The diagnostic and therapeutic management of pulmonary embolism

Hulle, T. van der

CHAPTER 6

Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

T. van der Hulle, W.Y. Cheung, S. Kooij, L.F.M. Beenen, T. van Bemmel, J. van Es, L.M. Faber, G.M. Hazelaar, C. Heringhaus, H. Hofstee, M.M.C. Hovens, K.A.H. Kaasjager, R.C.J. van Klink, M.J.H.A. Kruip, R.F. Loeffen, A.T.A. Mairuhu, S. Middeldorp, M. Nijkeuter, L.M. van der Pol, S. Schol-Gelok, M. ten Wolde, F.A. Klok, M.V. Huisman

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ABSTRACT

Background

Validated diagnostic algorithms in patients with suspected pulmonary embolism are often not used correctly or only benefit subgroups of patients, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule that incorporates differential D-dimer cutoff values at presentation, has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. We aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

Methods

We did a prospective, multicentre, cohort study in 12 hospitals in the Netherlands, including consecutive patients with suspected pulmonary embolism between Oct 5, 2013, and July 9, 2015. Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of three items (clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, pulmonary embolism was considered excluded. All other patients had CTPA. The primary outcome was the number of independently adjudicated events of venous thromboembolism during 3 months of follow-up after pulmonary embolism was excluded, and the secondary outcome was the number of required CTPA compared with the Wells' diagnostic algorithm. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. This trial is registered with the Netherlands Trial Registry, number NTR4193.

Findings

3616 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 151 (4%) were excluded. The remaining 3465 patients were assessed of whom 456 (13%) were diagnosed with pulmonary embolism at baseline. Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0.61%, 95% CI 0.36–0.96) of whom six had fatal pulmonary embolism (0.20%, 0.07–0.44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16).

Interpretation

In our study pulmonary embolism was safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients is the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

INTRODUCTION

The clinical diagnosis of pulmonary embolism is non-specific and should therefore be followed by objective testing. Because of its diagnostic accuracy and wide availability, multidetector row computed tomography pulmonary angiography (CTPA) is the imaging test of choice to confirm acute pulmonary embolism in most patients. Increasing use of CTPA with diminishing prevalence of pulmonary embolism —to even less than 10% [1]— has led to overdiagnosis of mostly subsegmental pulmonary embolism and unnecessary risks of radiation exposure and contrast medium induced nephropathy [2–6]. To avoid these problems, validated diagnostic algorithms for suspected acute pulmonary embolism, using sequential testing, have been introduced [7]. In these algorithms, a normal D-dimer test result in patients with low probability safely excludes pulmonary embolism [8]. Correct application of these algorithms obviates the need for CTPA in 20–30% of patients, with an overall 3-month diagnostic failure rate of less than 1.5% after initial negative ruling of the algorithm [7–9]. An age-adjusted D-dimer threshold (age × 10 ng/mL for patients aged >50 years) has been validated prospectively, reporting an absolute reduction of 11.6% (95%CI 10.5–12.9) in the need for CTPA [10]. Importantly, only patients aged 50 years or older, and foremost those older than 75 years benefit from this strategy whereas when considering the life-time attributable cancer risk, the exposure to unnecessary radiation is considered more relevant to younger individuals, particularly women [3].

Despite firm evidence of its safety and efficiency, adherence to recommended diagnostic strategies in clinical practice is variable. This variation might be partly due to complexity of these strategies, and insufficient time at busy emergency departments, which hampers the use of sequential tests [11–14]. In daily practice, D-dimer testing is frequently ordered and known at low clinical threshold or even before the clinical assessment [15,16]. Improved adherence to the algorithm, for instance by implementation of a clinical decision support system, has been shown to significantly decrease the mean number of diagnostic tests used along with —and more importantly— the number of diagnostic failures [17,18].

On the basis of a post-hoc derivation and validation study [19], three items of the original Wells' clinical decision rule —ie, clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis— were the most predictive for pulmonary embolism. They allowed the use of a differential D-dimer threshold based on the presence of one of these items, without losing sensitivity. Hence, this algorithm —which we call YEARS— involves the simultaneous assessment of only the three abovementioned items and a D-dimer test threshold of 500 ng/mL in presence, and 1000 ng/mL in absence of one of the YEARS items. The YEARS algorithm was designed to be more easily applied in a busy clinical practice than currently used diag-

nostic strategies, and to further decrease the number of necessary CTPA examinations in patients of all ages. In this study, we aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

METHODS

Study design and patients

We did a prospective, multicentre, cohort outcome study evaluating the safety and efficiency of the YEARS algorithm in patients with suspected acute pulmonary embolism between Oct 5, 2013, and July 9, 2015 **(Figure 1)** [19]. The algorithm was implemented as standard diagnostic strategy in 12 participating hospitals in the Netherlands. The full study protocol is available at www.thelancet.com.

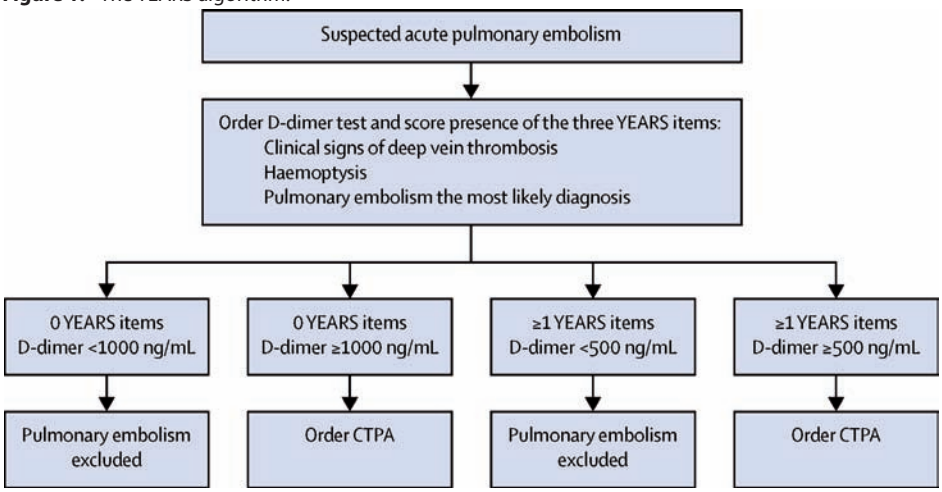
Consecutive outpatients and inpatients with clinically suspected acute (first or recurrent) pulmonary embolism were eligible for inclusion if they were aged 18 years or older. Exclusion criteria were treatment with therapeutic doses of anticoagulants initiated 24 hours or more before eligibility assessment, life expectancy less than 3 months or geographic inaccessibility precluding follow-up, pregnancy, or allergy to intravenous contrast agent. The protocol was centrally approved by the institutional review board of the Leiden University Medical Center, Leiden, Netherlands, which waived the need for informed consent; this decision was endorsed by the local institutional review board of each participating centre.

Procedures

An attending physician who suspected acute pulmonary embolism assessed the patients, and then evaluated the YEARS score by assessing the presence or absence of each of the YEARS items —ie, symptomatic deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis— (scored as yes or no) with the pretest probability dependent threshold of the D-dimer test **(Figure 1)**. D-dimer concentrations were measured upon presentation of the patient, according to local practice, with automated well validated high-sensitive quantitative D-dimer assays (Vidas D-dimer Exclusion, Biomerieux, Marcy-L'Étoile, France; Tinaquant, Roche Diagnostica, Mannheim, Germany; STA-LIA, DiagnosticaStago, Asnieres, France; and Innovance, Siemens, Marburg, Germany). Our study reflected daily clinical practice in which D-dimer concentrations are often determined at presentation to the emergency ward. Physicians were not blinded for the D-dimer test result when they assigned the YEARS items.

In patients with no YEARS items and a D-dimer concentration less than 1000 ng/mL, pulmonary embolism was considered excluded and further testing was withheld. In patients with one or more YEARS items and a D-dimer concentration less than 500 ng/mL,

Figure 1. The YEARS algorithm.



Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA=computed tomography pulmonary angiography.

pulmonary embolism was also considered excluded and further testing was withheld. All other patients —ie, either with no YEARS item and a D-dimer concentration of 1000 ng/mL or more, or with one or more items and a concentration of 500 ng/mL or more— were referred for CTPA to show or exclude the diagnosis of pulmonary embolism. The appendix available at www.thelancet.com shows the full CTPA scan protocol. Patients in whom pulmonary embolism was ruled out were left untreated and followed up for 3 months. They were instructed to return to the hospital in the event of symptoms of venous thromboembolism, after which objective diagnostic tests were done to confirm or refute the disease. Follow-up consisted of a scheduled outpatient visit or telephone interview after 3 months. At this visit, information about complaints suggestive of venous thromboembolism was obtained. Patients in whom acute pulmonary embolism was confirmed at baseline were treated with anticoagulants according to international guidelines.

Outcomes

The primary outcome was the 3-month incidence of symptomatic venous thromboembolism in the overall population and in patients managed with and without CTPA separately. The diagnosis of pulmonary embolism or deep vein thrombosis was based on predefined criteria (appendix, available at www.thelancet.com). In case of clinically suspected pulmonary embolism or deep vein thrombosis, objective diagnostic tests were required, including CTPA for suspected pulmonary embolism and compression ultrasonography for suspected deep vein thromboembolism. In case of death, information was obtained from the hospital records. Deaths were classified as caused by pulmonary

embolism if it was confirmed by autopsy, was shown by objective testing before death, or could not be confidently excluded as a cause of death. An independent adjudication committee assessed and adjudicated all suspected venous thromboembolism and deaths during follow-up.

The secondary outcome was the proportion of required CTPA examinations to complete the YEARS algorithm at baseline, as compared post-hoc with the theoretical proportion of CTPA examinations that would have been required if the algorithm, using the two-level Wells' rule outcome and fixed D-dimer threshold of less than 500 ng/mL, would have been applied in the study population and to historical data [20]. Finally, we compared the efficiency to the scenario in which the age-adjusted D-dimer concentration would have been applied (calculated by age ×10 µg/L in patients >50 years). This comparison was done post hoc because the final evidence supporting this approach was not available at the moment of drafting of the protocol [10]. The Wells' rule was calculated by an independent researcher (TvdH) based on the YEARS criteria entered in the case record form and information from the medical charts.

Statistical analysis

On the basis of derivation cohort of the YEARS algorithm, we expected a failure rate of 1.2% in patients managed without CTPA [19]. The sample size was based on this assumption, with the aim to keep the upper limit of the 95% CI of this point estimate below 2.7% [21]. This number reflects the 3-month incidence of venous thromboembolism after normal conventional pulmonary angiography. Any venous thromboembolism incidence with a complete confidence interval below this safety threshold was considered to be safe. We calculated that we needed to include 1333 patients managed without CTPA, with a two-sided α of 5% and a β of 80%. Because 44% of patients in the combined YEARS derivation and validation cohort could have been managed without CTPA and accounting for up to 7.5% loss to follow-up, a total of 3260 patients with suspected pulmonary embolism would be required [19]. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. The difference between approaches was how to report the number of CTPA that were done but not indicated by the strategy. By using this approach, pulmonary embolism diagnosed at presentation on a CTPA that was not indicated was considered as failures of the diagnostic strategy.

For the secondary outcome analysis, we determined the absolute difference in the number of required CTPA examinations between the different clinical scenarios. Finally, we reported outcomes of not predefined post-hoc analyses for relevant subgroups: patients with malignancy, patients 50 years or older, patients with a history of venous thromboembolism, and inpatients and patients with complaints for more than 7 days.

All descriptive parameters and exact 95% CIs around the observed incidences were calculated. All analyses were done with SPSS (version 23). This study is registered with the Netherlands Trial Register, number NTR4193.

Role of the funding source

This study was an academically sponsored trial. The steering committee, consisting of the authors, had final responsibility for the study design, oversight, and data verification and analyses. The sponsor was not involved in the study. All members of the steering committee contributed to the interpretation of the results, approved the final version of the manuscript, and vouch for the accuracy and completeness of the data reported. The final decision to submit the manuscript was made by the corresponding author on behalf of all coauthors.

RESULTS

From Oct 5, 2013, to July 9, 2015, 3616 consecutive patients with clinically suspected pulmonary embolism were screened in the 12 participating hospitals, of whom 151 (4.2%) were excluded (**Figure 2**). **Table 1** summarises the baseline characteristics. Overall, pulmonary embolism was detected in 456 (13%) of 3465 patients: in 55 (3**.**2%) of 1743 patients with none of the YEARS items and 401 (23%) of 1722 patients with one or more YEARS items.

Table 1. Baseline characteristics of patients with suspected pulmonary embolism.

Mean age, years (SD)	53 (18)
Female, n (%)	2154 (62)
Duration of complaints, days (median and IQR)	3 (1-8)
COPD with treatment, n (%)	423 (12)
Heart failure with treatment, n (%)	137 (4.0)
Estrogen use, n (% of women)	337 (16)
Immobilization or surgery in the previous 4 weeks	407 (12)
Outpatient, n (%)	2996 (86)
Heart rate greater than 100/min, n (%)	683 (20)
Previous history of PE or DVT, n (%)	359 (10)
Malignancy, n (%)	336 (9.7)

Note: n=number, SD=standard deviation,COPD=chronic obstructive pulmonary disease.

According to the intention-to-diagnose approach, of the 2946 (85%) patients in whom pulmonary embolism was ruled out at baseline, who remained untreated, and completed the follow-up period, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0.61% (95% CI 0.36–0.96). The incidence of fatal pulmonary embolism was 0.20% (six patients, 95% CI 0.07–0.44; **Table 2**). In a worst case scenario, accounting the five patients who were lost to follow-up (four patients had pulmonary embolism excluded without CTPA and one patient had a negative CTPA) as recurrent venous thromboembolism, the 3-month incidence would have been 0.78% (23 of 2951 patients, 95% CI 0.49–1.2). For the per-protocol approach, the failure rate of the diagnostic algorithm was 0.51% (15 of 2943 patients, 95% CI 0.31–0.84) with a 0.20% 3-month risk of fatal pulmonary embolism (six of 2943 patients, 0.08–0.46).

Table 2. Primary outcomes of venous thromboembolism events during 3-month follow-up.

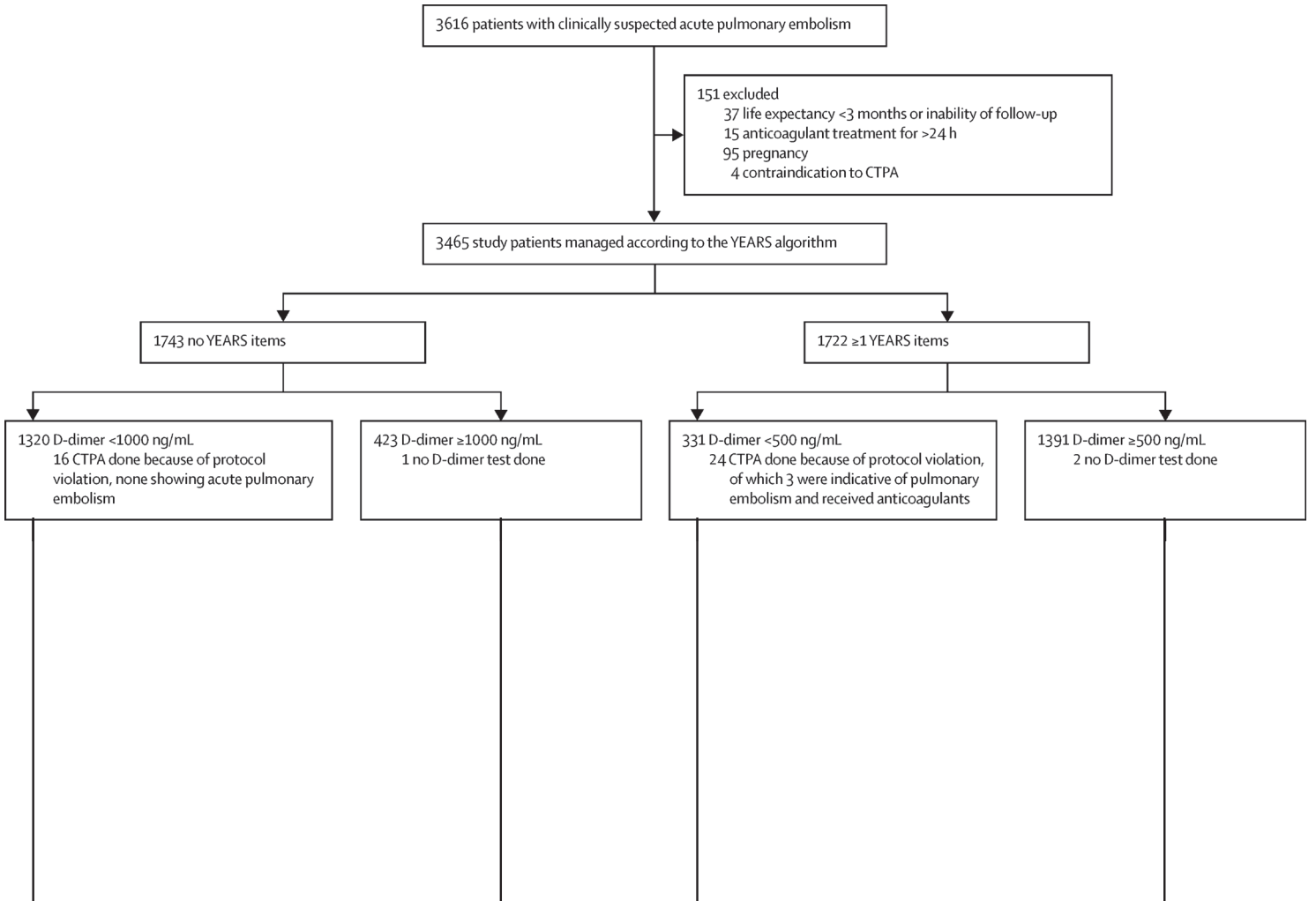
Category	Patients, n	Total VTE, n (%) [95% CI]	Fatal PE, n (%) [95% CI]
Complete algorithm	2946	18 (0.61%) [0.36-0.96]	6 (0.20%) [0.07-0.44]
Patients managed without CTPA	1629	7 (0.43%) [0.17-0.88]	2 (0.12%) [0.01-0.44]
Patients managed with CTPA	1317	11 (0.84%) [0.47-1.5]	4 (0.30%) [0.12-0.78]

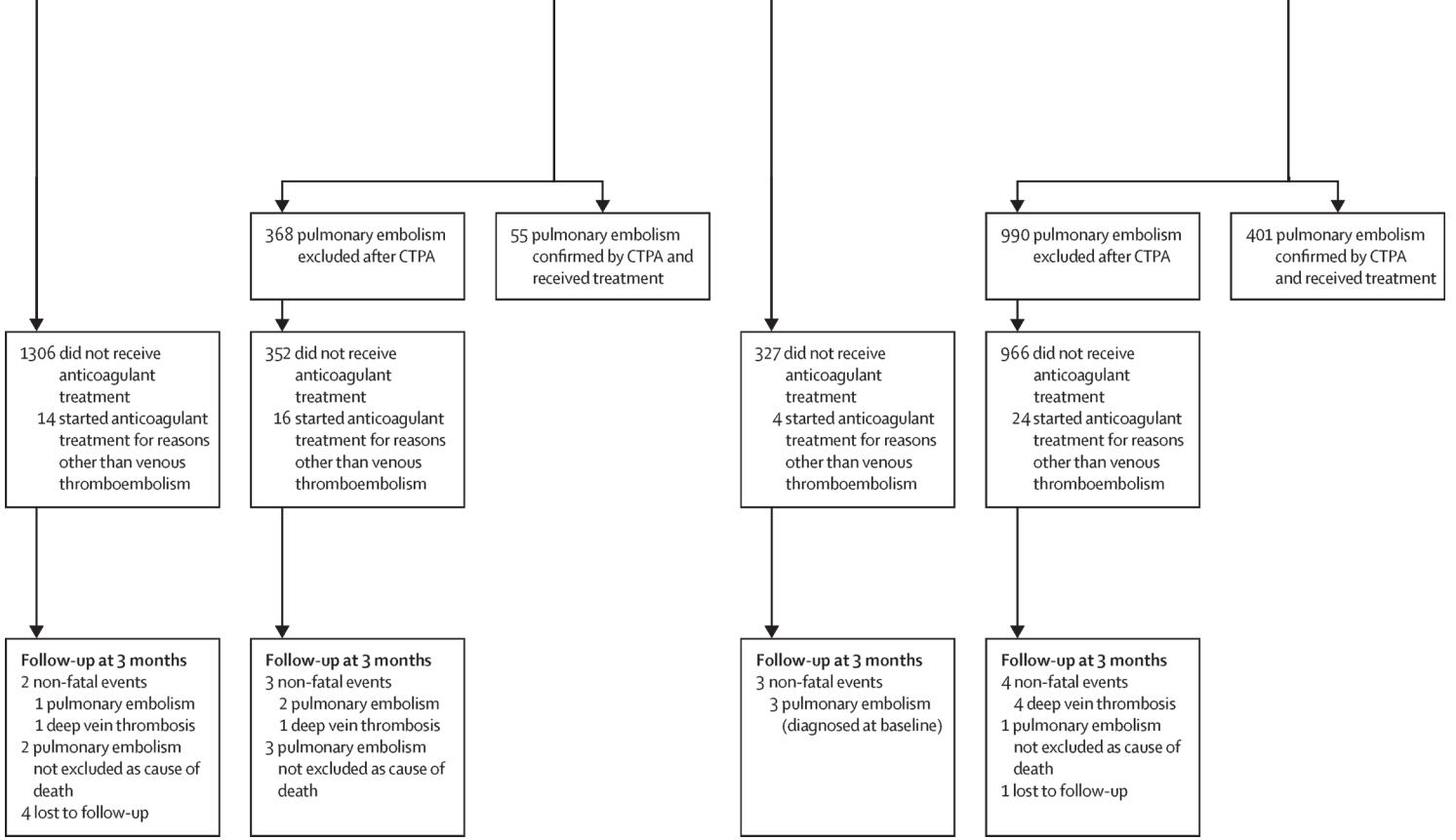
Note: Patients in whom pulmonary embolism was excluded by either a low YEARS score or CT scanning were left untreated. Outcomes calculated for patients who remained untreated and were not lost to follow-up. CTPA=computed tomography pulmonary angiography.

In the intention-to-diagnose approach, CTPA was not done in 1611 (46%) patients and it was not indicated in 1651 (48%) patients following the per-protocol approach. If the standard diagnostic algorithm using Wells' rule and D-dimer with fixed threshold of <500 ng/mL would have been applied, 1174 (34%) patients could have been managed without CTPA at baseline, for an absolute difference of 13% (difference in intention-to-diagnose approach 437 CTPA examinations, 95% CI 10–15%) and 14% (difference in per-protocol approach 477 CTPA examinations, 12–16%) in favour of the YEARS algorithm.

If Wells' rule and the age-adjusted D-dimer threshold would have been applied, 1348 (39**%**) patients could have been managed without CTPA at baseline, an absolute difference of 8.7% (difference in per-protocol approach CTPA examinations 303, 95% CI 6.4–11%) and of 7.6% (difference in intention-to-diagnose approach CTPA examinations 263, 95% CI 5.3–9.9%).

Figure 2. Flowchart of study patients.





Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography; [1)]16 CTPA performed due to protocol violation, none showing acute PE; [2)]14 started anticoagulation for other reasons than VTE; [3)]1 no D-dimer test performed; [4)]16 started anticoagulation for other reasons than VTE; [5)]24 CTPA performed due to protocol violation of which 3 were indicative of PE; all three patients were treated with anticoagulants; [6)]4 started anticoagulation for other reasons than VTE; [7)]2 no D-dimer test performed; [8)]24 started anticoagulation for other reasons than VTE.

In the subgroups of patients younger than 50 years and 50 years and older, a 14% absolute reduction in the number of required CTPA examinations was observed when the YEARS algorithm was applied compared with the standard diagnostic algorithm, with failure rates of 0.11% (one of 894 patients, 95% CI 0.02–0.63) and 0.81% (six of 740 patients, 0.37–1.8), respectively. **Table 3** summarises the results for the other subgroups.

Figure 2 shows the management of all 3465 included patients. Of the 1651 patients who should have been managed without CTPA, the protocol was violated in 40 patients. CTPA showed pulmonary embolism in three patients who were treated with anticoagulants. These observations were considered diagnostic failures and are included in the primary outcome. Furthermore, 18 (1.1%) of 1651 patients were treated with oral anticoagulants for other reasons (ie, eight atrial fibrillation, one superficial thrombophlebitis, and nine other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and four (0.24%) of 1651 patients were lost to follow-up. Four of the remaining 1589 patients returned with symptomatic events of venous thromboembolism (**Table 4**). The 3-month incidence of venous thromboembolism in patients who did not have CTPA according to the YEARS algorithm was 0.43% (seven of 1629 patients, 95% CI 0.17–0.88) and of fatal pulmonary embolism was 0.12% (two of 1629 patients, 0.01–0·44; **Table 2**). Seven other patients (0.43%) died of non-venous-thromboembolism-related causes.

Of the 1358 patients in whom CTPA ruled out pulmonary embolism, 40 patients (2.95%) were treated with anticoagulants for other reasons (ie, 20 atrial fibrillation, three superficial thrombophlebitis, one splanchnic vein thrombosis, one thrombus in the left ventricle, one high-dose thrombosis prophylaxis, one suspected but later ruled out pulmonary vein thrombosis, one vena cava superior syndrome due to mediastinal mass, and 12 other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and one patient (0.07%) was lost to follow-up. Of the 1317 remaining patients, 11 patients returned with symptomatic events of venous thromboembolism (**Table 5**). The 3-month incidence of venous thromboembolism was 0.84% (11 of 1317 patients, 95% CI 0.47–1.5) and incidence of fatal pulmonary embolism was 0.30% (four of 1317 patients, 0.12–0.78; **Table 2**). 85 other patients (6.5%) died of non-venous-thromboembolism-related causes.

DISCUSSION

Our study showed that the YEARS algorithm safely excluded acute pulmonary embolism. An absolute 14% decrease in the need for CTPA was achieved, compared with the standard algorithm. The 3-month incidence of venous thromboembolism in patients who

Table 3. Diagnostic failures in patients who were managed without CTPA at baseline.

Sex	Age	Years score	Wells score (as calculated post-hoc)	D-dimer, ng/mL	Interval, days	Outcome	Circumstances of outcome event	Adjudicated as
Female	59	0	0	609	54	Death	Developed cardiac arrest during admission for acute severe pancreatitis. Known with myotonic dystrophy type 1 with severe cardiomyopathy and arrhythmias. ICD was earlier deactivated after regular unjustified defibrillations. Resuscitation was unsuccessful	PE not excluded as cause of death
Male	78	0	1	898	11	Death	Diagnosed with end-stage metastasized oropharyngeal carcinoma. Found deceased in nursing home	PE not excluded as cause of death
Female	89	0	1.5	610	18	PE	Subsegmental PE diagnosed on CTPA during admission for pneumonia and acute heart failure related to severe aortic valve stenosis and mitral valve insufficiency. Patient died seven days after treatment was voluntarily withheld	Non-fatal PE
Male	52	0	1	560	49	DVT	DVT 14 days after surgery for glioblastoma multiforme	DVT
Female	21	2	5.5	380	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE
Male	58	1	3	420	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE
Female	71	1	6	410	0	PE	CTPA performed due to protocol violation at baseline	Non-fatal PE

Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography.

Table 4. Diagnostic failures in patients who were managed with CTPA at baseline.

Sex	Age	Years score	Wells score (as calculated post-hoc)	D-dimer, mg/mL	Interval, days	Outcome	Circumstances of outcome event	Adjudicated as
Male	50	0	1.5	1070	34	DVT	Vena cava superior syndrome caused by thrombosis at the site of pacemaker leads	Thrombosis of the vena cava superior
Female	73	0	3	1480	69	Death	Died in hospital under the clinical diagnosis of a pneumonia and acute heart failure	PE not excluded as cause of death
Female	79	0	3	2400	26	PE	Initiation of anticoagulation because of suspected PE without CTPA confirmation after hospital admission because of heart failure and COPD exacerbation	Non-fatal PE
Female	82	0	0	2550	Unknown	Death	Died in nursing home after hospital admission because of acute heart failure and exacerbation of COPD	PE not excluded as cause of death
Female	57	0	1	4170	12	PE	Known with a recurrent sarcoma of the uterus. Subsegmental PE diagnosed postoperatively. Died 33 days after diagnosis of PE during palliative care in a hospice	Non-fatal PE
Female	70	0	1	2400	17	Death	Died after sudden collapse followed by unsuccessful resuscitation 1 day after surgery for gastric carcinoma	PE not excluded as cause of death
Female	73	1	5.5	2500	6	DVT	Known with leukemia. Developed thrombosis of the brachial vein after superficial thrombophlebitis related to an intravenous catheter	DVT
Male	84	1	4	5000	32	DVT	Known with metastasized prostate cancer. Developed DVT after immobilization during admission at the hospital	DVT
Female	66	1	7	1325	43	Death	Known with lung cancer for which curative treatment. Post-radiation stenosis of the trachea for which a stent placed. Died at home after sudden hemoptysis	PE not excluded as cause of death
Male	70	1	3	5000	68	DVT	Subclavian vein thrombus associated with intravenous catheter	DVT
Female	48	1	3	747	78	DVT	Developed DVT and was diagnosed with antiphospholipid syndrome	DVT

Note: PE= pulmonary embolism; DVT= deep vein thrombosis; CTPA= computed tomography pulmonary angiography.

Table 5. Primary endpoint and efficacy in subgroups of the total study population.

				VTE risk during 3 months of follow-up			Efficiency compared to Wells rule in combination with a D-dimer threshold of <500 ng/mL	
Subgroup	**Patients (n)**	**PE at baseline (n, %)**	**Managed without CTPA (n)**	**3-month VTE incidence in patients managed without CTPA events/patients at risk (%; 95%CI)**	**VTE incidence in patients managed with CTPA events/patients at risk (%; 95%CI)**	**Overall VTE incidence after PE was excluded at baseline events/patients at risk % (95%CI)**	**Managed without CTPA (n)**	**Difference with YEARS algorithm n/total % (95%CI)**
Malignancy	336	57 17%	62	2/61 3.2% (0.90-11)	5/211 2.4% (1.0-5.4)	7/272 2.6% (1.3-5.2)	37	25/336 7.4% (5.0-11)
No malignancy	3129	399 13%	1590	5/1573 0.32% (0.14-0.74)	6/1106 0.54% (0.25-1.2)	11/2679 0.41% (0.23-0.73)	1137	453/3129 15% (13-16)
Age < 50 years	1448	126 8.7%	900	1/894 0.11% (0.02-0.63)	1/415 0.24% (0.04-1.4)	2/1309 0.15% (0.04-0.56)	704	196/1448 14% (12-15)
Age ≥ 50 years	2017	330 16%	752	6/740 0.81% (0.37-1.8)	10/902 1.1% (0.6-2.0)	16/1642 0.98% (0.6-1.6)	470	282/2017 14% (13-16)
No history of VTE	3106	349 11%	1529	6/1517 0.40% (0.18-0.86)	10/1193 0.84% (0.46-1.5)	16/2710 0.59% (0.36-0.96)	1120	409/3106 13% (12-14)
History of VTE	359	107 30%	123	1/117 0.85% (0.15-4.7)	1/124 0.81% (0.14-4.6)	2/241 0.83% (0.23-3.0)	54	69/359 19% (15-24)
Inpatient	469	66 14%	200	1/195 0.51% (0.09-2.9)	3/198 1.5% (0.52-4.4)	4/393 1.0% (0.40-2.6)	135	65/469 14% (11-17)
Outpatient	2996	390 13%	1452	6/1439 0.42% (0.19-0.91)	8/1119 0.71% (0.36-1.4)	14/2558 0.55% (0.33-0.92)	1039	413/2996 14% (13-15)
Complaints ≤7 days	2599	362 14%	1266	7/1253 0.56% (0.27-1.2)	9/942 0.96% (0.50-1.8)	16/2195 0.73% (0.45-1.2)	901	365/2599 14% (13-15)
Complaints >7 days	866	94 11%	386	0/381 0% (0-1.0)	2/375 0.53% (0.15-1.9)	2/756 0.26% (0.07-0.96)	273	113/866 13% (11-15)

Note: n=number, CI= confidence interval, CTPA= computed tomography pulmonary angiography, VTE = Venous Thromboembolism.

did not undergo CTPA was in line with that observed in studies using algorithms with sequential diagnostic testing and traditional two-level Wells' score, and a fixed cutoff concentration of D-dimer of 500 ng/mL: 0.43% (95% CI 0.17–0.88) in our study versus 0.34% (0.036–0.96) reported by a meta-analysis [20]. Moreover, the risk of recurrent venous thromboembolism in patients with a normal CTPA was comparable to the risk observed in previous studies using standard algorithms: 0.84% (95% CI 0.47–1.5) versus 1.2% (0.8–1.8) [22]. Additionally, fatal pulmonary embolism occurred in 0.30% (95% CI 0.12–0.78) of patients in our study compared with 0.6% (0.4–1.1) in another study using standard algorithms [22].

The advantage of the YEARS algorithm over existing algorithms is the large reduction in the need for CTPA, which reduces radiation exposure and overdiagnosis,[1-4,23] and is achieved by using variable D-dimer thresholds depending on the clinical probability. This study is the first prospective outcome study that validated a D-dimer threshold of 1000 ng/mL in patients with a low clinical probability.

While our study was ongoing, another strategy to reduce the number of CTPA has been validated in a prospective outcome study: the age-adjusted D-dimer threshold [10]. If this strategy would have been applied to our study population, the YEARS algorithm would have led to an absolute reduction of 8.7% (95% CI 6.4–11) of CTPA. The main reason for this difference is the applicability of the YEARS algorithm to patients with suspected acute pulmonary embolism in all ages, and not only in patients older than 50 years. In patients younger than 50 years, the YEARS algorithm leads to a 14% absolute reduction of CTPA. Of note, reducing the number of CTPA is very relevant for young patients, particularly women, in whom concerns have been raised about long-term effects of radiation on the risk of breast cancer.

Methodological strengths of the study include the large number of consecutive patients, the near complete follow-up, and the independent adjudication of endpoints. Furthermore, by studying a real-world cohort of patients in daily practice, we expect that the YEARS algorithm can be easily implemented outside the participating study sites, and that our data for safety and efficiency are representative for non-trial conditions. Additionally, our results are in line with the numbers reported in the initial derivation and retrospective validation study of our algorithm [19]. Of note, although haemodynamic instability was not a formal exclusion criterion of this study, we have described a cohort of only haemodynamically stable patients.

Limitations of our the study are the absence of a control group because we did not do a randomised study and could therefore not directly compare the risk of venous thromboembolism with a control group that would have been managed with traditional algorithms. However, the low observed 3-month risk of venous thromboembolism and near complete follow-up strongly support the chosen study design. Moreover, although an independent committee evaluated and adjudicated all endpoints, autopsy was

hardly scarcely done. As a consequence, it was difficult to exclude pulmonary embolism as a possible cause of death in six patients during follow-up. These patients already had or developed extensive comorbidity, or went into the final stage of a terminal illness during the follow-up period, with most of them dying in an outpatient setting. Even so, although pulmonary embolism was conservatively adjudicated as the cause of death in these patients, the recurrence rate observed in our study remained well below the safety threshold, reinforcing the validity of our findings. Furthermore, the prevalence of pulmonary embolism was higher than observed in large cohorts in North America, but lower than observed in previous studies in Europe. The study patients were relatively young, but identical to those in an earlier large diagnostic management study by our group [7]. The results of the subgroup analyses, however, confirm the validity of applying the YEARS algorithm in a patient cohort with higher pulmonary embolism prevalence of up to 30% and provide evidence of the generalisability of our findings. Lastly, there were 43 violations of the study protocol, with a D-dimer test not done in three patients and a non-indicated CTPA done in 40 patients, of which three confirmed the presence of acute pulmonary embolism. This number is comparable to that in the Christopher study, in which two of 25 unjustified CTPA examinations revealed pulmonary embolism [7]. Finally, because of the small number of patients with cancer included in our study, the safety of this algorithm for patients with suspected pulmonary embolism in the presence of cancer remains to be determined.

In conclusion, the YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in patients presenting with clinically suspected pulmonary embolism, with a low risk for venous thromboembolism during a 3-month follow-up. The main advantage of the YEARS algorithm is the absolute 14% decrease in the number of CTPA examinations that is applicable to all ages and was shown to be consistent across subgroups.

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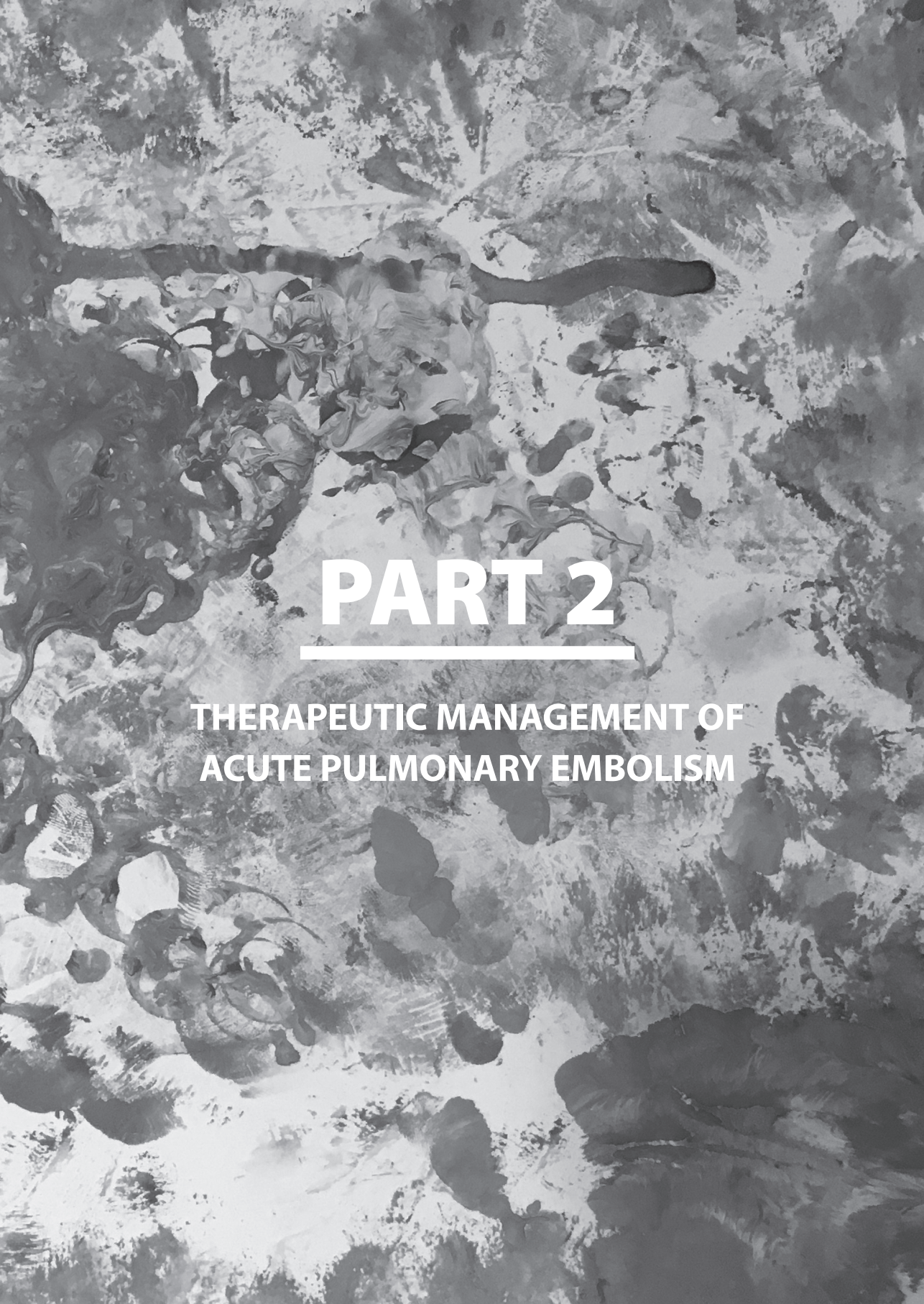

PART 2

THERAPEUTIC MANAGEMENT OF ACUTE PULMONARY EMBOLISM