 1) delay in diagnosing CTEPH is associated with poor outcome while this has never been shown for CTEPD, 2) 'screening' for CTEPD would involve pulmonary imaging in all symptomatic cases as well as considerable expertise that cannot be captured in a simple algorithm applicable to a wide range of healthcare settings.

Strengths of our study include the prospective design, the large study population, near complete follow-up and adjudication of suspected endpoints by expert PH teams. Performing the study across several European countries and hospital settings, using different NT-proBNP assays and reading the ECG locally after simple instruction all support external validity of our results and the wide applicability of the algorithm. Good interobserver agreement for the assessment of the prediction score and the rule-out criteria have been demonstrated in earlier studies.[19,21,22] Some limitations need to be mentioned as well, in particular the absence of echocardiographic follow-up in 5.2% of the study patients. The fact that none of these patients had developed any symptoms

suggestive of CTEPH over a 2-year period or before they died, is reassuring. Furthermore, our study lacked a control group. Hence, we cannot exactly determine to what extent the application of the algorithm would have led to an earlier CTEPH diagnosis and to potential benefits in use of healthcare resources, compared to the usual care setting.

In conclusion, the InShape II algorithm for follow-up after acute PE accurately ruled out CTEPH, while avoiding echocardiograms in 81% of PE patients. The algorithm led to a much earlier detection of CTEPH than is common in current routine practice.

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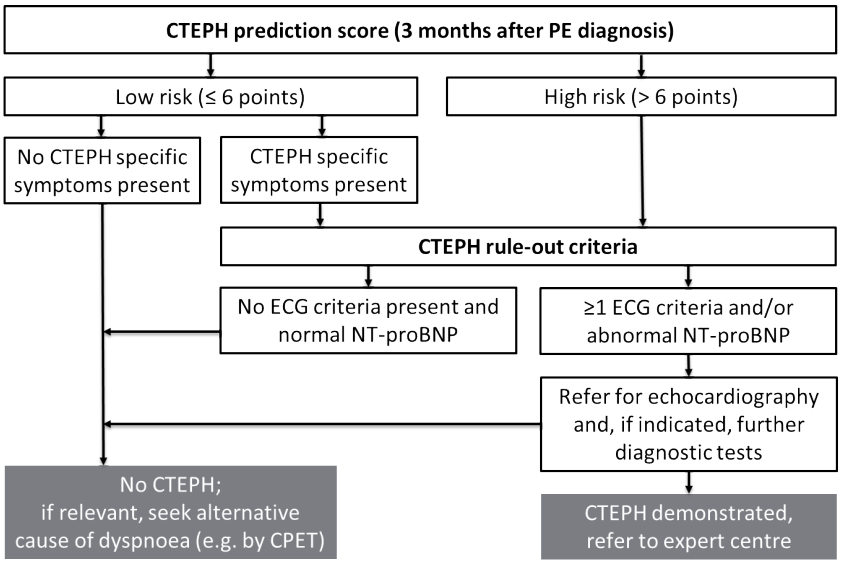
Appendix A: CTEPH screening algorithm applied three months after diagnosis of acute PE



Note: The ECG criteria of RV pressure overload are: 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°.

Abbreviations: ECG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension.

Appendix B: CTEPH prediction score[19]

CTEPH prediction score	
Unprovoked PE	+6 points
Known hypothyroidism	+3 points
Diagnostic delay > 2 weeks	+3 points
Right ventricular dysfunction on CTPA or echocardiography at the moment of PE diagnosis	+2 points
Known diabetes mellitus	-3 points
Thrombolytic therapy or embolectomy for the acute PE event	-3 points

Cut-off points: low risk (-6 to 6 points), high risk (>6 points)

Definition of right ventricular dysfunction:

RV/LV ratio ≥1.0 on CTPA or any of the following echocardiographic findings at the moment of PE diagnosis:

- RV/LV end-diastolic diameter ratio ≥ 0.9 (apical or subcostal 4-chamber view)
- RV end-diastolic diameter > 30 mm (parasternal long-axis or short-axis view)
- RV free wall hypokinesis (any view)
- Tricuspid regurgitation velocity > 2.8 m/s (apical or subcostal 4-chamber view, or the parasternal short-axis view)
- Inferior vena cava diameter > 21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)

Abbreviations: CTPA, computed tomography pulmonary angiography; RV, right ventricle; LV, left ventricle.

Appendix C: CTEPH rule-out criteria 20,21

Assessment of the presence of:

- Abnormal age- and gender-dependent NT-proBNP level (as defined by the assay's manufacturer); OR:
- Any of the following 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°.

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECG, electrocardiography; RV, right ventricular.

Appendix D: List of reasons for study exclusion

Reason	**Number of patients**
No CTPA proven acute symptomatic PE (i.e. dyspnoea and confirmed deep vein thrombosis or incidental PE)	n=53
Age under 18 years	n=3
Known CTEPH or PH	n=3
Known NYHA class III or IV chronic heart failure (i.e. echocardiographically confirmed LV systolic or diastolic dysfunction, or significant valvular lesions)	n=1
Severe renal failure (eGFR <15 ml/min) or renal replacement therapy	n=2
Medical or psychological condition that would not permit completion of the study (e.g. advanced cancer)	n=55
No informed consent	n=23
Inability to adhere to the follow-up visits	n=22

Abbreviations: LV, left ventricle; NYHA, New York Heart Association; PH, pulmonary hypertension

Appendix E: Causes of death during follow-up

	Age	Sex	Symptoms suggestive of CTEPH present	CTEPH prediction score	CTEPH rule-out criteria	Echocardiography performed somewhere during follow-up?	Comorbidities	Cause of death
No 1	81	Female	Yes	6	None present	No	Malignant mesothelioma	Parapneumonic effusion
No 2	74	Female	No	8	None present	No	-	Ileus, aspiration and pneumonia
No 3	65	Male	No	0	N.A.	No	Gastric cancer, anaemia	Progressive malignant disease with multiple metastases
No 4	69	Female	Yes	3	Elevated NT-proBNP	Yes: no signs of PH	COPD	Passed away shortly after hip replacement, presumably 'acute cardiac death'. Acute PE not established or ruled out.
No 5	70	Male	No	0	N.A.	No	-	Otherwise unexplained acute cardiac death. Acute PE not established or ruled out.
No 6	68	Male	Yes	9	None present	Yes: no signs of PH	COPD	Unknown: no signs of (new) heart, lung or infectious disease at laboratory testing or on CTA chest, echocardiography, abdominal ultrasound and spirometry shortly before he died.
No 7	78	Female	No	2	N.A.	No	-	CPR in the setting of suspected acute recurrent PE
No 8	19	Female	No	0	N.A.	No	Osteosarcoma, anaemia	Progressive malignant disease with multiple metastases
No 9	63	Male	Yes	0	None present	Yes: no signs of PH	COPD, anaemia	Acute cardiac death, echocardiography 4 months prior to death had not revealed any sign of PH. PE not established or ruled out.

Abbreviations: CPR, cardiopulmonary resuscitation; CTA, computed tomography angiography; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; N.A., not applicable; PH, pulmonary hypertension.

Appendix F: List of reasons for not performing the scheduled follow-up echocardiography at 2 years in 34 patients

Reason	Number of patients
Died before performing follow-up	n=9
Lost to follow-up	n=3
Refusal by patient	n=19
Patient no longer mentally competent	n=2
Protocol deviation	n=1