

# Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism

## A Randomized Clinical Trial

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**IMPORTANCE** Uncontrolled studies suggest that pulmonary embolism (PE) can be safely ruled out using the YEARS rule, a diagnostic strategy that uses varying D-dimer thresholds.

**OBJECTIVE** To prospectively validate the safety of a strategy that combines the YEARS rule with the pulmonary embolism rule-out criteria (PERC) rule and an age-adjusted D-dimer threshold.

**DESIGN, SETTINGS, AND PARTICIPANTS** A cluster-randomized, crossover, noninferiority trial in 18 emergency departments (EDs) in France and Spain. Patients (N = 1414) who had a low clinical risk of PE not excluded by the PERC rule or a subjective clinical intermediate risk of PE were included from October 2019 to June 2020, and followed up until October 2020.

**INTERVENTIONS** Each center was randomized for the sequence of intervention periods. In the intervention period (726 patients), PE was excluded without chest imaging in patients with no YEARS criteria and a D-dimer level less than 1000 ng/mL and in patients with 1 or more YEARS criteria and a D-dimer level less than the age-adjusted threshold (500 ng/mL if age <50 years or age in years × 10 in patients ≥50 years). In the control period (688 patients), PE was excluded without chest imaging if the D-dimer level was less than the age-adjusted threshold.

**MAIN OUTCOMES AND MEASURES** The primary end point was venous thromboembolism (VTE) at 3 months. The noninferiority margin was set at 1.35%. There were 8 secondary end points, including chest imaging, ED length of stay, hospital admission, nonindicated anticoagulation treatment, all-cause death, and all-cause readmission at 3 months.

**RESULTS** Of the 1414 included patients (mean age, 55 years; 58% female), 1217 (86%) were analyzed in the per-protocol analysis. PE was diagnosed in the ED in 100 patients (7.1%). At 3 months, VTE was diagnosed in 1 patient in the intervention group (0.15% [95% CI, 0.0% to 0.86%]) vs 5 patients in the control group (0.80% [95% CI, 0.26% to 1.86%]) (adjusted difference, -0.64% [1-sided 97.5% CI, -∞ to 0.21%], within the noninferiority margin). Of the 6 analyzed secondary end points, only 2 showed a statistically significant difference in the intervention group compared with the control group: chest imaging (30.4% vs 40.0%; adjusted difference, -8.7% [95% CI, -13.8% to -3.5%]) and ED median length of stay (6 hours [IQR, 4 to 8 hours] vs 6 hours [IQR, 5 to 9 hours]; adjusted difference, -1.6 hours [95% CI, -2.3 to -0.9]).

**CONCLUSIONS AND RELEVANCE** Among ED patients with suspected PE, the use of the YEARS rule combined with the age-adjusted D-dimer threshold in PERC-positive patients, compared with a conventional diagnostic strategy, did not result in an inferior rate of thromboembolic events.

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The optimal diagnostic strategy for patients with suspected pulmonary embolism (PE) remains debated. A conventional algorithm uses a bayesian approach with an initial subjective estimate of pretest probability, D-dimer testing (in patients with non-high clinical probability) and if the D-dimer level is above a certain threshold, chest imaging (computed tomography pulmonary angiography (CTPA), or pulmonary ventilation/perfusion [ $\dot{V}/\dot{Q}$ ] scanning). Because clinical signs of PE and D-dimer testing have low specificity, CTPA is frequently used, with a reported diagnostic yield of only about 10%.<sup>1-3</sup> CTPA use has increased over the past 2 decades, resulting in added costs and patient radiation exposure.<sup>4,5</sup>

Various strategies have been derived to safely reduce the use of CTPA. In patients with a low subjective pretest probability of PE, the absence of all 8 PE rule-out criteria (PERC) (age  $\geq 50$  years, pulse rate  $\geq 100$ /min, arterial oxygen saturation  $< 95\%$ , unilateral leg swelling, hemoptysis, recent trauma or surgery, prior PE or deep venous thrombosis, and exogenous estrogen use) or use of an age-adjusted D-dimer cutoff (age  $\times 10$  ng/mL in patients aged  $\geq 50$  years) safely excluded PE.<sup>2,6</sup> It was reported that the YEARS rule can also safely exclude PE.<sup>5,7</sup> This rule uses a raised D-dimer cutoff of 1000 ng/mL (instead of 500 ng/mL) in patients with no YEARS criteria (PE is the most likely diagnosis, clinical sign of deep venous thrombosis, and hemoptysis).<sup>2,8</sup> However, the YEARS rule has not been investigated in a randomized trial, and its safety when combined with the PERC rule and the age-adjusted D-dimer threshold has not been evaluated.

The objective of this cluster-randomized, crossover, noninferiority trial was to determine whether in emergency department (ED) patients with suspicion of PE that was not excluded by the PERC rule, a strategy that combines the YEARS rule and the age-adjusted D-dimer cutoff can safely rule out the diagnosis (Figure 1). Whether this strategy decreased the use of chest imaging was also determined.

## Methods

### Study Design

The design of this cluster-randomized, crossover, noninferiority trial has been published previously,<sup>9</sup> and the protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. The trial was funded by the French Ministry of Health and sponsored by the Assistance Publique-Hôpitaux de Paris [APHP]; Paris, France). The Paris-East (URCEST, DRICI-APHP) clinical research unit monitored the study by conducting on-site visits and handled the collection, storage, and analysis of the study data. Approval of the study was obtained by the appropriate ethics committees in Spain and France (Comité de Ética de la Investigación con Medicamentos del Hospital Clínic de Barcelona and Comité de Protection des Personnes Ile-de-France XI). Informed consent was sought for each patient before inclusion in the study: oral in France and written in Spain.

A cluster-randomized design was chosen to facilitate recruitment in the EDs. This design also minimized the risk

### Key Points

**Question** Among emergency department patients with suspicion of pulmonary embolism (PE) not ruled out by the pulmonary embolism rule-out criteria (PERC) rule, does use of a diagnostic strategy that combines the YEARS rule and age-adjusted D-dimer threshold safely exclude the diagnosis of venous thromboembolism?

**Findings** In this cluster-randomized, crossover, noninferiority trial that included 1414 patients with a suspicion of PE in France and Spain, the 3-month risk of a missed thromboembolic event using the intervention diagnostic strategy, compared with a conventional strategy, was 0.15% vs 0.80%; the confidence interval of this difference did not cross the noninferiority margin of 1.35%.

**Meaning** Among emergency department patients with suspected PE who were PERC positive, the use of the YEARS rule combined with the age-adjusted D-dimer threshold did not lead to an inferior rate of thromboembolic events compared with a conventional diagnostic strategy.

of contamination between the 2 groups because the ED physicians all used the same diagnostic algorithm during each 4-month period.

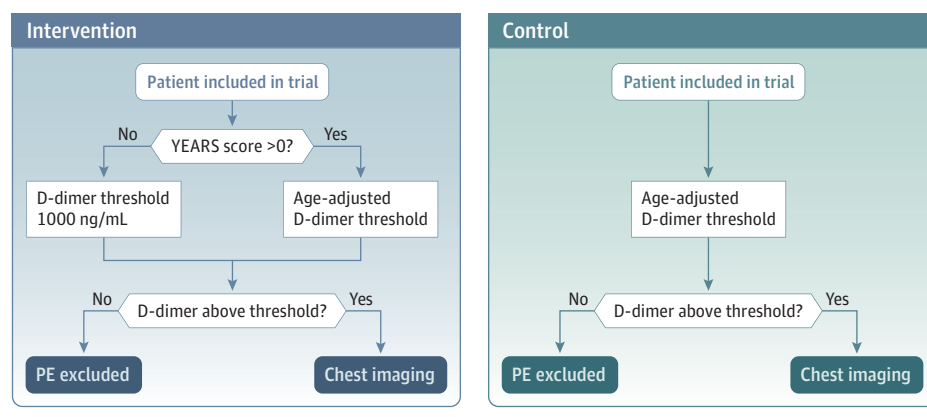
### Patients

Of 24 adult EDs affiliated with or partners of the Improving Emergency Care Research Federation (FHU IMPEC) that were invited to participate, 18 accepted: 2 in Spain and 16 in France (eTable 1 in Supplement 3). Patients were included from October 1, 2019, to October 8, 2020. However, during the first COVID-19 wave in Spain and France, recruitment was halted because eligible patients were also suspected of having COVID-19 and most underwent chest imaging. Furthermore, all non-COVID-19 research was stopped in France and Spain. Recruitment was therefore halted on March 15, 2020, and resumed (depending on the local situation) after 4 to 6 weeks.

The diagnostic strategy for PE was semistructured. The first step was the assessment of a pretest clinical probability by the emergency physician. The subjective clinical probability (known as the unstructured clinician's gestalt) was chosen because it has similar risk stratification performances to structured scores and is proven to be safe when used in conjunction with the PERC score.<sup>2,10</sup>

Patients were included if there was clinical suspicion of a PE (eg, acute onset of chest pain, worsening acute dyspnea, and/or syncope) and either a low subjective probability ( $< 15\%$ ) with 1 or more PERC score elements or an intermediate subjective probability (16%-50%) of PE.<sup>11,12</sup> Patients with a high subjective probability of PE ( $> 50\%$ , ie, those who should undergo chest imaging without further workup), and those with a low subjective probability of PE with a PERC score of zero (ie, those for whom PE is ruled out without a D-dimer), were excluded from the study.<sup>2,6,13,14</sup> Other exclusion criteria were severe illness (respiratory distress, hypotension, peripheral oxygen saturation  $< 90\%$ ), current anticoagulant treatment, a current diagnosis of thromboembolism, pregnancy, being a correctional facility inmate, or having symptoms obviously related to a cause other than PE.

Figure 1. Diagnostic Strategy for Pulmonary Embolism (PE)



YEARS score ranges from 0 to 3, 1 point per item: PE is the most likely diagnosis, hemoptysis, and clinical sign of deep vein thrombosis. Chest imaging included computed tomography pulmonary angiography or pulmonary ventilation/perfusion scan.

### Randomization

The randomization sequence was computer generated by a statistician who was not otherwise involved in the trial using PROC PLAN (SAS version 9.4; SAS Institute). This was concealed until the center was instructed by the global project manager to begin the study. Each ED was randomized to either the control strategy period for 4 months, followed, after a 2-month washout period, by the intervention strategy period for 4 months, or to the reverse order. The randomization ratio was 1:1. Randomization was stratified by country and ED size (small vs large defined as <50 000 or ≥50 000 patients per year), using 4 blocks of 4 and 1 block of 2. The patients were enrolled by the ED physicians. Blinding was not feasible.

### Intervention

The intervention was a diagnostic strategy to rule out PE that involved both an assessment of the YEARS criteria and D-dimer testing. PE was ruled out in (1) patients with no YEARS criteria and a D-dimer level below the elevated threshold of 1000 ng/mL or (2) patients with 1 or more YEARS criteria and a D-dimer level below the age-adjusted threshold (age × 10 ng/mL in patients aged ≥50 years). The 3 YEARS items were assessed by the treating emergency physician. PE was considered as the most likely diagnosis if alternative diagnoses were less likely than PE. A D-dimer level above the relevant threshold triggered chest imaging (Figure 1).

During the control period, the diagnostic strategy was based on current recommendations: all patients underwent D-dimer testing with the threshold set at the age-adjusted level.<sup>8</sup> A D-dimer level above the age-adjusted threshold triggered chest imaging (Figure 1).

### Outcomes

Outcomes were analyzed at the individual patient level. The primary outcome was failure of the diagnostic strategy, defined as venous thromboembolism (VTE) diagnosis at 3 months after exclusion of PE during the initial ED visit. VTE was defined as deep vein thrombosis confirmed by venous Doppler ultrasonography, an intraluminal defect on CTPA, or a  $\dot{V}/\dot{Q}$  mismatch by  $\dot{V}/\dot{Q}$  scanning that had a high probability of being caused by a PE. There were 8 secondary end points,

of which 6 were analyzed in this study: chest imaging (CTPA or  $\dot{V}/\dot{Q}$  scan) ordered by ED physicians, ED length of stay, hospital admission following the ED visit, anticoagulant administration, all-cause mortality, and all-cause readmissions at 3 months. Two prespecified secondary end points were not included in this analysis; the safety of the 4PEPS score and the cost-effectiveness of the intervention will be reported in an ancillary analysis.

A sensitivity analysis on the primary end point after exclusion of isolated subsegmental PE was also performed because the need for treatment of these small emboli is controversial.<sup>15,16</sup>

Occurrence of the primary outcome was determined during a telephone interview with the patient 3 months after the index ED visit. All patients were instructed to return to the same hospital if they developed worsening or recurrent symptoms. A clinical research technician reviewed the medical records in the event of return visits to the ED or of hospital admission. If the patient could not be contacted after 3 attempts, the primary care physician was contacted. When neither the patient nor the primary care physician could be contacted by telephone 3 months after the initial ED visit, the death records at the patient's place of birth were consulted.

The primary outcome was adjudicated by 3 clinicians with expertise in thromboembolic disease, had no other involvement in the study, worked independently, and were blinded to study period. Disagreements were resolved by consensus among the 3 experts. The adjudication committee reviewed cases of death without evidence of VTE to determine whether the deaths were probably related to PE or to another cause.<sup>17</sup> In cases of unexpected death with no identified cause, the experts adjudicated a PE as cause of the death.

### Sample Size Estimation

The complete statistical plan is provided in Supplement 2. The noninferiority margin was set at 1.35%, ie, at a more conservative value than used previously.<sup>2,18,19</sup> In line with recent International Society on Thrombosis and Haemostasis recommendations for diagnosing PE, safety of the intervention strategy was also assessed based on the upper bound of the 1-sided 97.5% CI for the failure rate in the intervention group,

which was deemed acceptable if less than 1.85%.<sup>20</sup> With an anticipated failure rate of 0.5% in the control group, the 2-sided  $\alpha$  risk set at 5% and  $\beta$  set at 20%, 857 patients were needed.<sup>2,7,8</sup> Assuming a within-site intraclass correlation coefficient of 0.018, an interperiod correlation of 0.0115, and a mean cluster size for 1 period (4 months) of 22 patients, the cluster design effect would be 1.37.<sup>2,21,22</sup> Assuming that 5% of patients would not be evaluable, with 18 EDs and 2 periods per ED, 1234 patients were needed.

### Statistical Analysis

Because this was a noninferiority study, the primary end point was assessed in the per-protocol population to avoid favoring the noninferiority hypothesis.<sup>23,24</sup> The per-protocol population excluded patients who did not meet all inclusion and non-inclusion criteria, were not treated using the strategy allocated to the ED, had a missing value for the primary end point, or had any other major protocol deviation identified during the data review just before the database was locked. In the as-randomized population, patients with missing values for the primary end point were classified as not meeting the end point because the prevalence of the primary end point was anticipated to be less than 2%. A sensitivity analysis of the primary outcome was performed using multiple imputation to account for missing data (as-randomized-with-multiple-imputation population). Multiple imputation was performed using the Full Conditional Specific Model of PROC MI (SAS/STAT version 14.3). The discriminative function was used for categorical variables, and 15 data sets were created. All results were combined using PROC MIANALYZE. Only the unadjusted difference was computed for the primary end point because computation of the adjusted difference was technically impossible.

In addition, in line with recent suggestions that the safety of a new strategy should also be evaluated among patients where the strategy was actually applied, a post hoc analysis on the per-protocol population was performed on the subgroup of patients that had a YEARS score of zero, ie, those in whom the strategy was different in the intervention group.<sup>25,26</sup> The rate of chest imaging in this subpopulation was also described in the 2 groups. Diagnostic yields of chest imaging were computed by dividing the number of diagnosed PEs by the number of performed chest imaging.

Baseline patient characteristics were described overall and for each group using the number (percentage) for categorical variables and the mean (SD) or median (IQR) according to distribution for quantitative variables. Unadjusted differences and 95% CIs were calculated using the exact method for binary variables and the Brookmeyer and Crowley method for continuous variables.<sup>27</sup>

The frequency of VTE at 3 months was assessed using a generalized linear-regression mixed model with the Bernoulli distribution (logit link), considering strategy, period, and strategy-by-period interaction as fixed effects and cluster as a random effect.<sup>28</sup> Secondary end points were compared between groups in the as-randomized population, under the superiority hypothesis. Because of the potential for type I error due to multiple comparisons, findings for analyses of second-

ary end points should be interpreted as exploratory. Sensitivity analyses of the secondary end points were performed on the per-protocol population. Missing values for secondary criteria were not replaced. SAS software (version 9.4; SAS Institute), Stata software (version 16; StataCorp), and R freeware (version 3.6.3; The R Foundation) were used for the statistical analyses. Statistical significance was considered when the upper bound of the 1-sided 97.5% CI of the primary end point was below the predefined margin for noninferiority analyses, and when the 95% CI of the secondary end points did not include the null value.

## Results

The trial included 1414 patients in the as-randomized population: 726 in the intervention strategy group and 688 in the control strategy group (Figure 2; eTable 1 in Supplement 3). The primary end point was missing in 37 patients (2.6%), which were replaced by zero in the as-randomized population. After exclusion of 67 further ineligible patients and 39 patients with major protocol deviations, 1271 were included in the per-protocol analysis (648 in the intervention group and 623 in the control group) (eTable 2 in Supplement 3). Table 1 lists the main patient characteristics. The mean (SD) age was 55 (19) years, and 58% were female. PE was diagnosed in the ED in 100 patients: 54 (7.4%) and 46 (6.7%) in the intervention and control groups, respectively (difference, -0.8% [95% CI, -2.0% to 3.5%]). A total of 9 VTEs at 3 months were adjudicated in the as-randomized population, including 5 unexpected deaths with no other identified cause (eTable 3 in Supplement 3). D-dimer distribution and positivity in the 2 groups are presented in the eFigure in Supplement 3.

### Primary Outcome

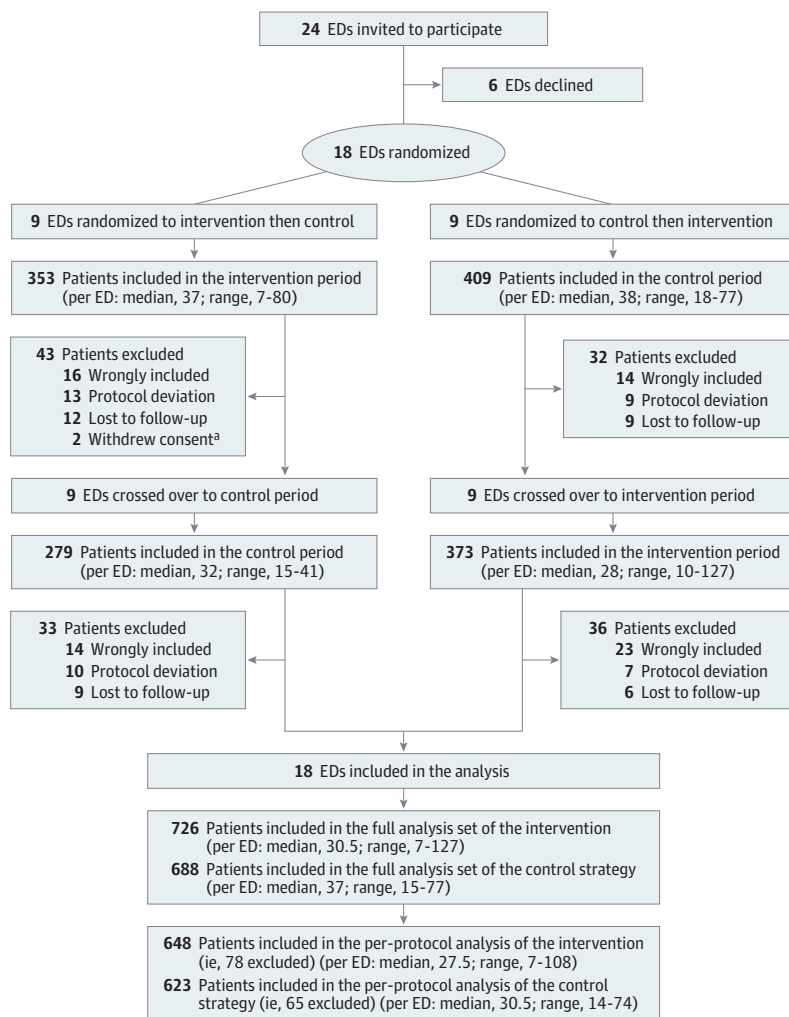
In the per-protocol population ( $n = 1271$ ), 6 PEs were diagnosed at 3 months (1 in the intervention group and 5 in the control group) (Table 2). The failure rate was 0.15% (95% CI, 0.00% to 0.86%) and 0.80% (95% CI, 0.26% to 1.86%) in the intervention and control groups, respectively. The adjusted difference of the failure rate between the 2 groups was -0.64% (1-sided 97.5% CI,  $-\infty$  to 0.21%), which was less than the noninferiority margin of 1.35%. The results were similar in the as-randomized population, with or without multiple imputations (Table 2).

### Secondary Outcomes

In the as-randomized population, chest imaging was performed in the ED in 496 patients (35.1%): 221 (30.4%) in the intervention group and 275 (40.0%) in the control group (difference, -9.6%; adjusted difference, -8.7% [95% CI, -13.8% to -3.5%]). The median ED length of stay was 6.0 hours (IQR, 4.0-8.0) vs 6.0 hours (IQR, 5.0-9.0) (adjusted difference, -1.6 hours [95% CI, -2.4 to -0.9]). Similar results were found in the per-protocol population (eTable 4 in Supplement 3).

None of the other secondary outcomes differed statistically significantly in frequency between the 2 groups (Table 3).

Figure 2. Patient Flow Diagram



ED indicates emergency department.

<sup>a</sup> One of the patients who withdrew consent was diagnosed with a pulmonary embolism on day 0 and, therefore, did not meet the primary end point.

No significant period effect was demonstrated in the per-protocol, as-randomized, or as-randomized-with-multiple-imputation populations ( $P = .78$ ,  $P = .49$ , and  $P = .50$ , respectively). The order of the 2 strategies was not associated with the risk of VTE at 3 months (strategy-by-period interaction term coefficient  $\beta = 0.25$  [95% CI,  $-2.64$  to  $3.15$ ],  $P = .86$  for the as-randomized population and  $\beta = -0.17$  [95% CI,  $-3.09$  to  $2.75$ ],  $P = .90$  for the as-randomized population with multiple imputation; not computed for the per-protocol population due to model nonconvergence) and was not kept in the model. The Donner formula showed that the interperiod correlation coefficient was 0.0002 and the intracluster coefficient was 0.0.<sup>29</sup> Diagnostic yields of chest imaging studies are reported in eTable 5 in Supplement 3. The sensitivity analysis after exclusion of isolated subsegmental PE showed similar results and confirmed the noninferiority of the intervention (eTable 6 in Supplement 3).

In the per-protocol population, there was a total of 956 patients with a YEARS score of zero (515 in the intervention group and 441 in the control group). In a post hoc analysis limited to these patients, there were no missed PEs in the intervention

group (failure rate, 0.00% [95% CI, 0.00% to 0.71%], below the noninferiority margin) and 3 missed PEs in the control group (failure rate, 0.68% [95% CI, 0.00% to 1.45%]). In this post hoc analysis, chest imaging was performed in 22.9% of patients in the intervention group vs 37.2% in the control group (absolute reduction, 14.3% [95% CI, 8.3% to 20.2%]).

## Discussion

In this multicenter, cluster-randomized, crossover trial of PERC-positive ED patients with suspicion of a PE, a strategy consisting of a combination of the YEARS rule with an age-adjusted D-dimer cutoff resulted in a noninferior proportion of VTEs at 3 months compared with a conventional strategy. The intervention was associated with a statistically significant reduction in chest imaging use.

The YEARS rule has been prospectively validated but not assessed in a randomized trial, nor used in combination with the PERC rule and an age-adjusted D-dimer cutoff.<sup>7</sup> In this trial, using PERC, YEARS, and an age-adjusted D-dimer cutoff was

Table 1. Patient Characteristics

Characteristic	No./total (%) <sup>a</sup>	
	Intervention group (n = 726)	Control group (n = 688)
Age at inclusion, mean (SD) [range], y	54.4 (19.0) [18-98]	55.9 (19.6) [19-100]
Sex, No. (%)		
Female	397 (54.7)	426 (61.9)
Male	329 (45.3)	262 (38.1)
Congestive or ischemic heart disease <sup>b</sup>	63/722 (8.7)	78 (11.3)
Chronic respiratory insufficiency <sup>c</sup>	38/722 (5.3)	40 (5.8)
Chronic kidney failure <sup>c</sup>	12/724 (1.7)	13 (1.9)
Stroke <sup>c</sup>	15/720 (2.1)	15/687 (2.2)
Cancer <sup>c</sup>		
Not active	692/720 (96.1)	645 (93.8)
Active	28/720 (3.9)	43 (6.3)
Past PE and/or DVT	56/723 (7.7)	54/687 (7.9)
Chest pain	525 (72.3)	494/687 (71.9)
Dyspnea	391/725 (53.9)	396/687 (57.6)
Syncope	79/722 (10.9)	72 (10.5)
Respiratory rate, median (IQR) [No.], per min	18.0 (16.0-20.0) [680]	18.0 (16.0-20.0) [609]
Heart rate		
Median (IQR) [No.], bpm	90.0 (76.0-105.0) [723]	90.0 (77.0-107.0) [687]
>100 bpm	237/723 (32.8)	243/687 (35.4)
Temperature, median (IQR) [No.], °C	36.7 (36.3-37.1) [724]	36.7 (36.4-37.1) [685]
Systolic blood pressure, mm Hg	139.5 (20.5)	139.8 (22.5) [687]
SaO <sub>2</sub>		
Median (IQR) [No.], %	98.0 (96.0-99.0) [721]	98.0 (96.0-99.0) [686]
<95%	83/721 (11.5)	88/686 (12.8)
Exogenous estrogen use	68/720 (9.4)	56/687 (8.2)
Immobilization or surgery <1 mo	35/720 (4.9)	25/687 (3.6)
Calf painful to palpation	19/720 (2.6)	32/687 (4.7)
Unilateral leg edema	7/720 (1.0)	14/687 (2.0)
Anticoagulant therapy in the ED	16/718 (2.2)	23/686 (3.4)
D-dimers, No. (%)		
<Age-adjusted threshold	432 (59.5)	410/686 (59.8)
<1000 ng/mL	562 (77.4)	501/686 (73.0)
YEARS score = 0, No. (%) <sup>d</sup>	585 (80.6)	
CTPA or V/Q scan performed, No. (%) <sup>e</sup>	221 (30.4)	275 (40.0)
PE diagnosed in the ED, No. (%)	54 (7.4)	46 (6.7)
Type of PE		
Isolated subsegmental	1/51 (2.0)	3/42 (7.1)
Subsegmental	8/51 (15.7)	2/42 (4.8)
Segmental	18/51 (35.3)	20/42 (47.6)
Lobar	24/51 (47.1)	17/42 (40.5)
ED discharge disposition		
Hospital admission	140/725 (19.3)	166 (24.1)
Transfer to another hospital	17/725 (2.3)	12 (1.7)
Discharged home	568/725 (78.3)	510 (74.1)

Abbreviations: bpm, beats per minute; CTPA, computed tomography pulmonary angiogram; DVT, deep vein thrombosis; ED, emergency department; PE, pulmonary embolism; SaO<sub>2</sub>, arterial oxygen saturation; V/Q, pulmonary ventilation/perfusion.

<sup>a</sup> No. = numbers of patients included in the analysis.

<sup>b</sup> Estimated creatinine clearance less than 30 mL/min.

<sup>c</sup> Chronic respiratory insufficiency, chronic cardiac failure, stroke, and cancer were determined by the ED physician, based on available patient medical history.

<sup>d</sup> YEARS score ranges from 0 to 3, 1 point per item: PE is the most likely diagnosis, hemoptysis, and clinical sign of deep vein thrombosis.

<sup>e</sup> One patient in the control group had CTPA and V/Q scan.

associated with lower use of chest imaging compared with a conventional strategy, with the absolute difference between the 2 groups being 10%. This decrease was smaller than found in a previous prospective cohort study (14% absolute reduction).<sup>7</sup> This was partly because the previous study included patients with a low clinical probability of PE and no

PERC criteria (not included in the present study), who would have had no YEARS criteria and therefore would not have had chest imaging. That applying the YEARS criteria was associated with a significant decrease in chest imaging use in a population of PERC-positive patients emphasizes the value of combining the 2 criteria sets.

Table 2. Primary End Point (Occurrence of a VTE Event at 3 Months)

Variable	Intervention group (n = 726)		Control group (n = 688)		Difference (97.5% 1-sided CI)	
	No.	No. (%) [95% CI]	No.	No. (%) [95% CI]	Adjusted <sup>a</sup>	Unadjusted
<b>Per-protocol population<sup>b</sup></b>						
No.	648		623			
VTE at 3 mo, No. (%) [95% CI]	1 (0.15) [0.00 to 0.86]		5 (0.80) [0.26 to 1.86]		-0.64 (-∞ to 0.21)	-0.65 (-∞ to 0.17)
<b>Randomized population<sup>c</sup></b>						
No.	726		688			
VTE at 3 mo, No. (%) [95% CI]	3 (0.41) [0.09 to 1.20]		6 (0.87) [0.32 to 1.89]		-0.49 (-∞ to 0.36)	-0.46 (-∞ to 0.45)
<b>As-randomized population with multiple imputation<sup>d</sup></b>						
No.	726		688			
VTE at 3 mo	3.2 <sup>e</sup>		6.1 <sup>e</sup>			
% (95% CI)	0.42 (-0.06 to 0.90)		0.88 (0.18 to 1.58)		NA <sup>f</sup>	-0.46 (-∞ to 0.39)

Abbreviations: NA, not available; VTE, venous thromboembolism.

<sup>a</sup> Differences were adjusted for periods as fixed effects and cluster as a random effect. The differences are expressed as intervention minus control.

<sup>b</sup> All patients with the primary end point available, all inclusion/noninclusion criteria met, and management with the strategy assigned by randomization.

<sup>c</sup> All randomized patients; missing data on the primary outcome for 37 patients were replaced by 0 (no pulmonary embolism).

<sup>d</sup> All randomized patients; missing data on the primary outcome for 37 patients were replaced using multiple imputation.

<sup>e</sup> Average across 15 multiply-imputed data sets.

<sup>f</sup> Computation of adjusted differences after multiple imputations was not feasible.

Table 3. Secondary End Points

Variable	Intervention group (n = 726)		Control group (n = 688)		Difference (95% CI)	
	No.	No. (%) [95% CI]	No.	No. (%) [95% CI]	Adjusted <sup>a</sup>	Unadjusted
Chest imaging <sup>b</sup>	726	221 (30.4) [27.1 to 33.9]	688	275 (40.0) [36.3 to 43.7]	-8.7 (-13.8 to -3.5)	-9.5 (-14.5 to -4.3)
Undue initiation of anticoagulation regimen	718	5 (0.7) [0.2 to 1.6]	686	11 (1.6) [0.8 to 2.9]	-1.4 (-3.1 to 0.4)	-0.9 (-2.2 to 0.2)
Admitted from the ED	725	157 (21.7) [18.7 to 24.8]	688	178 (25.9) [22.6 to 29.3]	-3.0 (-7.7 to 1.6)	-4.2 (-8.7 to 0.3)
All-cause hospital admission at 3 mo	647	85 (13.1) [10.6 to 16.0]	627	99 (15.8) [13.0 to 18.9]	-2.0 (-6.0 to 2.0)	-2.7 (-6.6 to 1.2)
All-cause mortality at 3 mo	689	12 (1.7) [0.9 to 3.0]	660	13 (2.0) [1.1 to 3.3]	0.11 (-1.6 to 1.8)	-0.2 (-1.8 to 1.3)
ED length of stay, median (IQR), h	726	6.0 (4.0 to 8.0)	688	6.0 (5.0 to 9.0)	-1.6 (-2.3 to -0.9)	0.0 (-0.7 to 0.7)

Abbreviation: ED, emergency department.

<sup>a</sup> Differences were adjusted for periods as fixed effects and cluster as a random effect. The differences are expressed as intervention minus control.

<sup>b</sup> Chest imaging included computed tomography pulmonary angiography or pulmonary ventilation/perfusion scan.

The PE prevalence in this trial was 7%, which is below the 13% reported in the van der Hulle et al<sup>7</sup> study. This is explained by the fact that the latter study included patients with a high clinical probability, and that only 50% of patients had a YEARS score of zero. In the present trial, more than 80% of included patients had a YEARS score of zero, with a subsequent overall lower prevalence of PE. However, this prevalence is similar to the one of the PEGeD study and higher than previous studies that included only patients with a low pretest probability.<sup>2,12,13</sup> Furthermore, Pernod et al<sup>30</sup> reported an overall PE prevalence of 7.9% in patients with low and moderate clinical probability, which is the population of interest in this study.

One strength of the present trial was that most patients (80%) in the intervention group had none of the YEARS criteria, which resulted in a change in strategy consisting in performing chest imaging only if the D-dimer level was above the raised cutoff of 1000 ng/mL. Safety is best evaluated in patients for whom the strategy being studied actually changes the criterion for performing further investigations.<sup>25,26</sup> There were no missed PEs in patients with a YEARS score of zero who

received the intervention (failure rate, 0.00% [95% CI, 0.00% to 0.71%]). Consequently, these data demonstrating the safety of the intervention strategy are particularly robust.

### Limitations

This trial has several limitations. First, randomization occurred at the center level and not at the patient level. Consequently, the 2 patient groups may have had clinically important differences, although none were identified (Table 1). The crossover design allowed avoiding biases related to a center effect, confirmed by an intracluster coefficient value at 0.0. Similarly, there was no statistically significant sequence effect.

Second, protocol deviations occurred in both groups: 29 patients underwent chest imaging despite a negative D-dimer test (20 in the intervention group and 9 in the control group) and 11 patients did not undergo chest imaging despite a positive D-dimer (1 in the intervention group and 10 in the control group). Therefore, there was a very limited rate of contamination in this study, partially explained by the cluster design with a washout period.

Third, information on the primary outcome was missing for 37 patients. However, given the noninferiority design, the main analysis of the primary outcome focused on the per-protocol population. In the main analysis of the as-randomized population, these 37 patients were classified as not exhibiting the primary outcome given its low prevalence (<1%). Nevertheless, some of these patients may have had PE that was not diagnosed in the ED, in which case the analysis of the as-randomized population may not have confirmed the safety of the intervention. To address this potential bias, a sensitivity analysis of the primary outcome was performed after replacing the missing data with multiple imputation. The result was unchanged.

Fourth, the study was performed as a pragmatic trial and patients were included by the clinicians. Therefore, it is likely that some eligible patients were not included in the study; the magnitude of this selection bias cannot be determined.

Fifth, although the safety has been validated in the population of patients with a YEARS score of zero, there was a lack

of power to confirm that this is the case for the subgroup of patients of the intervention group that had a YEARS score of zero and a D-dimer level above the age-adjusted threshold but below 1000 ng/mL. No missed PEs were found in this subgroup, but the upper bound of the 95% CI of the failure rate was 5.36%, which was above the predefined safety threshold.

Sixth, the subjective criteria of the YEARS score may seem less reliable than a fully structured score, but it has been shown that a subjective assessment of the clinical probability of a PE is reliable.<sup>10,12</sup>

## Conclusions

Among ED patients with suspected PE, the use of the YEARS rule combined with the age-adjusted D-dimer threshold in PERC-positive patients, compared with a conventional diagnostic strategy, did not result in an inferior rate of thromboembolic events.

### ARTICLE INFORMATION

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### REFERENCES

1. Raja AS, Ip IK, Prevedello LM, et al. Effect of computerized clinical decision support on the use and yield of CT pulmonary angiography in the emergency department. *Radiology*. 2012;262(2):468-474. doi:10.1148/radiol.11110951
2. Freund Y, Cachanado M, Aubry A, et al; PROPER Investigator Group. Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: the PROPER randomized clinical trial. *JAMA*. 2018;319(6):559-566. doi:10.1001/jama.2017.21904
3. Abdelal Ahmed Mahmoud M Alkhatip A, Donnelly M, Snyman L, et al. YEARS algorithm versus Wells' score: predictive accuracies in pulmonary embolism based on the gold standard CT pulmonary angiography. *Crit Care Med*. 2020;48(5):704-708. doi:10.1097/CCM.0000000000004271



4. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171(9):831-837. doi:10.1001/archinternmed.2011.178
5. van der Pol LM, Dronkers CEA, van der Hulle T, et al. The YEARS algorithm for suspected pulmonary embolism: shorter visit time and reduced costs at the emergency department. *J Thromb Haemost*. 2018;16(4):725-733. doi:10.1111/jth.13972
6. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008;6(5):772-780. doi:10.1111/j.1538-7836.2008.02944.x
7. van der Hulle T, Cheung WY, Kooij S, et al; YEARS study group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet*. 2017;390(10091):289-297. doi:10.1016/S0140-6736(17)30885-1
8. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135
9. Philippon A-L, Dumont M, Jimenez S, et al. Modified diagnostic strategy to safely rule-out pulmonary embolism in the emergency department: study protocol for the non-inferiority MODIGLIANI cluster cross-over randomized trial. *Trials*. 2020;21(1):458. doi:10.1186/s13063-020-04379-y
10. Penalzoza A, Verschuren F, Meyer G, et al. Comparison of the unstructured clinician gestalt, the Wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. *Ann Emerg Med*. 2013;62(2):117-124.e2. doi:10.1016/j.annemergmed.2012.11.002
11. Raynal P-A, Cachanado M, Truchot J, et al. Prevalence of pulmonary embolism in emergency department patients with isolated syncope: a prospective cohort study. *Eur J Emerg Med*. 2019;26(6):458-461. doi:10.1097/MEJ.0000000000000625
12. Kearon C, de Wit K, Parpia S, et al; PEGeD Study Investigators. Diagnosis of pulmonary embolism with D-dimer adjusted to clinical probability. *N Engl J Med*. 2019;381(22):2125-2134. doi:10.1056/NEJMoa1909159
13. Penalzoza A, Soulié C, Moumneh T, et al. Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): a multicentre, prospective, observational study. *Lancet Haematol*. 2017;4(12):e615-e621. doi:10.1016/S2352-3026(17)30210-7
14. Konstantinides SV, Meyer G, Becattini C, et al; the Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54(3):1901647. doi:10.1183/13993003.01647-2019
15. Bariteau A, Stewart LK, Emmett TW, Kline JA. Systematic review and meta-analysis of outcomes of patients with subsegmental pulmonary embolism with and without anticoagulation treatment. *Acad Emerg Med*. 2018;25(7):828-835. doi:10.1111/acem.13399
16. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. *Clin Appl Thromb Hemost*. 2012;18(1):20-26. doi:10.1177/1076029611422363
17. Tritschler T, Kraaijpoel N, Girard P, et al; Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Definition of pulmonary embolism-related death and classification of the cause of death in venous thromboembolism studies: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020;18(6):1495-1500. doi:10.1111/jth.14769
18. Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet*. 2008;371(9621):1343-1352. doi:10.1016/S0140-6736(08)60594-2
19. Prins MH, Lensing AW. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. *Thromb J*. 2013;11(1):13. doi:10.1186/1477-9560-11-13
20. Dronkers CEA, van der Hulle T, Le Gal G, et al; Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15(5):1040-1043. doi:10.1111/jth.13654
21. Freund Y, Goulet H, Leblanc J, et al. Effect of systematic physician cross-checking on reducing adverse events in the emergency department: the CHARMED cluster randomized trial. *JAMA Intern Med*. 2018;178(6):812-819. doi:10.1001/jamainternmed.2018.0607
22. Freund Y, Cachanado M, Delannoy Q, et al. Effect of an emergency department care bundle on 30-day hospital discharge and survival among elderly patients with acute heart failure: the ELISABETH randomized clinical trial. *JAMA*. 2020;324(19):1948-1956. doi:10.1001/jama.2020.19378
23. Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med*. 2017;377(14):1357-1367. doi:10.1056/NEJMr1510063
24. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA*. 2006;295(10):1152-1160. doi:10.1001/jama.295.10.1152
25. Behringer W, Freund Y. Clinical translation of diagnostic studies: pitfalls of the usual reported characteristics. *Eur J Emerg Med*. 2021;28(3):165-166. doi:10.1097/MEJ.0000000000000830
26. Freund Y, Roussel M, Kline J, Roy P-M, Bloom B. The failure rate does not equal the false-negative rate: a call for tailoring diagnostic strategy validation in low prevalence populations. *J Thromb Haemost*. 2021;19(7):1832-1833. doi:10.1111/jth.15353
27. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38(1):29-41. doi:10.2307/2530286
28. Molenberghs G, Verbeke G. *Models for Discrete Longitudinal Data*. Springer-Verlag; 2005. doi:10.1007/0-387-28980-1
29. Donner A, Klar N, Zou G. Methods for the statistical analysis of binary data in split-cluster designs. *Biometrics*. 2004;60(4):919-925. doi:10.1111/j.0006-341X.2004.00247.x
30. Pernod G, Caterino J, Maignan M, Tissier C, Kassis J, Lazarchick J; DIET study group. D-dimer use and pulmonary embolism diagnosis in emergency units: why is there such a difference in pulmonary embolism prevalence between the United States of America and countries outside USA? *PLoS One*. 2017;12(1):e0169268. doi:10.1371/journal.pone.0169268