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

*Tom van der Hulle, Whitney Y Cheung, Stephanie Kooij, Ludo F M Beenen, Thomas van Bemmel, Josien van Es, Laura M Faber, Germa M Hazelaar, Christian Heringhaus, Herman Hofstee, Marcel M C Hovens, Karin A H Kaasjager, Rick C J van Klink, Marieke J H A Kruip, Rinske F Loeffen, Albert T A Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Liselotte M van der Pol, Suzanne Schol-Gelok, Marije ten Wolde, Frederikus A Klok, Menno V Huisman, for the YEARS study group**

Summary

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, to 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.

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*YEARS study group is listed at the end of this paper

Department of Thrombosis and Hemostasis (T van der Hulle MD, F A Klok MD, Prof M V Huisman MD) **and Department of Emergency Medicine** (C Heringhaus MD), **Leiden University Medical Center, Leiden, Netherlands; Department of Vascular Medicine** (W Y Cheung MD, Prof S Middeldorp MD) **and Department of Radiology** (L F M Beenen MD), **Academic Medical Center, Amsterdam, Netherlands; Department of Internal Medicine, Haga Hospital, The Hague, Netherlands** (S Kooij MD, A T A Mairuhu MD, L M van der Pol MD); **Department of Medicine, Gelre Hospital, Apeldoorn, Netherlands** (T van Bemmel MD); **Department of Pulmonology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, Netherlands** (J van Es MD); **Department of Medicine, Red Cross Hospital, Beverwijk, Netherlands** (L M Faber MD); **Department of Pulmonology** (G M Hazelaar MD) **and Department of Medicine** (M M C Hovens MD), **Rijnstate Hospital, Arnhem, Netherlands; Department of Medicine, Medisch Centrum Haaglanden, The Hague, Netherlands** (H Hofstee MD); **Department of Medicine, University Medical Center**

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

Utrecht, Utrecht, Netherlands (Prof K A H Kaasjager MD, M Nijkeuter MD)**; Department of Hematology, Erasmus Medical Center, Rotterdam, Netherlands** (M J H A Kruip MD, S Schol-Gelok MD)**; Department of Medicine** (R F Loeffen MD) **and Department of Pulmonology** (R C J van Klink MD)**, Alrijne Hospital, Leiderdorp, Netherlands; and Department of Medicine, Flevo Hospital, Almere, Netherlands** (M ten Wolde MD)

Correspondence to: Prof Menno V Huisman, Department of Thrombosis and Hemostasis, Leiden University Medical Center, 2300 RC Leiden, Netherlands **m.v.huisman@lumc.nl**

Research in context

Evidence before this study

We did not do a systematic search on this topic. However, on the basis of several prospective management studies, patients with clinically suspected pulmonary embolism should be managed according to a validated diagnostic algorithm consisting of clinical decision rule such as the Wells' rule, which predicts the pretest probability of pulmonary embolism, a D-dimer test, and eventually a multirow detector computed tomography pulmonary angiography (CTPA). By using such a diagnostic algorithm, pulmonary embolism can be excluded without CTPA in 20–30% of patients, thereby omitting radiation exposure. In a meta-analysis, the 3-month risk of venous thromboembolism in patients managed without CTPA is 0·65% (95% CI 0·38–1·11). Importantly, most CTPA results are still negative for pulmonary embolism, indicating that many patients are exposed to unnecessary radiation. An age-adjusted D-dimer threshold (age × 10 ng/mL for patients >50 years) has been validated prospectively, reporting an absolute reduction of 11·6% (95% CI 10·5–12·9) in the need for CTPA. Only patients aged 50 years or older, and foremost those older than 75 years benefit from this strategy whereas the exposure to unnecessary radiation might be more relevant to younger individuals, particularly women. Therefore, one of the remaining challenges is to further reduce the number of CTPA without reducing the safety of diagnostic management.

Additionally, despite firm evidence of its safety and efficiency, several studies reported that adherence to recommended diagnostic algorithms outside clinical studies is poor. This finding might be partly due to its complexity, and insufficient time at busy emergency departments, which hampers the use of sequential tests. Improved adherence to the algorithm has been shown to significantly decrease the mean number of diagnostic tests used along with—and more importantly—the number of diagnostic failures. For instance, one study reported a failure rate of 7·7% in patients who were managed inappropriately compared with only 1·2% in patients managed appropriately.

Added value of this study

In this study, a novel and simplified diagnostic algorithm for suspected acute pulmonary embolism (the YEARS algorithm) has been prospectively investigated. The YEARS algorithm consists of only 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 found to be the most predictive for pulmonary embolism. This simplified clinical decision rule was combined with variable D-dimer threshold depending on the presence of one of these items. In patients in whom none of the items were present, a D-dimer test threshold of 1000 ng/mL was used whereas a D-dimer threshold of 500 ng/mL was used when one or more items were present.

Our study showed that the YEARS algorithm is safe during 3 months of follow-up in all patients who had pulmonary embolism excluded. In patients managed without CTPA, the 3-month risk of venous thromboembolism was well comparable to the risk reported by a meta-analysis after the current standard algorithm was used. The advantage of the YEARS algorithm is an absolute reduction of 14% of CTPA compared with the current standard algorithm and, importantly, an 8·7% reduction compared with the age-adjusted D-dimer threshold. In this context, patients younger than 50 years also benefit from the YEARS algorithm.

Implications of all the available evidence

There are two main advantages of the YEARS algorithm. First, the YEARS algorithm leads to an absolute 14% decrease in the number of CTPA examinations that is applicable to all ages. This decrease is a major step forward in reducing unnecessary radiation exposure in patients with suspected pulmonary embolism. Second, the YEARS algorithm leads to a simpler and more efficient diagnostic management of patients with suspected pulmonary embolism than standard diagnostic algorithms such as the Christopher Study algorithm, which is likely to improve the adherence to correct diagnostic management of suspected pulmonary embolism and thereby lead to better safety and efficiency in daily clinical practice.

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 a 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 above-mentioned 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 diagnostic 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 in the appendix.

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, 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 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.

See Online for appendix

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). 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

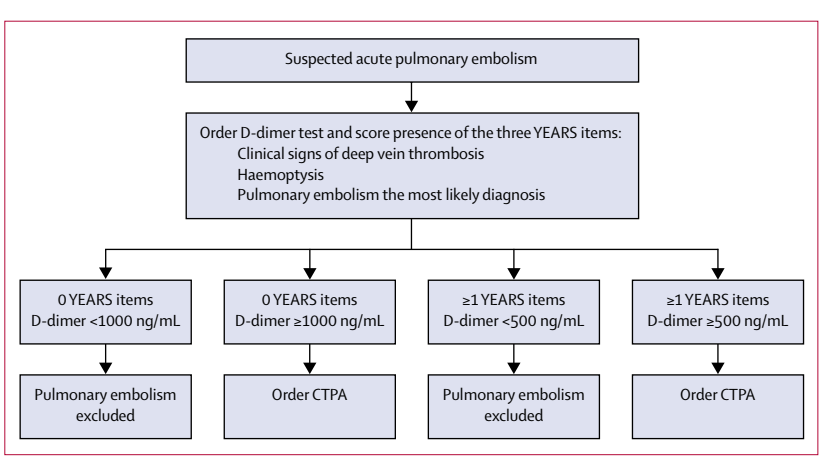

Figure 1: **YEARS algorithm**
CTPA=computed tomography pulmonary angiography.

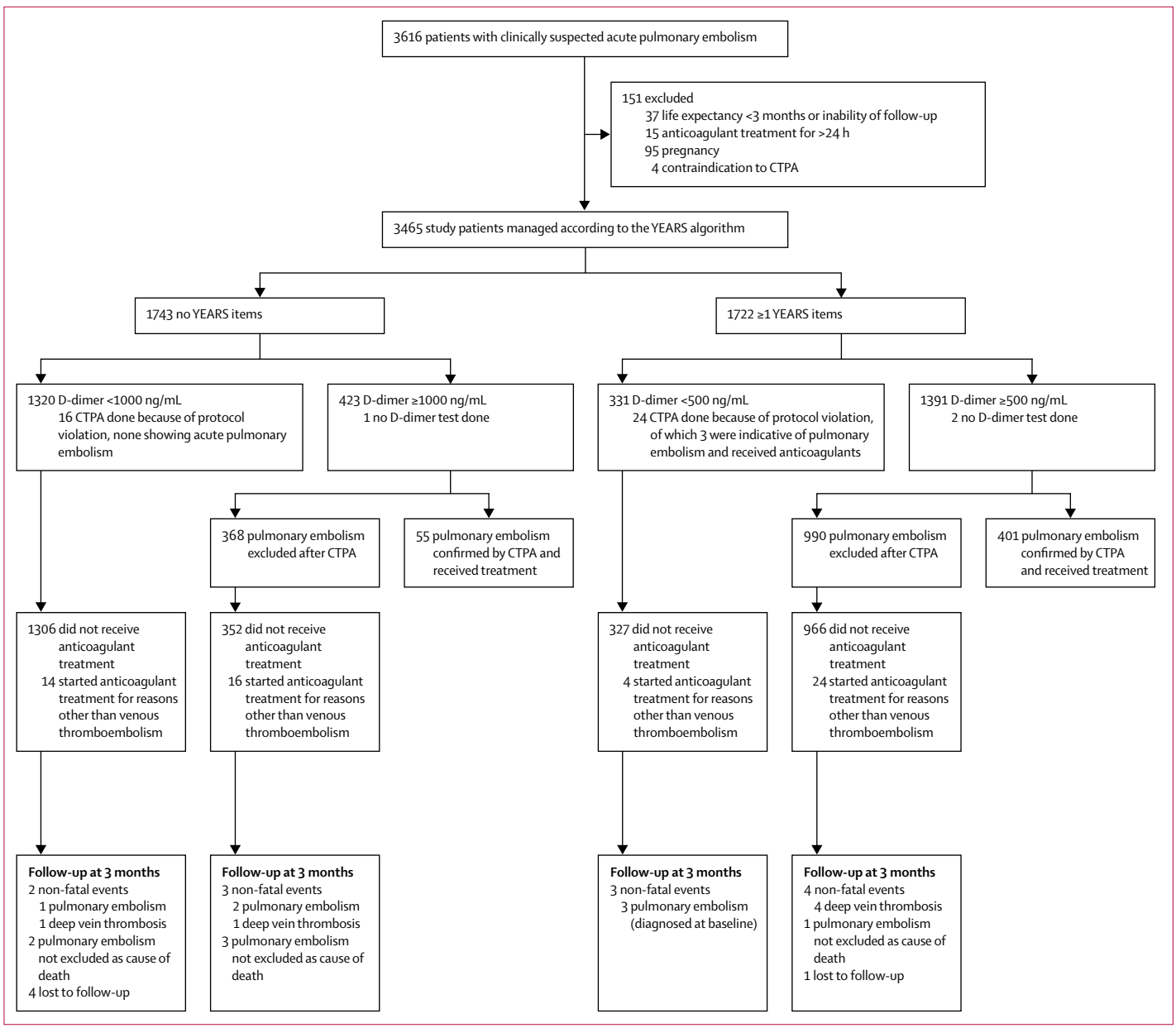

Figure 2: **Flowchart of study patients**
CTPA=computed tomography pulmonary angiography.

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.

	Patients (n=3465)
Mean age (years)	53 (18)
Women	2154 (62%)
Median duration of complaints (days)	3 (1–8)
COPD with treatment	423 (12%)
Heart failure with treatment	137 (4%)
Oestrogen use (% of women)	337 (16%)
Immobilisation or surgery in the past 4 weeks	407 (12%)
Outpatient	2996 (86%)
Heart rate greater than 100 beats per min	683 (20%)
History of pulmonary embolism or deep vein thrombosis	359 (10%)
Malignancy	336 (9·7%)

Data are mean (SD), n (%), or median (IQR). COPD=chronic obstructive pulmonary disease.

Table 1: **Baseline characteristics of patients with suspected pulmonary embolism**

	Patients (n)	Total venous thromboembolism (n [%, 95% CI])	Fatal pulmonary embolism* (n [%, 95% CI])
Completed 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)

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

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

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.

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

	Patients	PE at baseline	Managed without CTPA	Risk of VTE during 3-month follow-up						Efficiency compared with Wells' rule in combination with a D-dimer threshold of <500 ng/mL			
				Incidence in patients managed without CTPA		Incidence in patients managed with CTPA		Overall incidence after pulmonary embolism was excluded at baseline		Managed without CTPA (n)	Difference with YEARS algorithm		
				Events/ patients	% (95% CI)	Events/ patients	% (95% CI)	Events/ patients	% (95% CI)		n/N	% (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)	
Aged <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)	
Aged ≥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)	
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)	
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)	
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)	

Data are n or n (%), unless otherwise specified. PE=pulmonary embolism. CTPA=computed tomography pulmonary angiography. VTE=venous thromboembolism.

Table 3: **Primary outcome and efficiency in subgroups of the total study population**

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, 0·08–0·46).

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%).

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, 95% CI 0·02–0·63) and 0·81% (six of 740, 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, 95% CI 0·17–0·88) and of fatal pulmonary embolism was 0·12% (two of 1629, 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

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer concentration (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	Female	59	0	0	609	54	Death	Patient developed cardiac arrest during admission for acute severe pancreatitis, and was known to have myotonic dystrophy type 1 with severe cardiomyopathy and arrhythmias; implantable cardioverter-defibrillator was deactivated after regular unjustified defibrillations; resuscitation was unsuccessful	Pulmonary embolism not excluded as cause of death
Patient 2	Male	78	0	1	898	11	Death	Patient was diagnosed with end-stage metastasised oropharyngeal carcinoma; found deceased in nursing home	Pulmonary embolism not excluded as cause of death
Patient 3	Female	89	0	1·5	610	18	Pulmonary embolism	Patient diagnosed on CTPA with subsegmental pulmonary embolism during admission for pneumonia and acute heart failure related to severe aortic valve stenosis and mitral valve insufficiency. Patient died 7 days after treatment, which was voluntarily withheld	Non-fatal pulmonary embolism
Patient 4	Male	52	0	1	560	49	Deep vein thrombosis	Patient had deep vein thrombosis 14 days after surgery for glioblastoma multiforme	Deep vein thrombosis
Patient 5	Female	21	2	5·5	380	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 6	Male	58	1	3	420	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 7	Female	71	1	6	410	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism

CTPA=computed tomography pulmonary angiography. *Calculated post hoc.

Table 4: **Diagnostic failures in patients who were managed without CTPA at baseline**

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, 95% CI 0·47–1·5) and incidence of fatal pulmonary embolism was 0·30% (four of 1317, 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 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

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer concentration (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	Male	50	0	1·5	1070	34	Deep vein thrombosis	Patient had vena cava superior syndrome caused by thrombosis at the site of the pacemaker leads	Thrombosis of the vena cava superior
Patient 2	Female	73	0	3	1480	69	Death	Patient died in hospital under the clinical diagnosis of a pneumonia and acute heart failure	Pulmonary embolism not excluded as cause of death
Patient 3	Female	79	0	3	2400	26	Pulmonary embolism	Initiation of anticoagulation because of suspected pulmonary embolism without CTPA confirmation after hospital admission because of heart failure and COPD exacerbation	Non-fatal pulmonary embolism
Patient 4	Female	82	0	0	2550	Unknown	Death	Patient died in nursing home after hospital admission because of acute heart failure and exacerbation of COPD	Pulmonary embolism not excluded as cause of death
Patient 5	Female	57	0	1	4170	12	Pulmonary embolism	Patient was known to have recurrent sarcoma of the uterus; subsegmental pulmonary embolism diagnosed postoperatively; patient died 33 days after diagnosis of pulmonary embolism during palliative care in a hospice	Non-fatal pulmonary embolism
Patient 6	Female	70	0	1	2400	17	Death	Patient died after sudden collapse followed by unsuccessful resuscitation 1 day after surgery for gastric carcinoma	Pulmonary embolism not excluded as cause of death
Patient 7	Female	73	1	5·5	2500	6	Deep vein thrombosis	Patient was known to have leukaemia; developed thrombosis of the brachial vein after superficial thrombophlebitis related to an intravenous catheter	Deep vein thrombosis
Patient 8	Male	84	1	4	5000	32	Deep vein thrombosis	Patient was known to have metastasised prostate cancer; developed deep vein thrombosis after immobilisation during admission at the hospital	Deep vein thrombosis
Patient 9	Female	66	1	7	1325	43	Death	Patient had curative treatment for lung cancer and a stent placed for post-radiation stenosis of the trachea; patient died at home after sudden haemoptysis	Pulmonary embolism not excluded as cause of death
Patient 10	Male	70	1	3	5000	68	Deep vein thrombosis	Patient had subclavian vein thrombus associated with intravenous catheter	Deep vein thrombosis
Patient 11	Female	48	1	3	747	78	Deep vein thrombosis	Patient developed deep vein thrombosis and was diagnosed with antiphospholipid syndrome	Deep vein thrombosis

CTPA=computed tomography pulmonary angiography. COPD=chronic obstructive pulmonary disease. *Calculated post hoc.

Table 5: **Diagnostic failures in patients who were managed with CTPA at baseline**

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 consistently across subgroups.

Contributors

TvdH, FAK, JvE, SM, and MVH designed the study. TvdH, FAK, and MVH managed the study with support and input from all other authors. TvdH, FAK, and MVH analysed the data, which were interpreted by all other authors. TvdH, FAK, and MVH wrote the first draft of the manuscript, which was reviewed, modified, and approved by all other authors. All authors vouch for the accuracy and completeness of the data reported and for keeping the study to the protocol.

Declaration of interests

We declare no competing interests.

YEARS study group

Writing group: Netherlands T van der Hulle, F A Klok, C Heringhaus, M V Huisman (Leiden University Medical Center, Leiden); W Y Cheung, S Middeldorp, L F M Beenen (Academic Medical Center, Amsterdam); S Kooij, A T A Mairuhu, L M van der Pol (Haga Hospital, The Hague); H Hofstee (Medisch Centrum Haaglanden, The Hague); M J H A Kruip, S Schol-Gelok (Erasmus Medical Center, Rotterdam); M ten Wolde (Flevo Hospital, Almere); G M Hazelaar, MMC Hovens; T van Bemmel; J van Es (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam); L M Faber (Red Cross Hospital, Beverwijk); K A H Kaasjager, M Nijkeuter (University Medical Center Utrecht, Utrecht); R F Loeffen, R C J van Klink (Alrijne Hospital, Leiderdorp).

Contributing authors: Netherlands A J Fogteloo, L J M Kroft (Leiden University Medical Center, Leiden); M P Brekelmans (Academic Medical Center, Amsterdam); R M J Vermaire, H Bastiaansen-Bergsma (Haga Hospital, The Hague); J S Biedermann (Erasmus Medisch Centrum, Rotterdam); A Klijn, S van der Voort, A W E Lieveld (Flevo Hospital, Almere); P Y de Jong (Rijnstate Hospital, Arnhem); C G Schaar (Gelre Hospital, Apeldoorn); A Iglesias del Sol (Alrijne Hospital, Leiderdorp).

Adjudication committee: Netherlands H ten Cate, K Hamulyak (Maastricht University Medical Center, Maastricht).

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