Diagnosis, treatment and long-term effects of venous thromboembolism
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Chapter 3

Simplified diagnostic management of suspected pulmonary embolism

the YEARS study

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Chapter 3

Abstract

**Importance:** Validated diagnostic algorithms in patients with suspected pulmonary embolism (PE) are often not used correctly due to complexity, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule has been developed to overcome this complexity and to reduce the number of CTPA.

**Objective:** To prospectively validate the YEARS clinical decision rule in combination with pre-test probability dependent D-dimer level thresholds.

**Design, setting and patients:** A multicenter prospective management cohort study in 12 hospitals in the Netherlands between October 2013 and July 2015 including consecutive patients with clinically suspected PE.

**Intervention:** Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of 3 items (clinical signs of deep venous thrombosis, haemoptysis, PE most likely diagnosis), and D-dimer level. In patients without YEARS items and D-dimer <1000 ng/mL, or ≥1 YEARS items and D-dimer <500 ng/mL, PE was considered excluded. All other patients underwent CTPA. Anticoagulants were withheld from patients in whom PE was excluded, and patients were followed for 3 months.

**Main Outcomes:** The primary outcome was independently adjudicated venous thromboembolism (VTE) events during 3 months of follow-up after PE was excluded at baseline. The secondary outcome was the number of required CTPA compared to the Wells diagnostic algorithm.

**Results:** In total 3465 patients were studied, with an overall PE prevalence of 13%. Of the 2944 patients in whom PE was ruled out at baseline and remained untreated, 18 were diagnosed with symptomatic VTE during the 3-month follow-up period, for an incidence of 0.61% (95%CI 0.36-0.96). The incidence of fatal VTE was 0.20% (95%CI 0.07-0.44). CTPA was not indicated in 1651 patients (48%). The absolute reduction in CTPA examinations compared to the algorithm using the Wells rule and fixed D-dimer threshold of <500 ng/mL was 14% (95%CI 11-16).

**Conclusions and Relevance:** PE can be safely excluded by the YEARS diagnostic algorithm in patients with suspected PE, with a low risk of VTE during 3-months follow-up. The main advantage of the YEARS algorithm is the 14% absolute decrease in the number of CTPA examinations.
Introduction

The clinical diagnosis of pulmonary embolism (PE) is non-specific and must therefore be followed by objective testing. Because of its diagnostic accuracy and wide availability, multi-row detector computed tomography pulmonary angiography (CTPA) is the imaging test of choice to confirm acute PE. Increasing use of CTPA with diminishing prevalence of PE - to even less than 10% - has led to overdiagnosis - of mostly subsegmental PE - as well as unnecessary risks of radiation exposure and contrast induced nephropathy. To avoid this, validated diagnostic algorithms for suspected acute PE, using sequential testing, have been introduced. In these, a normal D-dimer test result in patients with unlikely probability safely excludes PE. 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.

Despite firm evidence of its safety and efficacy, adherence to recommended diagnostic strategies in clinical practice is variable. This may be partly due to its complexity and lack of time at busy emergency departments, which hampers the use of sequential tests. Importantly, improved adherence to the algorithm, for instance by implementing 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.

The aim of this study was to prospectively evaluate a novel and simplified diagnostic algorithm for suspected acute PE, the YEARS algorithm. This algorithm involves the simultaneous assessment of only three items – clinical signs of deep venous thrombosis (DVT), haemoptysis, and PE most likely diagnosis – and a highly sensitive D-dimer test with a pre-test probability dependent threshold. These three items of the original Wells clinical decision rule were found to be the most predictive for PE. The YEARS algorithm was designed to further decrease the number of necessary CTPA examinations as well as to improve implementation and adherence in clinical practice, compared to the current diagnostic standard.

Materials and Methods

Study design

The study was a prospective multicenter cohort outcome study evaluating the safety and efficiency of the YEARS diagnostic algorithm in patients with suspected acute PE (Figure 3.1). The algorithm was implemented as standard diagnostic strategy in all participating hospitals.

This 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 protocol was centrally approved by
the institutional review board (IRB) of the Leiden University Medical Center which waived the need for informed consent; this decision was endorsed by the local IRB of each participating center (Netherlands Trial Registry number NTR4193). All members of the steering committee contributed to the interpretation of the results, approved the final version of the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data reported.

**Patients**

Consecutive out- and inpatients with clinically suspected acute (first or recurrent) PE were eligible for inclusion if they were 18 years of age or older. Exclusion criteria were: treatment with therapeutic doses of anticoagulants initiated ≥ 24 hours prior to eligibility assessment, life expectancy less than three months or geographic inaccessibility precluding follow-up, pregnancy, or contraindication to CTPA due to allergy to intravenous contrast agent.

**YEARS diagnostic algorithm**

Patients were evaluated by an attending physician who suspected acute PE, and then assessed the YEARS score by combining the number of YEARS items (scored as yes or no) with the pre-test probability dependent threshold of the D-dimer test. D-dimer levels were measured upon presentation of the patient, using automated well-validated high-sensitive quantitative D-dimer assays (according to local practice Vidas D-dimer Exclusion®, Biomerieux, Marcy-L’Étoile, France; Tinaquant®, Roche Diagnostica, Mannheim, Germany; STA-LIA® DiagnosticaStago, Asnieres, France; Innovance®, Siemens, Marburg, Germany). Our study reflected daily clinical practice in which D-dimer levels were 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 level <1000 ng/mL, PE was considered excluded and further testing was withheld. In patients with one or more YEARS items and a D-dimer level <500 ng/mL, PE was considered excluded and further testing was withheld. All other patients, i.e. either with no YEARS item and a D-dimer level ≥1000 ng/mL, or with one or more YEARS items and a D-dimer level of ≥500 ng/mL, were referred for CTPA, which demonstrated or excluded the diagnosis of PE. Patients in whom PE was ruled out were left untreated and followed for three months. They were instructed to return to the hospital in the event of symptoms of venous thromboembolism (VTE), after which objective diagnostic tests were performed to confirm or refute the disease. Follow-up consisted of a scheduled outpatient visit or telephone interview after three months. At this visit, information was obtained on complaints suggestive of VTE. Patients in whom acute PE was confirmed at baseline were treated with anticoagulants according to international guidelines.
Simplified diagnostic management of pulmonary embolism

Figure 3.1 | YEARs algorithm

Abbreviations: PE, pulmonary embolism; DVT, deep venous thrombosis; CTPA, computed tomography pulmonary angiography.
Figure 3.2 | Flowchart of study patients

PE, pulmonary embolism; DVT, deep venous thrombosis; CTPA, computed tomography pulmonary angiography; ¹16 CTPA performed due to protocol violation, none showing acute PE; ²14 started anticoagulation for other reasons than VTE; ³1 no D-dimer test performed; ⁴16 started anticoagulation for other reasons than VTE; ⁵24 CTPA performed due to protocol violation of which 3 were indicative of PE; all three patients were treated with anticoagulants; ⁶4 started anticoagulation for other reasons than VTE; ⁷2 no D-dimer test performed; ⁸26 started anticoagulation for other reasons than VTE
Simplified diagnostic management of pulmonary embolism

151 Excluded
- 37 Life expectancy <3 months or inability of follow-up
- 15 Anticoagulant treatment for >24 hours
- 95 Pregnancy
- 4 Contra-indication to CTPA

1722 ≥1 YEARS items

331 D-dimer <500 ng/mL³

Follow-up at 3 months
- 3 Nonfatal events
  - 3 PE (diagnosed at baseline)
  - 0 DVT
- 0 Confirmed fatal PE
- 0 PE not excluded as cause of death
- 0 Lost to Follow-up

327 did not receive anticoagulant treatment⁶

964 did not receive anticoagulant treatment⁸

Follow-up at 3 months
- 4 Nonfatal events
  - 4 DVT
- 0 Confirmed fatal PE
- 1 PE not excluded as cause of death
- 1 Lost to Follow-up

1391 D-dimer ≥500 ng/mL²

- 2 no D-dimer test performed

990 PE Excluded after CTPA

401 PE confirmed by CTPA and received treatment
Study outcome

The primary study outcome was the 3-month incidence of symptomatic VTE in the overall population as well as in patients managed without CTPA or with CTPA separately. In case of clinically suspected PE or DVT, objective diagnostic tests were required, including CTPA for suspected PE and compression ultrasonography for suspected DVT. In case of death, information was obtained from the hospital records. Deaths were classified as caused by PE if: 1) PE was confirmed by autopsy, 2) PE was demonstrated by objective testing prior to death or 3) PE could not be confidently excluded as a cause of death. An independent adjudication committee evaluated and adjudicated all suspected VTE and deaths during follow-up.

The secondary study outcome was the proportion of required CTPA examinations to complete the YEARS diagnostic algorithm at baseline, as compared to the proportion of CTPA examinations that would have been required if the algorithm, using the 2-level Wells rule outcome and fixed D-dimer threshold of <500 ng/mL would have been applied in the study population, as well as to historical data.6,8,16

Statistical analysis

Based on the derivation cohort of the YEARS algorithm, we expected a failure rate of 1.2% in patients managed without CTPA.15 The sample size was based on this assumption, with the aim to keep the upper limit of the 95% confidence interval (CI) of this point estimate below 2.7%.17 We calculated that we needed to include 1333 patients managed without CTPA, using a 2-sided alpha of 5% and a beta of 80%. Since 44% of patients in the combined YEARS derivation and validation cohort15 could have been managed without CTPA and accounting for up to 7.5% loss to follow-up, a total of 3260 patients with suspected PE would be required.

For the secondary outcome analysis, we determined the absolute difference in the number of required CTPA examinations between the different clinical scenarios. All descriptive parameters and exact 95% CIs around the observed incidences were calculated. All analyses were performed using SPSS software (version 23), Chicago, Ill, USA.

Results

Study Patients

From October 2013 to July 2015, 3616 consecutive patients with clinically suspected PE were screened in the 12 participating hospitals, of whom 151 (4.2%) were excluded for the following reasons: more than 24 hours of therapeutic anticoagulation (n=15), life expectancy less than three months or geographic inaccessibility precluding follow-up (n=37), pregnancy (n=95), and contra-indication
to CTPA due to allergy to intravenous contrast agent (n=4) (Figure 3.2). The final study population of 3465 participants included 3060 (88%) outpatients. Patients had a mean age of 53 years (SD 18) and 62% were female (Table 3.1).

Table 3.1 | Baseline characteristics of 3465 included patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>53 (18)</td>
</tr>
<tr>
<td>Female</td>
<td>2154 (62)</td>
</tr>
<tr>
<td>Duration of complaints, days (median and IQR)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>COPD with treatment</td>
<td>423 (12)</td>
</tr>
<tr>
<td>Heart failure with treatment</td>
<td>137 (4.0)</td>
</tr>
<tr>
<td>Estrogen use, women</td>
<td>337 (16)</td>
</tr>
<tr>
<td>Immobilisation or surgery in the previous 4 weeks</td>
<td>407 (12)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>3060 (88)</td>
</tr>
<tr>
<td>Heart rate greater than 100/min</td>
<td>683 (20)</td>
</tr>
<tr>
<td>Previous history of PE or DVT</td>
<td>359 (10)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>336 (9.7)</td>
</tr>
</tbody>
</table>

Abbreviations: n, number; SD, standard deviation; IQR, Interquartile range

Safety of the overall YEARS algorithm

Of the 2949 patients in whom PE was ruled out at baseline, who remained untreated and completed the follow-up period, 18 patients were diagnosed with symptomatic VTE during the 3-month follow-up period, for an incidence of 0.61% (95%CI 0.36-0.96). The incidence of fatal VTE was 0.20% (6 patients; 95%CI 0.07-0.44; Table 3.2). In a worst case scenario, accounting the 5 patients who were lost to follow-up (in 4 patients PE was excluded without CTPA and 1 patient had a negative CTPA) as recurrent VTE, the 3-month VTE incidence would be 0.82% (95%CI 0.52-1.2).

Efficiency of the overall YEARS algorithm

According to the YEARS algorithm, CTPA was not indicated in 1651 (48%). If the diagnostic algorithm, using Wells rule and D-dimer with fixed threshold of <500 ng/mL would have been applied, 1173 (34%) of patients could have been managed without CTPA at baseline, for an absolute difference of 14% (95%CI 12-16) in favor of the YEARS algorithm.
Chapter 3

Results of the YEARS diagnostic algorithm

Of the 3465 included patients, 1320 (38%) had no YEARS items and a D-dimer test result <1000 ng/mL, and 331 (9.6%) had one or more YEARS items and a D-dimer level <500 ng/mL (Figure 3.2). The 422 patients without a YEARS item and a D-dimer level ≥1000 ng/mL and one patient without a YEARS item in whom D-dimer testing was not performed, underwent CTPA imaging, which demonstrated PE in 55 of them. The 1389 patients with one or more YEARS items present and a D-dimer level ≥500 ng/mL and two patients with one or more YEARS items, in whom D-dimer testing was not performed, also underwent CTPA imaging, which demonstrated PE in 401 of them. The overall PE prevalence was 13%.

Patients managed without CTPA

Of the 1651 patients who should have been managed without CTPA, the protocol was violated in 40 patients, and CTPA, while not indicated, showed PE in three patients who were treated with anticoagulants. These were considered diagnostic failures and are included in the primary outcome. Further, 18 (1.1%) patients were treated with oral anticoagulants for other reasons (i.e., 8 atrial fibrillation, 1 thrombophlebitis and 9 other reasons, including idiopathic pulmonary hypertension and peripheral arterial disease) and 4 (0.24%) patients were lost to follow-up. Four of the remaining 1589 patients returned with symptomatic VTE events (1 non-fatal PE, 1 DVT; 2 deaths in which fatal PE could not be excluded). Therefore, the 3-month incidence of VTE in patients who did not undergo CTPA according to the YEARS algorithm was 0.43% (7/1629; 95% CI 0.17-0.88) and of fatal PE 0.12% (2/1629; 95% CI 0.01-0.44; Figure 3.2, Table 3.2). Seven other patients (0.43%) died of non-VTE related causes.

### Table 3.2

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, n</th>
<th>Total VTE, n (%)</th>
<th>Fatal PE, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[95% CI]</td>
<td>[95% CI]</td>
</tr>
<tr>
<td>Complete algorithm</td>
<td>2944</td>
<td>18 (0.61%)</td>
<td>6 (0.20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0.36-0.96]</td>
<td>[0.07-0.44]</td>
</tr>
<tr>
<td>Patients managed without CTPA</td>
<td>1629</td>
<td>7 (0.43%)</td>
<td>2 (0.12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0.17-0.88]</td>
<td>[0.01-0.44]</td>
</tr>
<tr>
<td>Patients managed with CTPA</td>
<td>1315</td>
<td>11 (0.84%)</td>
<td>4 (0.30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0.47-1.5]</td>
<td>[0.12-0.78]</td>
</tr>
</tbody>
</table>

Abbreviations: VTE, venous thromboembolism; n, number; CI, confidence interval; CTPA; computed tomography pulmonary angiography
Patients managed with CTPA

Of the 1358 patients in whom CTPA ruled out PE, 42 patients (3.1%) were treated with anticoagulants for other reasons (20 atrial fibrillation, 3 thrombo-phlebitis, 1 splanchic vein thrombosis, 1 thrombus in left ventricle, 1 high-dose thrombosis prophylaxis, 1 suspected but later ruled out pulmonary vein thrombosis, 1 vena cava superior syndrome due to mediastinal mass, and 14 other reasons, including idiopathic pulmonary hypertension and peripheral arterial disease) and one patient was lost to follow-up (0.07%). Of the 1315 remaining patients, 11 patients returned with symptomatic VTE events: seven patients had non-fatal VTE events (two non-fatal PE and five DVT) and in four patients who died, PE could not be excluded as a contributing cause of death, for a total 3-month VTE incidence of 0.84% (11/1315; 95%CI 0.47-1.5) and a fatal PE incidence of 0.30% (4/1315; 95%CI 0.12-0.78; Figure 3.2, Tables 3.2). Eighty-five other patients (6.5%) died of non-VTE related causes.

Discussion

This prospective study showed that the YEARS algorithm, with simultaneous assessment of YEARS items and D-dimer level, safely excluded acute PE and led to a significant absolute 14% decrease in the need for CTPA imaging compared to standard algorithms. The 3-month VTE incidence in patients who were not subjected to CTPA was fully in line with that observed in studies using algorithms with sequential diagnostic testing and traditional 2-level Wells score, and a fixed cut-off level of D-dimer of 500 ng/mL: 0.43% versus 0.34%.18 Despite the theoretical possibility that the increased efficiency of the YEARS algorithm would lead to lesser safety in the patients managed with CTPA, the risk of recurrent VTE in the latter group was comparable to this risk after normal CTPA observed in previous studies using standard algorithms: 0.84% (95%CI 0.47-1.5) versus 1.2% (95% CI 0.8-1.8).19 In addition, fatal PE occurred in 0.30% (95% 0.12-0.78) in the present study, compared to 0.6% (95%CI 0.4-1.1) using standard algorithms.19

Although this study for the first time integrates clinical probability assessment and D-dimer level with selective use of a higher cut-off, alternative higher cut-offs have been successfully evaluated in previous studies. A D-dimer cut-off of 1000 ng/mL was safely used in 678 patients with suspected PE and low clinical probability.20 Also, after our study had started, the ADJUST-PE study, using an age-dependent D-dimer cut-off level age x 10 µg/L in patients over 50 years of age has been published. In this study, the 3-month VTE incidence in patients in the PE unlikely category and with a D-dimer level >500 ng/mL but below the age-adjusted threshold was only 0.3% (95%CI 0.1–1.7).16

The gain of the YEARS algorithm over existing algorithms is the notable reduction in the need for CTPA imaging and with that, reduction in potential for radiation induced harm and overdiagnosis.21 In the current study, the YEARS algorithm was associated with an absolute 7.8% decrease in the num-
ber of CTPA examinations compared to the ADJUST study. Although not an originally planned endpoint of the current study, CTPA would not have been indicated in 1348 patients (37%) in our cohort when the ADJUST criteria would have been applied, for an absolute difference of 8.7% (95%CI 6.4-11) in favor of the YEARS algorithm. The main reason for this difference is the applicability of the YEARS algorithm to patients with suspected acute PE in all age categories, and not only in patients over the age of 50 years. Of note, our results are very relevant for younger women under the age of 50, 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 of the cohort and the independent adjudication of endpoints. Further, by studying a real-world cohort of patients in daily practice circumstances, we expect that the YEARS algorithm can be easily implemented outside the participating study sites, and that the presented data on safety and efficiency actually are representative for non-trial conditions. Also, our current results with regard to both the safety and efficiency of the algorithm are in line with the numbers reported in the initial derivation and retrospective validation study of our algorithm. This is a second argument that our results are robust and generalisable. Of note, although haemodynamic instability was not a formal exclusion criterion of this study, we have described a cohort of only haemodynamically stable patients.

We did not perform a randomised study and could therefore not directly compare the VTE risk with a control group that would have been managed with traditional algorithms. However, the low observed 3-month VTE risk and near complete follow-up strongly supports the chosen cohort design. Also, while an independent committee evaluated and adjudicated all endpoints, autopsy was hardly performed. As a consequence, it was very difficult to exclude PE as a (possible) cause of death in six patients during follow-up. These patients already had or developed extensive co-morbidity, 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 PE 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. Further, the prevalence of PE was higher than observed in large cohorts in North America, but somewhat lower compared to previous studies in Europe. Lastly, there were 43 violations of the study protocol, with a D-dimer test not performed in three patients and a non-indicated CTPA performed in 40 patients, of which three confirmed the presence of acute PE. This number is comparable to that in the Christopher study, in which 2 of 25 unjustified CTPA examinations revealed PE.

In conclusion, the YEARS diagnostic algorithm safely rules out acute PE in patients presenting with clinically suspected PE, with a low risk for VTE during 3-months follow-up, and it can replace current diagnostic algorithms. The main advantage of the YEARS algorithm is the absolute 14% decrease in the number of CTPA examinations that is applicable to all age categories.
Simplified diagnostic management of pulmonary embolism

Reference list


21. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ 2013;347:f3368. Figure 3.1 YEARS algorithm