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

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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

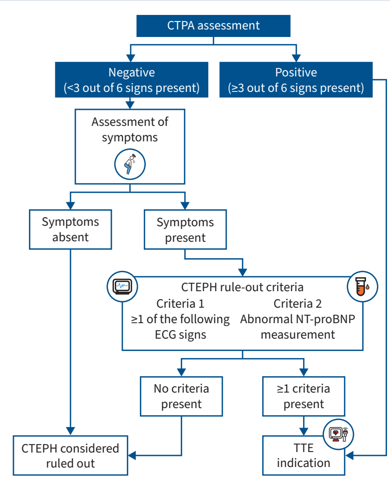
Can the InShape II algorithm be improved by adding detailed reading of the CTPA diagnosing the index PE?

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

GRAPHICAL ABSTRACT Overview of the study. CTEPH: chronic thromboembolic pulmonary hypertension; CTPA: computed tomography pulmonary angiogram; PE: pulmonary embolism; NRI: net reclassification index; NT-proBNP: N-terminal pro-brain natriuretic peptide; TTE: transthoracic echocardiogram.

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Shareable abstract (@ERSpublications)
The InShape IV algorithm, starting with CTPA reading of the index PE for 6 signs of CTEPH followed by ECG/NTproBNP assessment, performed best in detecting CTEPH in acute PE survivors with a need for TTE in 20% of patients and a failure rate of 0% https://bit.ly/459Mpwm

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Abstract

Introduction Chronic thromboembolic pulmonary hypertension (CTEPH) is often diagnosed late in acute pulmonary embolism 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 diagnosing the index pulmonary embolism.

Methods We evaluated 12 new algorithms, incorporating the CTEPH prediction score, ECG reading, N-terminal pro-brain natriuretic peptide levels and dedicated computed tomography pulmonary angiography reading, 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 pulmonary embolism patients in whom echocardiography was deemed unnecessary by the algorithm, and the overall net reclassification index compared to the InShape II algorithm.

Results The algorithm starting with computed tomography pulmonary angiography reading of the index pulmonary embolism for six signs of CTEPH, followed by ECG/N-terminal pro-brain natriuretic peptide level 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 a net reclassification index 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 a net reclassification index of +6.0%.

Conclusion Dedicated computed tomography pulmonary angiography reading of the index pulmonary embolism improved the performance of the InShape II algorithm and may improve the selection of pulmonary embolism 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 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].

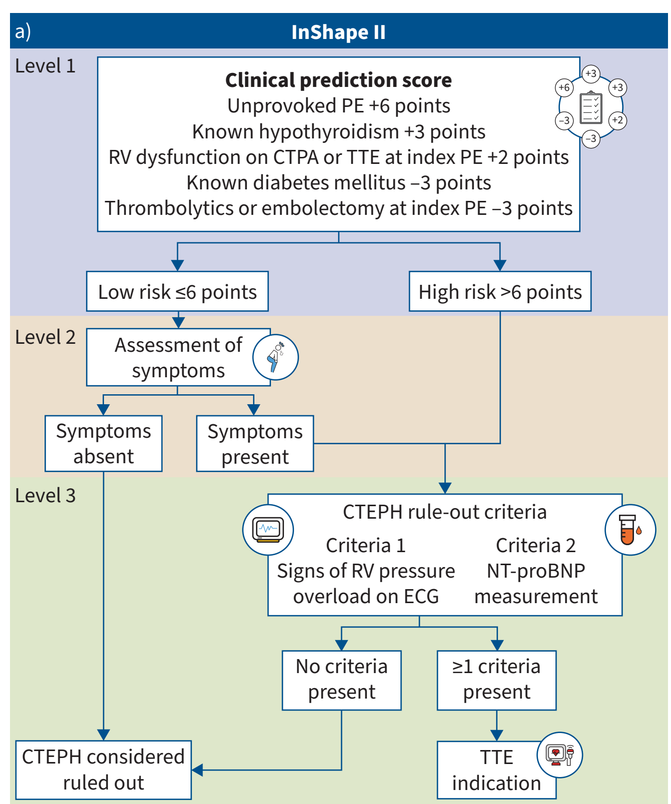

FIGURE 1 The InShape II algorithm and the new hypothetical algorithms. This figure depicts the a) InShape II algorithm and b) 12 hypothetical algorithms to improve the InShape II algorithm using CTPA assessment that were considered. (Continues.)

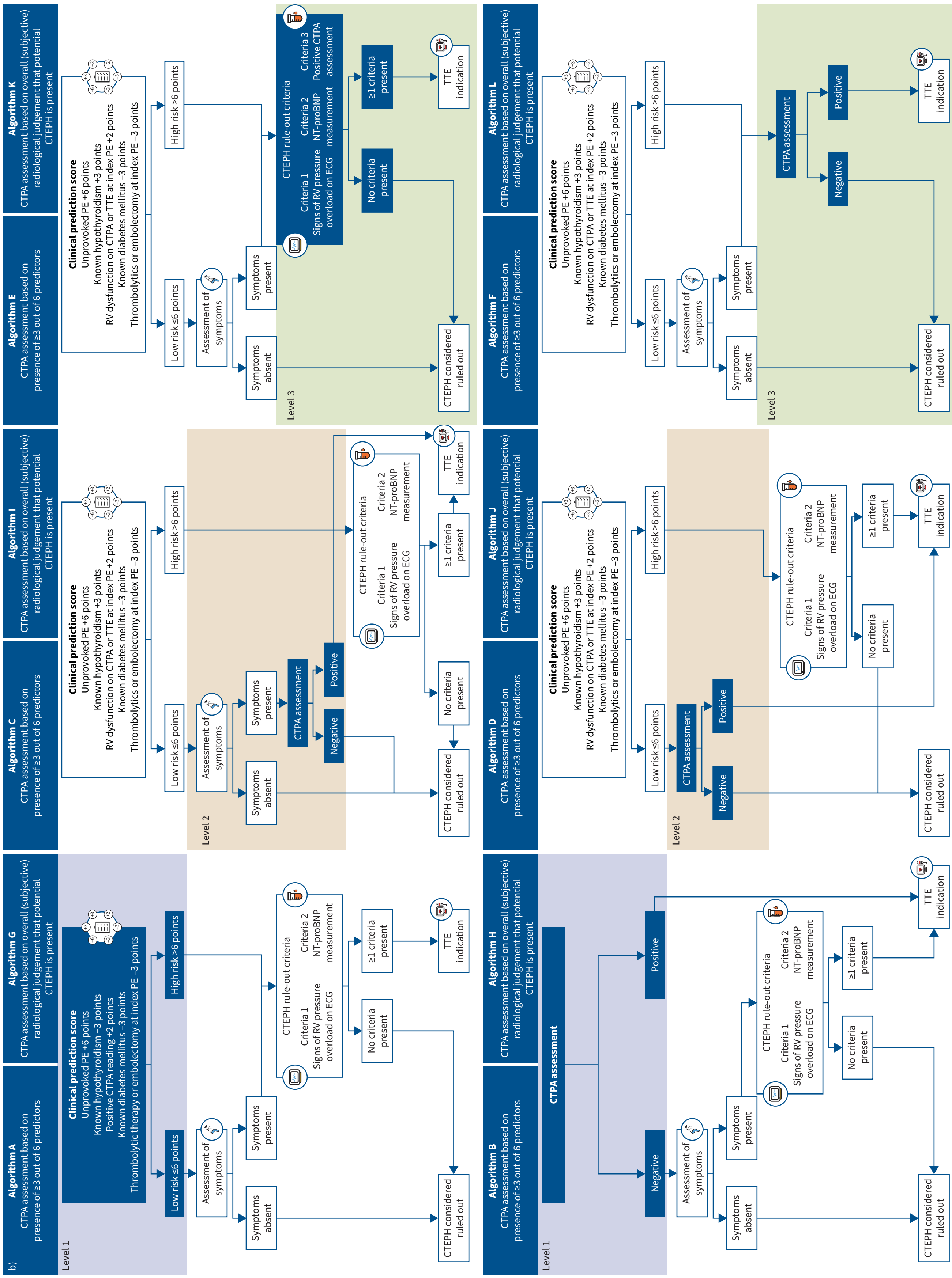
b)
Algorithm A
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm G
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Algorithm C
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm I
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Algorithm E
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm K
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Level 1
Level 2
Level 3
Clinical prediction score
Unprovoked PE +6 points
Known hypothyroidism +3 points
Positive CTPA reading +2 points
Known diabetes mellitus −3 points
Thrombolytic therapy or embolectomy at index PE −3 points
RV dysfunction on CTPA or TTE at index PE +2 points
Thrombolytics or embolectomy at index PE −3 points
Low risk ≤6 points
High risk >6 points
Assessment of symptoms
Symptoms absent
Symptoms 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
CTEPH considered ruled out
TTE indication
CTPA assessment
Negative
Positive
Algorithm B
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm H
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Algorithm D
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm J
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present
Algorithm F
CTPA assessment based on presence of ≥3 out of 6 predictors
Algorithm L
CTPA assessment based on overall (subjective) radiological judgement that potential CTEPH is present

FIGURE 1 (Continued.) b) The 12 hypothetical algorithms to improve the InShape II algorithm using CTPA assessment that were considered. Differences between these new hypothetical algorithms and the InShape II algorithm are depicted in the blue boxes. The CTPA assessment can be incorporated into the InShape II algorithm at three different levels: 1) integration in the CTEPH prediction score (algorithms A and G: by replacing the item "RV dysfunction on CTPA or TTE at index PE" with the CTPA assessment) or replacement of the score (algorithms B and H), 2) added as an extra step in symptomatic patients with a low CTEPH risk according to the prediction score (algorithms C and I) or replacement of this assessment (algorithms D and J) and 3) combined with the CTEPH rule-out criteria (algorithms E and K) or replacement of these criteria (algorithm F). For all algorithms for 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. Two methods of discriminating positive and negative CTPA assessments have been used, *i.e.* the presence of three or more out of six signs of CTEPH and overall judgement of the radiologist regarding the presence of CTEPH. With this in mind, algorithms A–F applied the assessment of six independent CTPA signs of CTEPH, while algorithms G–L were the same as A–F except 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 one or more of the following: 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°. For algorithms A–F, the six independent CTPA signs of CTEPH were 1) dilated pulmonary trunk (diameter >30 mm or larger than aortic diameter), 2) arterial retraction, 3) intravascular web, 4) dilated bronchial arteries, 5) RV wall hypertrophy (>4 mm) and 6) flattening of the interventricular septum. CTPA: computed tomography pulmonary angiogram; CTEPH: chronic thromboembolic pulmonary hypertension; ECG: electrocardiogram; NT-proBNP: N-terminal pro-brain natriuretic peptide; PE: pulmonary embolism; RV: right ventricular; TTE: transthoracic echocardiogram.

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 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 ventilation/perfusion (V/Q) scintigraphy and right heart catheterisation (RHC) [8]. CTEPH was defined as 1) one or more 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 after 4) ⩾3 months of adequate anticoagulant treatment [3, 8]. An independent interdisciplinary working group of pulmonary hypertension specialists adjudicated all results and CTEPH diagnoses. A 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 judgement 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 three or more out of the six signs were present, the patient was considered to have signs of CTEPH.

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 three different levels: 1) integration into the CTEPH prediction score (algorithms A or G) or replacement of the score (algorithms B or H), 2) added as an extra step in symptomatic patients with a low CTEPH risk according to the prediction score (algorithms C or I) or replacement of this assessment (algorithms D or J), or 3) combined with the CTEPH rule-out criteria (algorithms E or K) or replacement of these criteria (algorithms 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 three or more out of six 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 six 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.* the 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 five 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 judgement and 2) presence of three or more out of six 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 (F.A. Klok and S. Barco), 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 optimise 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 and is presented in percentages. The overall NRI was calculated as event NRI+non-event NRI. The event NRI was calculated for each algorithm as (number of CTEPH patients classified up–number of CTEPH patients classified down)/number of CTEPH patients. The non-event NRI was calculated as (number of non-CTEPH patients classified down–number of non-CTEPH patients classified up)/number of non-CTEPH patients [22]. Moreover, receiver operating characteristic 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 anticoagulant as treatment for the index PE (68%). At index PE, radiological signs of CTEPH were present in 12% when assessing presence of CTEPH with three or more out of six 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).

Performance of newly designed algorithms

Table 2 provides an overview of the performance of the potential new algorithms to rule out CTEPH. Application of the InShape II algorithm resulted in a failure rate of 0.34% (95% CI 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 had undergone CTEPH diagnostic work-up, including V/Q scan and RHC, 11 out of 12 CTEPH cases would have been identified by InShape II and algorithms A, B, E, G, H and K. For the other algorithms, three or more 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 three or more out of six 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, 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: tables 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).

TABLE 1 Baseline characteristics of the included patients

	InShape II cohort	FOCUS cohort
Participants, n	341	171
Age, years	56±16	60.7±15.7
Male gender	167 (49)	101 (59.1)
BMI, kg·m^{-2}	28±5.9	29.0±5.4
Unprovoked PE	187 (55)	67 (39.2)
RV dysfunction at index PE	96 (28)	119 (78.3)
Comorbidities		
Active malignancy	31 (9.1)	16 (9.4)
Anaemia	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		
DOAC	233 (68)	135 (80.8)
VKA	87 (26)	8 (4.8)
LMWH	29 (8.5)	24 (14.4)
Symptoms suggestive for CTEPH at 3-month follow-up	107 (31)	45 (26.3)
Predefined 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 out of 6 signs of CTEPH present	40 (12)	14 (8.2)
Overall judgement CTEPH present	27 (7.9)	27 (15.8)

Data are presented as mean±SD or n (%), unless otherwise indicated. Symptoms suggestive for CTEPH are dyspnoea on exertion, oedema, newly developed palpitations, syncope or chest pain. BMI: body mass index; CTEPH: chronic thromboembolic pulmonary hypertension; DOAC: direct oral anticoagulant; LMWH: low-molecular weight heparin; PE: pulmonary embolism; RV: right ventricular; VTE: venous thromboembolism; VKA: vitamin K antagonist. #: unknown.

TABLE 2 Overview of the performance of the hypothetical algorithms

	Failure rate,[#] % (95% CI)	Patients with an indication to perform ECG and NT-proBNP testing, n (%)	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)	NA	NA	NA
CTPA criteria: ⩾3 out of 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)	NA	NA	NA
CTPA criteria: ⩾3 out of 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

AUC: area under the curve; CTEPH: chronic thromboembolic pulmonary hypertension; CTPA: computed tomography pulmonary angiogram; ECG: electrocardiogram; NRI: net reclassification index; NA: not applicable; NT-proBNP: N-terminal pro-brain natriuretic peptide; PE: pulmonary embolism; ROC: receiver operating characteristic; TTE: transthoracic echocardiogram. #: 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 two to five non-CTEPH patients have been interpreted as not being able to rule-out CTEPH and therefore have an indication for TTE.

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 echocardiography and those with an intermediate-high probability of pulmonary hypertension had undergone CTEPH diagnostic work-up including V/Q scan and RHC, all CTEPH cases would have been detected by InShape II and algorithms B, H, 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%).

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 six 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.

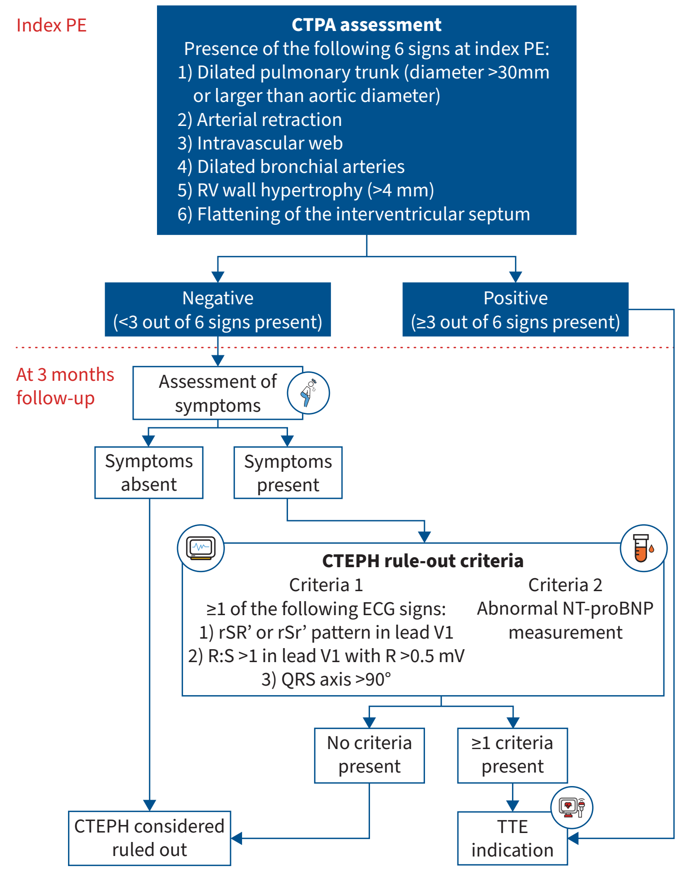

FIGURE 2 The InShape IV algorithm (algorithm B). Above the dashed red line is the CTPA reading of the index PE. While this CTPA reading uses the CTPA performed to diagnose the acute PE, the detailed reading for signs of CTEPH can be conducted at any point between the index PE and the scheduled outpatient visit. Below the dashed red line are the screening items performed during acute PE follow-up approximately 3 months after acute PE diagnosis. Six independent CTPA signs of CTEPH were evaluated: 1) dilated pulmonary trunk (diameter >30 mm or larger than aortic diameter), 2) arterial retraction, 3) intravascular web, 4) dilated bronchial arteries, 5) RV wall hypertrophy (>4 mm) and 6) 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 centre-, sex- or age-specific cut-off as defined by the assay's manufacturer. CTPA: computed tomography pulmonary angiogram; CTEPH: chronic thromboembolic pulmonary hypertension; ECG: electrocardiogram; NT-proBNP: N-terminal pro-brain natriuretic peptide; PE: pulmonary embolism; RV: right ventricular; TTE: transthoracic echocardiogram.

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 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 existence of three or more out of six signs of CTEPH to discriminate positive from negative CTPA. Compared to the radiologist's overall subjective evaluation of potential CTEPH, the use of three or more 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 pre-existing 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, minimising 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 of which 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-out 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 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 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 dyspnoea 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 be valuable to select PE survivors with a higher prevalence of CTEPH.

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